NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

STA Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

This pre-meeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness issues

- The key clinical evidence compared secukinumab with placebo (standard of care) in 2 international randomised controlled trials (MEASURE 1 [including [redacted]/371 patients from the UK] and MEASURE 2 [including [redacted]/219 patients from the UK]). In the trials some patients had been previously treated with biologics and others had not. These were pre-specified subgroups. Patients in the studies were required to be receiving stable doses of methotrexate, sulfasalazine and folic acid 4 weeks prior to randomisation, and patients who were on stable doses of corticosteroids and/or NSAIDs, paracetamol or aspirin were allowed to continue receiving those treatments during the study period. What is the committee's view

on the generalisability of studies included in the company's submission to clinical practice in England?

- In Measure 1, patients had intravenous loading doses of secukinumab up to 8 weeks (which does not have a license) followed by subcutaneous secukinumab, while in MEASURE 2 they had only subcutaneous injections of secukinumab. Is it appropriate for the company to use evidence from MEASURE 1 to estimate the clinical effectiveness of secukinumab?
- The primary outcome in the clinical trials was a definition of response based on ASA20 and the response in the base case model was based on BASDAI 50. However, the 2004 BSR guidelines (and the recent MTA TA 383) in ankylosing spondylitis define a response to TNF alpha inhibitors as a reduction to BASDAI of 50% of the pre-treatment value or a fall of 2 units or greater in BASDAI score and a reduction in the spinal pain VAS (in the last 1 week) by 2 cm or greater. What measures of response are most relevant in clinical practice?
- Is sequential anti-TNF alphas used routinely in the NHS in England for ankylosing spondylitis for people whose disease has not responded to treatment?
- There are two types of treatment experienced patients; those who are intolerant to and those who are have an inadequate response to anti-TNF alphas, but the company's submission does not seem to include people who have a loss of response to these agents. How relevant is the efficacy of secukinumab presented by the company in the biologic-experienced population to patients seen in clinical practice.
- The company performed 2 network meta-analyses: one for all patients (previously treated or treatment naive) and another for the treatment naive population alone. The company compared pooled data from MEASURE 1 and 2 at 16 weeks (although data were also collected at week 12) with pooled data from comparator treatments at 12 weeks. Pooling of different time points may favour secukinumab as the patients who are assessed later will have had more time to respond (and potentially an extra dose). The ERG preferred a network meta-analysis using only the 12 week data for all networks. What is the committee's view on the approaches taken by the company and the ERG with respect to the timepoint of assessment used in the network meta-analyses?

- In the company's base case network meta-analysis results (using pooled data from 12 and 16 weeks) secukinumab showed a statistically significant increase in the probability of achieving a response relative to placebo as measured by ASAS20, ASAS40 and BASDAI 50. In the ERG's 12 week sensitivity analysis the same comparisons are still statistically significant but the magnitude of the treatment effect is reduced for all three outcomes. A similar reduction in the effectiveness of secukinumab compared to all other treatments was observed when the analysis in based on 12 week data from all studies. What is the committee's view of the true relative efficacy of secukinumab with placebo and with TNF alpha inhibitors?
- **Cost effectiveness issues**
- The company used the York model used in NICE technology appraisal 383 without providing a justification for its use. What is the committee's view on the appropriateness of using the York model for this appraisal?
- In the modelling of the BASFI and BASDAI progression, the company used baseline scores conditional on whether a person's disease responded to the treatment which resulted in 'responders' having lower baseline BASDAI and BASFI scores compared with 'non‑responders. This assumption implies that people with more severe disease do not benefit as much from treatment as people with less severe disease, because someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to achieve a BASDAI 50 response. In TA383, the committee concluded that there was no evidence to suggest that people with severe disease are less likely to have a clinical meaningful benefit than those with less severe disease. What is the committee's interpretation of this?
- The company used change-in-baseline ratios specific to secukinumab, adalimumab and golimumab for BASDAI and BASFI. For all other biologics, the average proportional change in BASDAI and BASFI from baseline from secukinumab, adalimumab and golimumab were used in the absence of data for those comparators. What is the committee's interpretation of this?
- The choice of the MTC has a large impact on the response rates. The company base case used a mixed treatment comparison which had different time points for

response assessment and the ERG's used the same time point (12 weeks). What is the committee' view of the most appropriate timepoint to use for the mixed treatment comparison?

- The ERG preferred to use the same withdrawal rate for all treatments as per York model, rather than treatment specific withdrawal rates, does the committee have a view on this?
- The ERG exploratory base case for the biologic naïve population used change from baseline estimates from MEASURE 1 and 2 using 12 week data and withdrawal rates from York model). What is the committee's view on the results of this analysis?
- The ERG exploratory base case for the biologic experienced population used week 12 response data from MEASURE 1 and 2 and withdrawal rates from York model. What is the committee's view on the results of this analysis?
- Regression models (utility mapping model derived from MEASURE 1 and MEASURE 2 trials as the base case) and other published models in the literature were used to translate BASFI/ BASDAI to cost/QALY estimates. The ERG was not provided with the details of the utility mapping model and the model selection procedure were not provided by the company despite the request from the ERG. Is this a concern for the committee?
- The ERG base case leads to substantially different results than the company base case, but does not increase ICER for secukinumab compared with any of its comparators beyond what is usually considered cost-effective. Considering the economic modelling for secukinumab using the company's and the ERG's base case analysis and numerous deterministic sensitivity analyses and probabilistic analyses, what is the committee's view on the cost effectiveness of secukinumab for ankylosing spondylitis?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of secukinumab within its marketing authorisation for treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

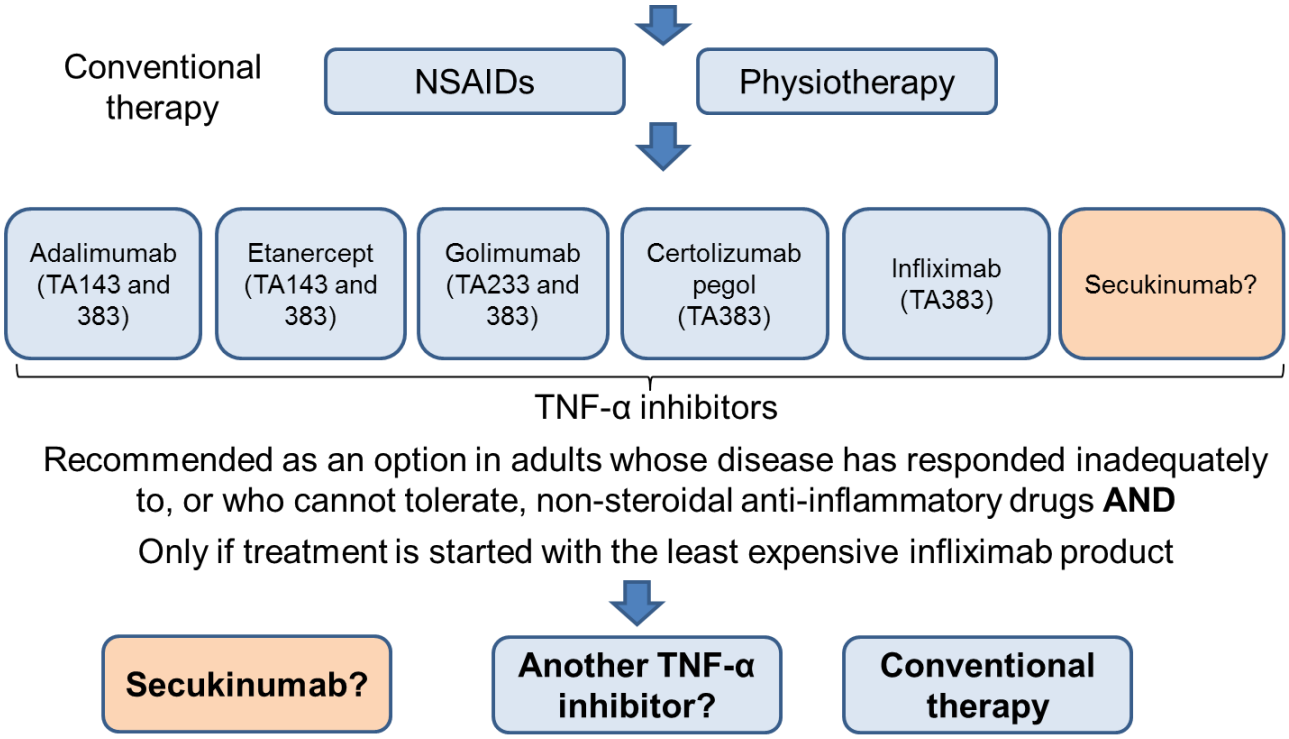
Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with active ankylosing spondylitis for whom non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors have been inadequately effective or not tolerated.	This submission considers the population of adult patients with active AS for whom conventional care has not been effective (biologic naïve population) or for whom conventional care and TNF-alpha inhibitors have not been effective or who had been intolerant to at least one administration of anti TNF alpha (biologic inadequate responder population)	NA	The ERG has 3 concerns: • the way disease severity is handled • the lack of distinction between non-response and intolerance (there is no consideration as to whether these 2 groups are clinically different or whether they might respond differently) • a possible mismatch between the company's summary of the decision problem and the eligibility criteria for title and abstract screening for generation of evidence
Int.	Secukinumab			
Com.	TNF-alpha inhibitors For people whose	Biologic naïve population: TNF-alpha inhibitors	There are no formal guidelines on sequencing of biologics (i.e. administering a second biologic following	Appropriate and inclusive of infliximab

	disease has responded inadequately to, or who are intolerant to TNF-alpha inhibitors: Established clinical management without secukinumab	Biologic experienced population: • Conventional care (base case): i.e. having discontinued their first biologic, patients move to conventional care • TNF-alpha inhibitors and conventional care (exploratory analysis): i.e. having discontinued their first biologic, patients can move to either conventional care or a TNF-alpha inhibitor	discontinuation of an initial biologic therapy), and there is a lack of robust clinical data to support use of the TNF-alpha inhibitors in the biologic experienced population, as acknowledged by the Assessment Group as part of the NICE MTA in AS and supported by the systematic literature review in Section **Error! Reference source not found.**. Therefore, for the biologic experienced population conventional care is considered to represent established clinical management. Comparison to biologics in this population is included as an exploratory analysis.	
Out.	• Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-	• Disease activity (ASAS20; ASAS40; BASDAI 50; BASDAI change from baseline; ASAS 5/6; ASAS partial remission; ASDAS-CRP [major improvement]; hsCRP change from baseline; patient's global assessment of disease activity) • Functional capacity (BASFI change from baseline; BASMI	NA	Appropriate and comprehensive

	articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • Adverse effects of treatment Health-related quality of life.	linear change from baseline) • Disease progression (mSASSS; MRI outcomes) • Pain (as captured by ASAS and BASDAI criteria) • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) (MASES) • Symptoms of extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis (captured under safety reporting) • Adverse effects of treatment • Health-related quality of life (ASQoL, EQ-5D, SF-36 PCS and MCS, FACIT-Fatigue) Impairment in work and activities (WPAI-GH)		

2 The technology and the treatment pathway



2.1 Secukinumab (Cosentyx, Novartis) is a human monoclonal antibody which specifically inhibits the interleukin 17A (IL-17A) receptor. Secukinumab is administered by subcutaneous injection.

2.2 Secukinumab has a marketing authorisation in the UK for 'treating active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate'. IL-17A has been implicated in processes that occur in the early phases of spondyloarthritic diseases, including tissue inflammation and enthesitis. It has a UK marketing authorisation for treating active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

Table 2 Technologies

Mechanism	**interleukin 17A receptor inhibitor**	**anti TNF-alpha**				
Non-proprietary name	**Secukinumab**	**Adalimumab**	**Certolizumab pegol**	**Etanercept**	**Golimumab**	**Infliximab (biosimilars)**
Proprietary name	Cosentyx	Humira	Cimzia	Enbrel	Simponi	Remicade (Inflectra and Remsima)
Company	Novartis	AbbVie	UCB	Pfizer	Merck Sharp & Dohme	Merck Sharp & Dohme (Hospira and Celltrion Healthcare)
Dose	150mg every week for 5 doses(induction) then 150mg every month (maintenance), review treatment if no response within 16 weeks of initial dose	40 mg every other week	400 mg at weeks 0, 2 and 4 (induction) then 200 mg every 2 weeks or 400 mg every 4 weeks (maintenance)	25 mg twice weekly or 50 mg once weekly	50 mg once a month (may be increased to 100 mg once a month in patients with a body weight greater than 100 kg)	5 mg/kg infusion doses at weeks 0, 2 and 6 (induction), then every 6–8 weeks (maintenance)

Mechanism	**interleukin 17A receptor inhibitor**	**anti TNF-alpha**				
Non-proprietary name	**Secukinumab**	**Adalimumab**	**Certolizumab pegol**	**Etanercept**	**Golimumab**	**Infliximab (biosimilars)**
Acquisition cost (BNF online accessed May 2016 unless otherwise stated)	£609.39 ([redacted]) for a 150 mg pre-filled pen or syringe. (MIMS online accessed May 2016)	£352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial	£357.50 for a 200 mg pre-filled syringe	£89.38 for a 25 mg pre-filled syringe or a 25 mg vial; £178.75 for a 50 mg pre-filled pen or pre-filled syringe	£762.97 for a 50 mg pre-filled pen or pre-filled syringe; £1525.94 for a 100 mg pre-filled pen	Remicade: £419.62 for a 100 mg vial Remsima: £377.66 for a 100 mg vial Inflectra, £377.66 for a 100 mg vial

Background

2.3 Ankylosing spondylitis (AS) is an inflammatory disease of unknown cause. It is one of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Spondyloarthritis can be categorised as having predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial spondyloarthritis, the predominant symptom is back pain, with inflammation of the sacroiliac joints (sacroiliitis), the spine or both. The onset of symptoms typically occurs in the third decade of life. Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. There may also be peripheral joint involvement or extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis.

2.4 If definite radiographic sacroiliitis (abnormalities seen in plain x-rays of the sacroiliac joints, such as erosions, sclerosis, and partial or total fusion of the spine) is present, the disease is classified as ankylosing spondylitis. The prevalence is thought to range from 0.05% to 0.23% and it is about 3 times more common in men than in women.

2.5 Not everyone with symptoms of axial spondyloarthritis will have x-ray evidence of the disease (although sacroiliitis or inflammation of the spine may be visible on MRI). This is referred to as axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. Limited epidemiological data are available for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but it affects approximately equal numbers of men and women.

2.6 Conventional therapy for axial spondyloarthritis includes acute anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Tumour necrosis factor-alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded

adequately to conventional therapy. NICE technology appraisal 383 recommends adalimumab, certolizumab pegol, etanercept, golimumab and infliximab as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or cannot tolerate, non−steroidal anti−inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product.

2.7 Three key disease components are assessed in clinical trials of ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: disease activity, physical function and structural damage. A number of assessment tools have been developed to measure these (presented in Table 10, Appendix B). For example, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most commonly used instrument to measure inflammatory activity. Physical function is widely assessed through the use of the Bath Ankylosing Spondylitis Functional Index (BASFI). Structural damage and disease progression are primarily evaluated using radiography, captured on the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

2.8 The Assessment of SpondyloArthritis international Society (ASAS) has developed a set of response criteria (presented in Table 11, Appendix B), which relate to improvement across a set of 4 domains. An ASAS 20 response (a common primary efficacy outcome in clinical trials) is defined as an improvement of greater than 20% and an absolute change of 1 or more points in at least 3 of the 4 domains. Other definitions of ASAS response (ASAS 40, 50 and 70, based on improvements of 40%, 50% and 70%, respectively) and an improvement of 50% or more in BASDAI score (BASDAI 50) are also used to measure outcomes in clinical studies.

3 Comments from consultees

3.1 Anti-TNF alpha therapies are the standard treatment for people with severe AS; in people with mild to moderate AS, symptoms can often be

managed effectively with a combination of anti-inflammatory medications and physiotherapy. Research conducted by one consultee indicates that anti-TNF alpha therapies have made a difference to the lives of people with AS who are taking them. However, some patients prefer technologies that are not injections and some are concerned about the potential long-term side effects (possible immunosuppression, infections and allergic reactions) of this treatment.

3.2 At present if the AS does not have an adequate response to an anti TNF alpha use of a second or third one is at the discretion of the Clinical Commissioning Group, if allowed there is evidence that there is loss of effect of 10% for each further attempt. Patients and clinicians believe it is important to have an alternative to anti TNF alpha inhibitors that can provide a similar benefit and consider secukinumab to offer an alternative to the current, limited options to people with AS. Monthly injection (after the loading dose) would very convenient for many patients and the needle and self-injection pen versions available which allow patient choice. Secukinumab would be used in place of existing technologies in secondary care and managed within specialist teams, and therefore have no impact on current services are anticipated.

3.3 One consultee stated that for many people with AS the burden of living with AS is invisible. Sleep disturbance, back pain and stiffness fatigue and depression are some of the main symptoms of AS. The spectrum of severity means that although many people with AS live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment.

3.4 Another consultee considered that because the average age of diagnosis is 24, a prime time for establishing a career, work disability can be a major problem with more than 50% of people who are affected suffering work instability. In addition, one-third of people with AS give up work before normal retirement age and another 15% reduce or change their work

because of axial spondyloarthritis. The work capacity of people with AS in the middle decades of life is similar to that of people with rheumatoid arthritis. Being unable to work has important consequences for the individual and his/her family through both loss of earnings and the loss of self-esteem that a career and income provide.

3.5 People with AS want their symptoms to be improved by treatments that prevent further spinal and joint damage associated with AS. They value treatments which reduce pain and stiffness which improve quality of life including an improved family life, social life and an increased ability to be economically active.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review of clinical effectiveness identified 2 relevant randomised controlled trials (RCTs) for secukinumab: MEASURE 2 and MEASURE 1. In the placebo arms of both trials concomitant medications such as NSAIDs and physical therapy were permitted which the company considered to represent a proxy for UK conventional care.

- MEASURE 2 (n=219) was a multicentre, international ([redacted] UK patients), double-blind RCT that compared secukinumab 75 mg, secukinumab 150 mg and placebo in the treatment of ankylosing spondylitis in adults with an inadequate response to conventional care. The study included adults with moderate to severe AS according to the Modified New York criteria with prior documented radiological evidence and a previous history of active AS despite current or previous treatment with NSAIDs, DMARDs, and TNF-alpha inhibitor therapy (39% of patients in the study had disease which inadequately responded to TNF-alpha inhibitor therapy). Patients received secukinumab 75 mg plus (unlicensed dose) placebo 150 mg, secukinumab 150 mg (licensed

dose) plus placebo 75 mg, or 150 mg placebo and 75 mg placebo subcutaneously weekly for 5 doses followed by the same dosing every 4 weeks. Patients in the placebo alone group who had an inadequate response were re-randomised at week 16 to either 75 mg or 150 mg of secukinumab every 4 weeks.

- MEASURE 1 (n=371) was a multicentre, international ([redacted] UK patients), double-blind RCT that compared secukinumab 75 mg, secukinumab 150 mg and placebo in the treatment of ankylosing spondylitis in adults with an inadequate response to conventional care. The study included adults with moderate to severe AS according to the Modified New York criteria with prior documented radiological evidence and a previous history of active AS despite current or previous treatment with NSAIDs, DMARDs, and TNF-alpha inhibitor therapy (27% of patients in the study had disease which inadequately responded to TNF-alpha inhibitor therapy). Patients received secukinumab 75 mg plus placebo 150 mg, secukinumab 150 mg plus placebo 75 mg, or 150 mg placebo and 75 mg placebo intravenously every 2 weeks for 3 doses followed by the same dosing every 4 weeks. Patients whose disease did not respond to treatment in the placebo alone group were re-randomised at week 16 to either 75 mg or 150 mg of secukinumab every 4 weeks. Patients whose disease did respond to placebo were re-randomised at week 24.
- The primary outcome measure for both studies was the proportion of patients achieving ASAS20 response at week 16. Secondary outcomes included the proportion of patients achieving ASAS40 response at week 16, the proportion of patients achieving ASAS 5/6 response criteria at week 16, BASDAI change from baseline at week 16, SF-36 PCS change from baseline at week 16, ASQoL change from baseline at week 16, and the proportion of patients achieving ASAS partial remission criteria at week 16.

- A pre-specified subgroup analysis was performed to explore any differences in outcomes between TNF-alpha inhibitor-IR patients and patients who were naïve to TNF-alpha inhibitor treatment.

ERG comments

4.2 The ERG noted that MEASURE 1 was based on intravenous administration of secukinumab, whereas MEASURE 2 was based on subcutaneous administration. The company acknowledged this in its submission as being a potential limitation of the evidence, in part because the initial dose of secukinumab in MEASURE 1 was different to the subcutaneous initial dose in MEASURE 2. The ERG considers that, although not ideal, inclusion of MEASURE 1 seems reasonable in the light of limited evidence for subcutaneous administration.

4.3 Uncertainty surrounds the disease severity of patients between trials and within trials, which brings into question their comparability.

Clinical trial results

4.4 For the primary outcome of the studies, ASAS20 at week 16, secukinumab shows marked benefit over placebo in MEASURE 2 and MEASURE 1.

Table 3 ASAS20 response using observed data for the full analysis set (based on CS, Tables 17 and 29, and table 14.2-1.3 of CSR)

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	60.8% (OR 3.89; 95% CI 2.28 to 6.65)	28.7%	61.1% (OR 4.38; 95% CI 2.14 to 8.96)	28.4%
52 weeks	76.7%	[redacted] (placebo –non responder --> secukinumab) [redacted] (placebo	73.8%	[redacted] (placebo --> secukinumab)

		responder --> secukinumab)		
104 weeks	79.3%	[redacted] (placebo –non responder --> secukinumab) [redacted] (placebo responder --> secukinumab)	[redacted]	[redacted] (placebo --> secukinumab)
ASAS = Assessment of Spondyloarthritis; CI = confidence interval; CS = company submission; CSR = Clinical Study report; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); OR = odds ratio; s.c. = subcutaneous				

4.5 Secondary outcomes are summarised in table 4 below. Patients who were unblinded prior to the scheduled time point were considered non-responders from the time of unblinding up to placebo-controlled period (Week 24). The company's primary analysis included the non-responder imputation for patients that were unblinded prior to week 24. Continuous variables (e.g. ASAS components) were analysed using a mixed-effect model repeated measures (MMRM) which is valid under the missing at random assumption. Single-point imputation of missing data was not performed (e.g., last observation carried forward). For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed and the patient's data was removed from the analysis of the corresponding variable.

Table 4 Secondary outcomes using observed data (12 weeks) and non-responder imputation (16 weeks)

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
ASAS40 response (based on CS, Tables 19 and 31)				
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	41.6% (p<0.0001)	13.1%	36.1% (p<0.001)	10.8%
BASDAI 50 response (based on CS, tables 23 and 35)				
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	[redacted]	[redacted]	30.6% (p<0.01)	10.8%
BASDAI change from baseline (based on CS, tables 21 and 33)				

12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	-2.32, SE 0.172 [n=121]	-0.59, SE 0.180 [n=108]	-2.19, SE 0.248 [n=67]	-0.85, SE 0.252 [n=64]

ASAS = Assessment of Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index CS = company submission; CSR = Clinical Study report; ; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); s.c. = subcutaneous

4.6 In both MEASURE 1 and 2, a large proportion of patients receiving secukinumab 150 mg maintained a treatment response up to 2 years as measured by the ASAS20 and other measures.

4.7 MEASURE 1 provided results for radiographic outcomes, which showed that disease progression was observed in approximately 80% of patients randomised to secukinumab at baseline (mSASSS change ≤0).

Subgroup analyses

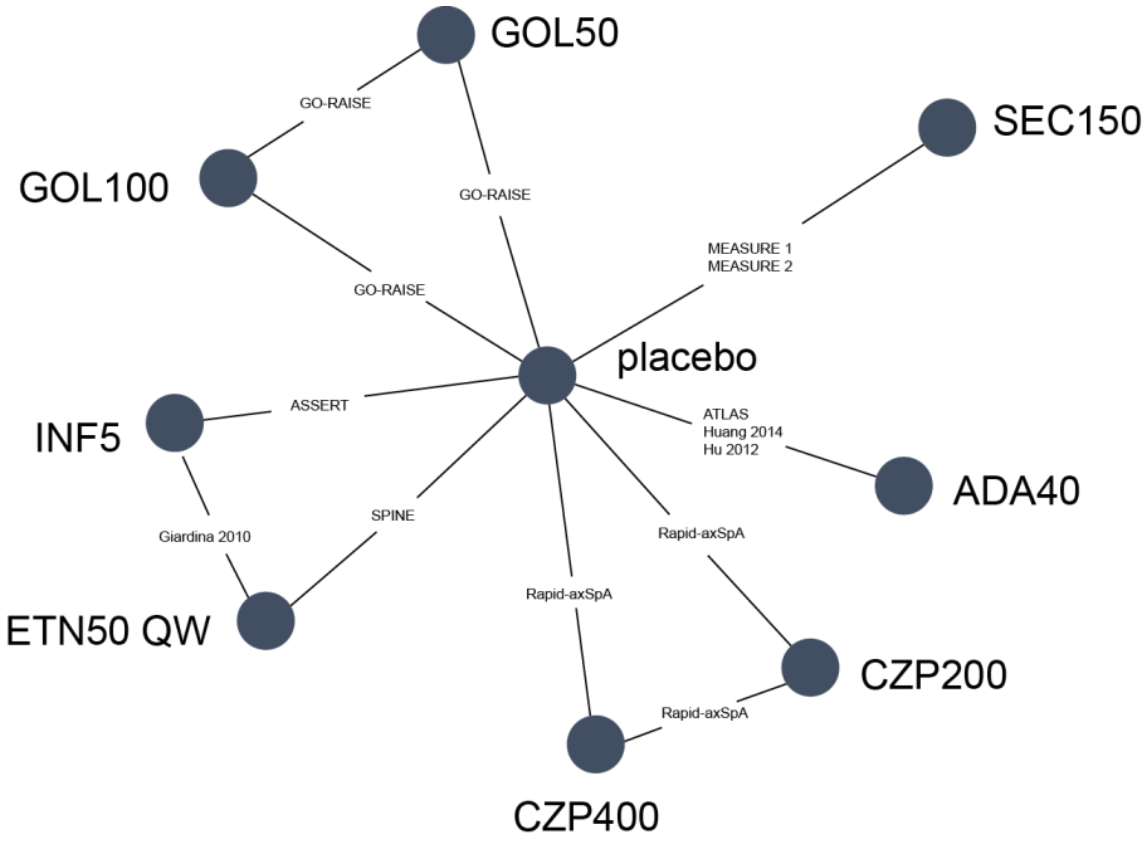
4.8 The company had pre-specified a subgroup analysis of the treatment outcomes based on whether a patient's disease responded to TNF-alpha inhibitors inadequately or had never received TNF alpha inhibitors previously. ASAS20 was analysed by previous TNF-alpha inhibitor status, depending on whether a patient's disease responded to TNF-alpha inhibitor inadequately or had never received TNF-alpha inhibitors. Secukinumab 150 mg resulted in a statistically significant increase in ASAS20 response rate compared with the placebo group at week 16, regardless of previous biologic treatment status, although a pattern of lower response to all outcomes in the group of patients whose disease had an inadequate response to prior TNF alpha treatment.

Table 5 ASAS20 response by TNF alpha inhibitor status at Week 16 using non-responder imputation (full analysis set) (based on CS, table 44)

Treatment group	Subgroup	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted
MEASURE 2						
Secukinumab 150 mg	TNF alpha inhibitor-naïve (N=44)	30/44 (68.2)	Placebo	4.72	(1.93, 11.56)	<0.001*
	TNF alpha inhibitor-inadequate response (N=28)	14/28 (50.0)	Placebo	4.37	(1.30, 14.68)	<0.05*
MEASURE 1						
Secukinumab 150 mg	TNF alpha inhibitor-naïve (N=92)	61/92 (66.3)	Placebo	4.12	(2.21, 7.66)	<0.0001*
	TNF alpha inhibitor-inadequate response (N=33)	15/33 (45.5)	Placebo	3.75	(1.21,11.56)	<0.05*

Meta-analyses

Figure 1 Network of RCTs (figure 20 from CS)



4.9 The company did a network meta-analysis (NMA) to estimate the relative effectiveness of secukinumab 150 mg and relevant comparator therapies. The base case analysis was based on the timepoint of the primary endpoint for each comparator between weeks 12 and 16, and included both the MEASURE 2 and MEASURE 1 studies of secukinumab. The population considered was a mixed population of biologic naive and biologic experienced patients, though subgroup analysis was conducted in the biologic naive population only; no such analysis was possible in the biologic experienced population due to lack of evidence for comparator therapies in this population.

4.10 The primary endpoint in both MEASURE 1 and MEASURE 2 was assessed at 16 weeks as specified in the summary of product characteristics. This is longer than the majority of other studies in ankylosing spondylitis which typically report outcomes after 12 weeks.

The 12 week time point reflects clinical practice as this is when a decision is typically made to continue with the current treatment or switch to an alternative treatment. Sensitivity analysis on the timepoint of the assessment was also conducted. The company conducted the comparison using separate networks for clinically relevant outcomes of ASAS20 response, ASAS40 response, BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline depending upon whether or not outcome data was available Most included trials had primary endpoints between 12-16 weeks and these were the timepoints considered for inclusion in the analysis. The company acknowledged the potential sources of bias by not using the same time point for its primary end point, but it considered that the studies were of sufficient quality to use in the comparison without introducing bias. A fixed effect and random effect model were used, and the company chose the fixed effect model based on comparable deviance information (DIC).

4.11 The company's mixed treatment comparison showed higher efficacy for secukinumab 150 mg versus placebo across all outcomes analysed and for both the analysis in the whole population and in the biologic naïve population. The efficacy of secukinumab 150 mg compared with comparator treatments was comparable (results for ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are presented in table 5 below).

Table 6 Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (based on CS, table 53)

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	ASAS20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)

Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BN, biological naïve; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg

ERG comments

4.12 The selection of studies for inclusion in the MTC appears to be appropriate and the application of the MTC methodology seems to be correct. The quality assessment of the studies included in the MTC highlighted a potential imbalance between treatment arms at study onset in three studies.

4.13 Although comparisons at 16 weeks for MEASURE 1 and MEASURE 2 with trials reporting outcomes after 12 weeks should be viewed with a degree of scepticism the ERG noted that the performance of secukinumab in relation to placebo seems relatively stable between 12 and 16 weeks for the main.

4.14 Sensitivity analysis using only data reported after 12 weeks for all studies including MEASURE 1 and MEASURE 2 reported that reduced effectiveness of secukinumab relative to all other treatments compared to the base case for most outcomes. The difference in the effectiveness estimates between the base case and the sensitivity analysis is unlikely to be large enough to substantially alter the ICER given the low cost of secukinumab compared to other treatments for AS.

Adverse effects of treatment

4.15 MEASURE 2 and MEASURE 1 assessed overall safety and tolerability compared with placebo, determined by vital signs, clinical laboratory values and adverse events (AEs), as secondary objectives. The overall incidence of treatment emergent AEs up to Week 16 in MEASURE 2 was comparable between the secukinumab 150 mg group (65.3%) and the placebo group (63.5%). In MEASURE 1 there was a higher rate in the secukinumab 150 mg group than placebo (69.6% vs. 55.7%). In both trials, the most frequently reported AE was nasopharyngitis. There were no treatment related deaths.

4.16 The EPAR states that the profile of induction and placebo controlled study phases in AS patients resembles closely the adverse effects profile observed in the secukinumab psoriasis studies , where up to week 12, the most common adverse effects were nasopharyngitis (placebo 8.6% vs. secukinumab 11.9%), headache (5.2% vs. 6.0%), diarrhoea (1.4% vs. 3.3%), pruritus (2.6% vs 3.2%), URTI (0.7% vs. 2.82%), oropharyngeal pain (1.7% vs. 2.3%), and arthralgia (2.4% vs. 2.1%). The adverse effects leading to discontinuation that occurred more than once in the secukinumab group were Crohn's disease, dyspnoea, haemoglobin decreased, hepatic enzyme increased, pregnancy, and increased transaminase levels.

4.17 There were 3 confirmed major adverse cardiovascular events in the studies in people who had disease or pre-existing risk factors at baseline. No cases of MACE were reported in the placebo group. However, the EPAR states that, due to the differences in the average length of follow-up for patients in the secukinumab group was 10 times that of patients in the placebo group. The CHMP concluded that there was no evidence of an increased risk of major cardiovascular events relative to the expected rate in people with AS.

5 Cost-effectiveness evidence

Model structure

5.1 The company's model consisted of a short term, three month (12 weeks) decision tree model, representing the period covering the induction therapy for the biologic and placebo treatment arms (figure 4 below) connected to a long-term Markov model consisting of three states (maintenance treatment with the biologic received in the induction therapy period, post-induction conventional care or death; figure 5 below). At each cycle, patients in the maintenance therapy state can remain in that health state or move to conventional care or death. Patients in the conventional care can remain in that state or move to the death state. The model used

by the company is the same for the base case analyses, that is for the 2 subgroups: biologic naïve and biologic experienced.

5.2 In the company's base case analysis, a lifetime (58 years) horizon was chosen and a discount rate of 3.5% was used for costs and benefits. The model adopted the perspective of NHS/PSS and had a cycle length of three months.

Figure 2 Decision tree model structure for the first three months, during induction period (based on figure 32 of CS)

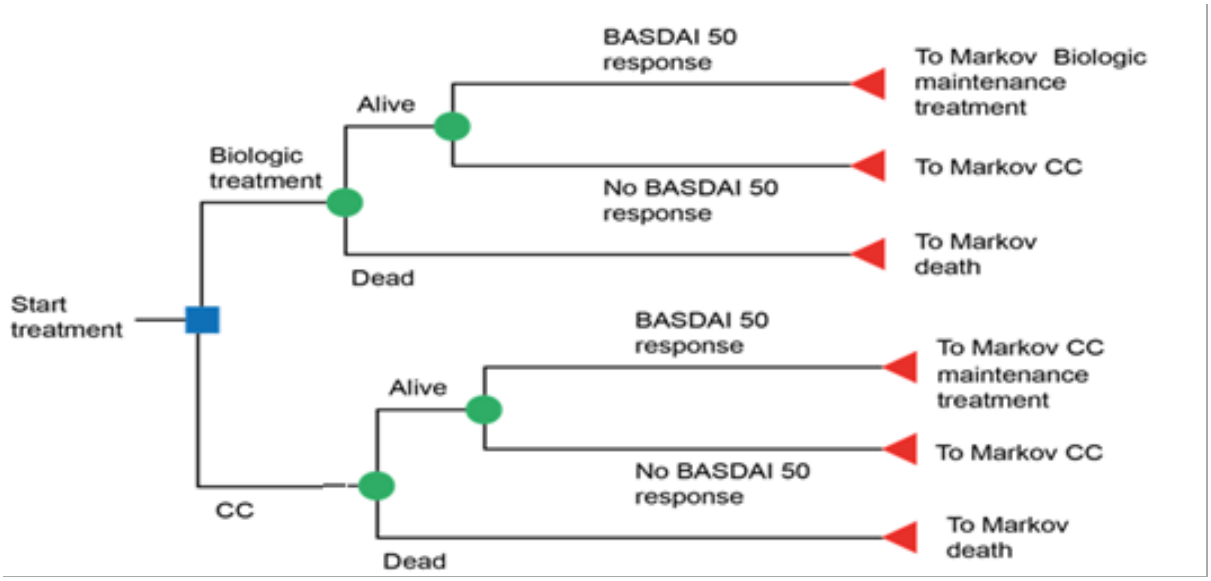
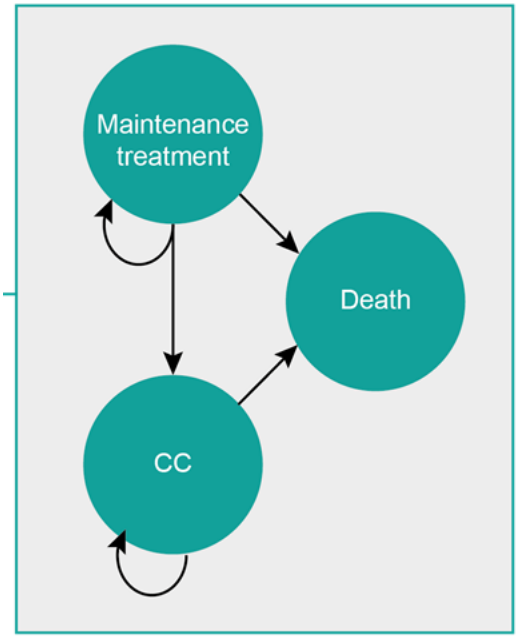


Figure 3 Markov structure of the post-induction period part of the model



ERG comments

5.3 The model structure is similar to the York model developed for NICE technology appraisal 383 (TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis) although there could be more suitable modelling types such as patient level simulation which could reflect patient heterogeneity and the dependence between baseline BASDAI/BASFI values, change from baseline values and response rates at the end of the induction period.

5.4 During clarification, the ERG identified errors in the company's economic model. The company provided a corrected and updated economic model and corrected results in its response to clarification. The results referred to in the premeeting briefing are based on the company's updated base case.

Model details

5.5 For the biologic naïve patients' subgroup, TNF-alpha inhibitors (adalimumab, etanercept, golimumab, infliximab and certolizumab pegol) were considered the comparators to secukinumab 150 mg. Baseline

characteristics were based on the population of the MEASURE 1 and 2 trials. The efficacy inputs for different administration schedules and doses of these therapies were assumed to be the same as those for certolizumab pegol 200 mg every two weeks and golimumab 50 mg as different administration doses and schedules did not lead to differences in efficacy between the TNF-alpha inhibitors. For etanercept, only the 50 mg weekly licensed dose was considered.

5.6 For the biologic experienced patients, conventional care was considered as the only comparator in the base case. The company made this assumption because that no valid data were available for the effectiveness of the comparator technologies in the biologic experienced population.

5.7 In the base case, the treatment effectiveness was translated to the model in terms of BASDAI 50 response, change from baseline BASDAI and BASFI scores and long term BASFI changes. All clinical treatment effectiveness parameters for the biologic naïve population were based on the pooled TNF alpha inhibitor naïve subpopulation data from MEASURE 2 and MEASURE 1 trials as well as the base case MTC (for relative effectiveness estimates of the biologics in the biologic naïve population).

Table 7 BASDAI 50 response applied in the model base case (CS, table 70)

Therapy	BASDAI 50 response for the modelled biologic naïve population	BASDAI 50 response for the modelled biologic experienced population
Secukinumab 150 mg	[redacted]	[redacted]
Adalimumab	[redacted]	
Etanercept	[redacted]	
Golimumab	[redacted]	
Infliximab	[redacted]	
Certolizumab pegol	[redacted]	
CC	[redacted]	[redacted]

5.8 In the original model, for the base case analysis, the response of a patient to the induction therapy was assessed according to that patient's BASDAI 50 status after week 12. A responding patient would continue to receive the corresponding treatment s/he had received during the induction period as a maintenance therapy after week 12. The treatment specific BASDAI 50 response rates used in the model were derived for biologic naïve and biologic experienced subgroups separately. For the biologic naïve population, in the base case, BASDAI 50 response rates for conventional care, etanercept, adalimumab, golimumab and secukinumab treatments were calculated from the log-odds (of achieving response) scores obtained from the fixed effects binomial model conducted as a part of the MTC analysis for the TNF alpha inhibitor naive population. BASDAI 50 response rate data was missing for certolizumab pegol and infliximab, therefore in the company's base case model, it is assumed that their log-odds scores would be equal to the average of the log odd scores of other three TNF alpha inhibitors: etanercept, adalimumab and golimumab. For the biologic experienced population, in the base case, only comparator to secukinumab was conventional care (placebo) and BASDAI 50 response rates used in the model were directly derived from the pooled data of the biologic experienced patients from MEASURE 1 and MEASURE 2 studies.

5.9 The company assumed that the initial mean changes in BASDAI and BASFI were maintained while patients remained on biologic treatment, and that those who remained on biologic treatment also experienced a slowed rate of BASFI progression. If treatment was stopped, the company assumed that the BASDAI score reverted to baseline on discontinuation. For BASFI, the company assumed that it rebounded to baseline in its base case; in a scenario analysis the company assumed BASFI rebounded to the natural history of the disease. Changes in BASDAI and BASFI scores over time were used to determine utilities and costs.

5.10 The company applied annual withdrawal probabilities for each of the treatments based on the MEASURE 1 and 2 studies for secukinumab and published sources for each of the anti-TNF alfa treatments. The model considered AS-related mortality by applying gender-specific relative risks of death to general population mortality rates sourced from Bakland et al (2011).

5.11 The only adverse events considered in the model were serious infections such as tuberculosis reactivation. The company based this on the results of a Cochrane systematic review which found that these were the only specific types of adverse events observed in patients receiving biologics compared to those receiving placebo. The company applied per-cycle probabilities of adverse events based on published sources for the biologics and the MEASURE 1 and 2 studies for secukinumab.

5.12 The company used a mapping algorithm to link BASDAI and BASFI scores to a generic utility measure, similar to those used in previous AS models. In the base case of the company's model, the algorithm was derived from MEASURE 1 and 2 where EQ-5D utility was derived from BASDAI and BASFI scores separately. The company then used a linear mixed model to fit EQ-5D utility score as a response variable with BASDAI and BASFI scores, age and sex as predictors.

ERG comments

5.13 The model structure was based on the York model, which was clinically validated and used in previous NICE TA383. EQ-5D data were available from the clinical studies to inform the utilities used in the model, thus providing good quality evidence for the cost effectiveness analysis. Extensive sensitivity and scenario analyses were performed, showing the robustness of the results.

5.14 The ERG commented that the company did not provide 12 week data as requested, but the company had previously provided details after 12 weeks for ASAS 20, ASAS 40, BASDAI 50, and BASDAI change from

baseline for MEASURE 2 only as appendices to the MEASURE 2 clinical study report. The ERG expressed concern that data from week 12 of MEASURE 1 was not presented, although it acknowledged that the treatment effect of secukinumab in relation to placebo seems relatively stable between 12 and 16 weeks for the main outcomes the ERG has been able to assess from MEASURE 2 (see Table 4 above).

5.15 The ERG noted that the way the response and BASDAI/BASFI change from baseline were modelled did not reflect clinical practice. In clinical practice, a patient whose BASDAI/BASFI baseline score is measured is given treatment. At the end of the 12 week induction period, there can be an improvement in that score which is compared to the baseline score and this determines whether a patient's disease has responded to treatment. In the model, however, the response rates and absolute change in baseline at the end of the induction period were derived independently from evidence synthesis. The company then calculated the baseline and change in baseline scores based on the response rates. This approach creates a situation where responders have lower and non-responders have higher baseline scores. This also creates the situation where it appears that people with more severe disease (higher baseline scores) do not benefit as much from treatment than people with less severe disease. The ERG explored the effect of this assumption in its analyses.

5.16 The ERG also noted that the evidence synthesis approach that was followed in the company's submission synthesised BASDAI, BASFI and BASDAI 50 separately. This approach may overlook the correlations between the treatment effectiveness parameters and may contribute to implausible outcomes such as having a BASDAI decline from the baseline higher than the baseline itself.

Company's base-case results and sensitivity analysis

5.17 In the company's base case which takes into account all the relevant patient access schemes, secukinumab is less expensive than all of its comparators in the biologic naive population, and therefore dominates or extendedly dominates all of its comparators. In the biologic experienced population, the ICER for secukinumab compared with conventional therapy is £2,245 per QALY gained.

Table 8 Summary base case results (based on company's response to clarification questions, table 82 and 83, page 115)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Biologic naïve population						
Secukinumab	£113,216	9.805				
Etanercept biosimilar	£114,234	8.759	£1,018	-1.046	dominated	dominated
Etanercept	£115,249	8.759	£2,033	-1.046	dominated	dominated
Certolizumab pegol – with PAS	£122,418	9.447	£9,202	-0.359	dominated	dominated
Adalimumab	£128,516	9.446	£15,300	-0.359	dominated	dominated
Golimumab	£129,919	9.830	£16,703	0.025	£674,914	£674,914
Infliximab biosimilar	£135,865	9.590	£22,649	-0.216	dominated	dominated
Infliximab	£139,439	9.590	£26,223	-0.216	dominated	dominated
Biologic experienced population						
Conventional care	£107,417	8.105	-	-	-	
Secukinumab	£109,164	8.883	£1,747	0.778	£2,245	

5.18 The company's probabilistic base case results were similar to its deterministic base case results: for the biologic naive population, secukinumab dominated all its comparators and for the biologic experienced population the ICER for secukinumab compared with conventional care was £1,815 per QALY gained.

Company scenarios

5.19 The company did 2 exploratory analyses for the biologic naïve population where a second line biologic treatment was allowed. In the first, the company assumed that a mixed treatment was administered in the second line, which is a basket of TNF-inhibitors, consisting of all but the TNF-inhibitor that was used first line. Secukinumab followed by treatment with a basket of biologics except secukinumab dominated (that is, was less costly and more effective than) its comparators with the exception of the comparison of golimumab versus secukinumab where the ICER for golimumab was £545,767 per QALY gained. In the second analysis, the company included conventional care as well as TNF-inhibitors. The results of this analysis are presented below.

Table 9: Summary results – exploratory comparison with TNF alpha inhibitors in biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,379	8.166			
Etanercept	£110,928	8.463	£3,549	0.297	Extendedly dominated by Secukinumab
Etanercept biosimilar	£111,571	8.463	£4,192	0.297	Extendedly dominated by Secukinumab
Secukinumab	£112,125	8.791	£4,746	0.625	£7,597
Certolizumab pegol – with PAS	£115,344	8.678	£7,965	0.512	Secukinumab dominates
Adalimumab	£119,876	8.680	£12,497	0.514	Secukinumab dominates
Golimumab	£121,114	8.796	£13,736	0.630	£1,614,375
Infliximab biosimilar	£125,438	8.778	£18,059	0.612	Golimumab dominates
Infliximab	£127,650	8.778	£20,271	0.612	Golimumab dominates

5.20 The company's deterministic sensitivity analysis showed that the ICER was most sensitive to the BASDAI 50 at 3 months for secukinumab, the annual rate of radiographic progression (rate of mSASSS change) for anti-TNF alphas and the discount rate for outcomes. None of the deterministic sensitivity analyses ICERs increase the ICER beyond £35,000 per QALY gained.

ERG comments

5.21 The various sensitivity analyses revealed that the ICER is relatively robust against changes in most input values although it was quite sensitive to changes in the treatment effectiveness estimates, i.e. by the MTC approach selected. The ERG noted that secukinumab remains below the threshold of £30,000 per QALY in all scenarios.

ERG exploratory analyses

5.22 The ERG defined an exploratory base case which took into account all relevant patient access schemes and included the following adjustments:

Biologic naïve population:

- Errors confirmed and corrected by the company
- Using MTC #3 for BASDAI 50 response rate and change from baseline estimates (MEASURE 1 and MEASURE 2, using week 12 data)
- Choice of MTC withdrawal rates from Corbett et al. 2014

Biologic experienced population:

- Errors confirmed and corrected by the company
- Using week 12 response data instead of week 16 from MEASURE 1 and MEASURE 2. (14/61 for secukinumab and 5/62 for conventional care)
- Choice of MTC withdrawal rates from Corbett et al 2014

5.23 In the ERG base case for the biologic naive population, only etanercept (both original and biosimilar versions) was dominated by secukinumab. All other anti TNF-alpha agents were associated with higher QALYs gained and higher costs, with ICERs compared to secukinumab ranging from £38,000 to £72,000 per QALY gained in the base case.

5.24 For the biologic experienced population, the ICER for secukinumab compared with conventional care was approximately £2,200 per QALY, almost the same as in the company's base case.

5.25 To assess parameter uncertainty, probabilistic sensitivity analyses were conducted. The ERG found some errors in the probabilistic sensitivity analysis (PSA) code of the original model, which was causing the average PSA results to differ from base case deterministic results substantially. The ERG has corrected these errors in the PSA code, which lead to more plausible average PSA results. Even though average PSA results are comparable to the deterministic base case results after corrections from the ERG, using PSA results may still be misleading, since the existing correlation between baseline BASDAI/BASFI, BASDAI/BASFI change from baseline and BASDAI 50 inputs were not reflected as they were sampled independently.

5.26 The ERG undertook 12 additional scenario analyses exploring the structural uncertainties in the company's base case (see section 5.3.4 of ERG report). The scenario analysis results show that etanercept (both original and biosimilar version) is dominated by secukinumab, that is associated with lower QALYs and higher costs versus secukinumab in all scenarios. Infliximab (both original and biosimilar version) is associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for infliximab versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained.

5.27 Adalimumab, golimumab and certolizumab pegol are mostly associated with higher QALYs and higher costs versus secukinumab: in all such

cases the ICER for comparator versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained. For the scenarios which different treatment effectiveness inputs were used (e.g. from different MTCs), secukinumab dominates these treatments, that is, secukinumab provides higher QALYs with lower costs.

Innovation

5.28 Justifications for considering secukinumab to be innovative:

- First in class IL-17A inhibitor which offers patients an alternative to other biologic treatments
- Treatment with secukinumab results in rapid, clinically significant and sustained improvements in signs and symptoms of AS.
- It is licensed for use with the SensoReady pen, which the company states has found high subject acceptability, particularly with patients with needle phobia. The pen also has the potential for reducing the risk of needle stick injuries.

6 Equality issues

6.1 No equality issues were raised during the scoping stage or in the submissions received for this appraisal.

7 Authors

Richard A. Diaz
Technical Lead(s)

Eleanor Donegan
Technical Adviser

with input from the Lead Team (Jane Adam, Anne McCune, Pamela Rees and Brian Shine).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003729/WC500199574.pdf

Appendix B: Supporting evidence

Outcome measures

Table 10. Disease assessment tools for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Disease component	Tool	Description
Physical function	BASFI	Patient assesses difficulty on a 10 point scale (1 is easy and 10 is impossible) for each of 10 items: • putting on socks or tights without help or aids • bending from the waist to pick up a pen from the floor without aid • reaching up to a high shelf without help or aids • getting up from an armless chair without hands or any other help • getting up off the floor without help from lying on back • standing unsupported for 10 minutes without discomfort • climbing 12–15 steps without using a handrail or walking aid • looking over shoulder without turning body • doing physically demanding activities • doing a full day's activities (at home or at work)
Disease activity	BASDAI	Patient describes the severity of 5 symptoms on a 10 point scale (1 is no problem and 10 is very severe): • fatigue • spinal pain • joint pain / swelling • areas of localised tenderness (also called enthesitis) • morning stiffness severity Duration of morning stiffness is also provided.
Disease activity	ASDAS	Calculated from BASDAI questions on spinal pain, peripheral arthritis, and duration of morning stiffness, patients global assessment of disease activity, and C-reactive protein (or erythrocyte sedimentation rate if C-reactive protein not available)
Disease activity Spinal mobility	BASMI	Clinician assessment of: lateral spine flexion, tragus to wall distance, lumbar side flexion (modified Schober), intermalleolar distance and cervical rotation

Disease component	Tool	Description
Structural damage	mSASSS	Clinician assessment of 24 sites on the lateral cervical and lumbar spine. Sites are scored on a 4 point scale (0 is normal; 1 is sclerosis, squaring or erosion; 2 is syndesmophyte; 3 is bony bridge). The total score ranges from 0 to 72.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology index; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score		

Table 11 Response criteria to evaluate treatments for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Response outcome	Response criteria
BASDAI 50	≥50% improvement in BASDAI score
ASAS 20	Improvement of ≥20% and ≥1 unit in at least 3 of the following 4 domains (each with a 10 point scale): • patient global disease assessment • spinal pain • function (BASFI score) • inflammation (using mean score from 2 questions of the BASDAI). No worsening of ≥20% and ≥1 unit in the 4th domain.
ASAS 40	Improvement of ≥40% and ≥2 units in at least 3 of the following 4 domains (each with a 10 point scale): • patient global disease assessment • spinal pain • function (BASFI score) • inflammation (using mean score from 2 questions of the BASDAI). No worsening at all in the 4th domain.
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of secukinumab within its marketing authorisation for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors.

Background

Ankylosing spondylitis belongs to a clinically heterogeneous group of inflammatory rheumatologic diseases which share common genetic, histological and clinical features (also including psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis and undifferentiated spondyloarthritis). People with these diseases often have the genetic marker human leukocyte antigen (HLA)-B27.

The clinical symptoms can vary from person to person, but usually develop slowly over several months or years. The main symptoms can include back pain, usually inflammatory in nature, arthritis (inflammation of the joints in other parts of the body), enthesitis (inflammation where a bone is joined to a tendon), and fatigue.

In the early stages of disease, radiographs of the sacroiliac joints and spine can be normal (so-called ‘non-radiographic’ disease) although sacroiliitis (inflammation of the sacroiliac joints) or inflammation of the spine may be visible on MRI before structural damage occurs. If definite radiographic sacroiliitis (abnormalities seen in plain x-rays of the sacroiliac joints, such as erosions, sclerosis, and partial or total ankylosis) is present, the disease can be classified as ankylosing spondylitis. Radiographic changes to the spine are not part of the classification criteria, but new bone formation (such as syndesmophytes and ankylosis of the vertebral column) is characteristic of ankylosing spondylitis.

Around 200,000 people have been diagnosed as having ankylosing spondylitis in the UK. The prevalence is thought to range from 0.05% to 0.23%, representing approximately 2,300 new diagnoses each year in England and Wales. Ankylosing spondylitis is about 3 times more common in men than in women.

Conventional therapy for ankylosing spondylitis includes anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and

physiotherapy. Tumour necrosis factor-alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy. NICE technology appraisals 143 and 233 recommend, adalimumab, etanercept and golimumab as treatment options for adults with severe active ankylosing spondylitis for people who have active spinal disease as assessed on two separate occasions 12 weeks apart and have tried at least two non-steroidal anti-inflammatory drugs but they have not worked, Infliximab is not recommended for people with ankylosing spondylitis. (NICE technology appraisal 143). Biosimilar versions of infliximab (Remsima, Celltrion Healthcare; Inflectra, Hospira) have been licensed for the same indications. A review of TA143 and TA233 is currently underway.

The technology

Secukinumab (Cosentyx, Novartis) is a human monoclonal antibody which specifically inhibits the interleukin 17A (IL-17A) receptor. Secukinumab is administered by subcutaneous injection.

Secukinumab does not have a marketing authorisation in the UK for ankylosing spondylitis. It has been studied in clinical trials compared with placebo in adults with radiologic evidence (X-ray) of moderate to severe ankylosing spondylitis whose disease had responded inadequately to or who are intolerant to non-steroidal anti-inflammatory drugs or TNF alpha inhibitors.

Intervention(s)	Secukinumab
Population(s)	Adults with active ankylosing spondylitis for whom non-steroidal anti-inflammatory drugs, or TNF-alpha inhibitors have been inadequately effective or not tolerated.
Comparators	• TNF-alpha inhibitors For people whose disease has responded inadequately to, or who are intolerant to TNF-alpha inhibitors: • Established clinical management without secukinumab

Outcomes	The outcome measures to be considered include: • disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	If evidence allows, the appraisal should consider people who have or have not had TNF-alpha inhibitors Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 233, August 2011, 'Golimumab for the treatment of ankylosing spondylitis'. Ongoing review with TA143. Technology Appraisal No. 143, May 2008, 'Adalimumab, etanercept and infliximab for ankylosing spondylitis'. Ongoing review with TA233.

	Technology appraisal in preparation, 'TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233)', Earliest anticipated date of publication TBC. Related NICE Pathways: NICE pathway on musculoskeletal conditions, available at: http://pathways.nice.org.uk/pathways/musculoskeletal-conditions
Related National Policy	Department of Health, NHS Outcomes Framework 2013-2014, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors [ID719]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Novartis (secukinumab) Patient/carer groups • Action on Pain • Arthritis Action • Arthritis & Musculoskeletal Alliance (ARMA) • Arthritis Care • BackCare • Black Health Agency • Disability Rights UK • Leonard Cheshire Disability • Muslim Council of Britain • National Ankylosing Spondylitis Society • Pain Concern • Pain Relief Foundation • Pain UK • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Surgeons of Great Britain and Ireland • British Geriatrics Society • British Health Professionals in Rheumatology • British Institute of Musculoskeletal Medicine • British Orthopaedic Association • British Pain Society • British Society for Rheumatology • British Society of Paediatric and Adolescent Rheumatology • British Society of Rehabilitation Medicine	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Abbvie (adalimumab) • Hospira (infliximab) • Merck, Sharp and Dohme (golimumab, infliximab) • Napp Pharmaceuticals / Celltrion Healthcare (infliximab) • Pfizer (etanercept) • UCB Pharma (certolizumab pegol) Relevant research groups • Arthritis Research UK • Bone Research Society • Chronic Pain Policy Coalition • Cochrane Musculoskeletal Group • MRC Clinical Trials Unit • National Institute for Health Research • Society for Back Pain Research •

Consultees	**Commentators (no right to submit or appeal)**
• Chartered Society of Physiotherapy • College of Occupational Therapists • Physiotherapy Pain Association • Primary Care Rheumatology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS England • NHS Fareham and Gosport CCG • NHS Guildford and Waverley CCG • Welsh Government	<u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Company evidence submission

February 2016

File name	Version	Contains confidential information	Date
		Yes/no	

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

List of Tables

Appendices

List of Figures

Appendices

List of Abbreviations and Definitions of Terms

ACR	American College of Rheumatology
ADA	Adalimumab
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of co-variance
AQoL	Assessment of Quality of Life
ARHP	Association of Rheumatology Health Professionals
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing Spondylitis Spine Magnetic Resonance Imaging Scoring System for Disease Activity
AST	Aspartate aminotransferase
AUC	Area under the curve
AxSPa	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BIM	Budget Impact Model
BIOSIS	Biosciences Information Services
BIW	Twice weekly
BMD	Bone mineral density
BMI	Body mass index
BSR	British Society for Rheumatology
BSRBR	British Society for Rheumatology Biologics Register
CADTH	Canadian Agency for Drug and Technologies in Health
CCL	Chemokine (C-C motif) ligand
CEAC	Cost-effectiveness acceptability curve
CfB	Change from baseline
CIL	Corner inflammatory lesion
CIOMS	Council for International Organizations of Medical Sciences
CMA	Cost-minimisation analysis
CONSORT	Consolidated Standards of Reporting Trials
COX	Cyclooxygenase
CRF	Case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost-utility analysis
CZP	Certolizumab pegol
DIC	Deviance information criterion
DKK	Dickkopf
DLQI	Dermatology Life Quality Index
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
DSU	Decision support unit
DXA	Dual energy X-ray absorptiometry

EAMS	Extra-articular manifestations
EASIC	European Ankylosing Spondylitis Infliximab Cohort
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5D questionnaire
ERG	Evidence review group
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European League against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FE	Fixed effects
GGT	Gamma-glutamyl transferase
GOL	Golimumab
HAQ	Health Assessment Questionnaire
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IgG	Immunoglobulin G
IL	Interleukin
INF	Infliximab
INLA	Integrated nested Laplacian approximation
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Healthcare
IR	Inadequate responder
IRT	Interactive Response Technology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IVR	Interactive Voice Response
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JAGs	Just another Gibbs sampler
JSEQ	Jenkins Sleep Evaluation Questionnaire
LDL	Low density lipoprotein
LEI	Leeds Enthesitis Index
LOCF	Last observation carried forward
LRiG	Liverpool Reviews and Implementation Group
LSM	Least squares mean
LYG	Life years gained
MACE	Major adverse cardiovascular event
MAR	Missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCMC	Markov chain Monte Carlo
MCS	Mental Component Summary

MeSH	Medical subject headings
MMRM	Mixed-effect model repeated measures
MNYC	Modified New York Criteria
MRI	Magnetic resonance imaging
MSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
MTA	Multiple Technology Appraisal
MTC	Mixed-treatment comparison
MTX	Methotrexate
NASS	National Ankylosing Spondylitis Society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NMA	Network meta-analysis
NMSC	Non melanoma skin cancer
NR	Not reported
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
PAS	Patient Access Scheme
PASI	Psoriasis Area Severity Index
PASS	Patient-acceptable symptom state
PBO	Placebo
PbR	Payment-by-results
PCS	Physical Component Summary
PDUS	Power Doppler ultrasound
PFS	Pre-filled syringe
PICOS	Patients, intervention, comparator, outcomes, study design
PPD	Purified protein derivative
PPRSU	Personal Social Services Research Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRN	Pro re nata or ‘as required’
PRO	Patient reported outcomes
PsA	Psoriatic arthritis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen and long-wave ultraviolet radiation
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality-adjusted life year
QOL	Quality of life
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red blood cell
RCT	Randomised controlled trial
RE	Random effects
SAIL	Secure anonymised information linkage
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SF-36	Short Form 36
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLR	Systematic literature review

SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
STA	Single Technology Appraisal
TBL	Total bilirubin
TG	Triglycerides
TNFα	Tumour necrosis factor alpha
TNT	Trinitrotoluene
TNFR	Tumour necrosis factor receptor
USpA	Undifferentiated spondyloarthropathy
VAS	Visual analogue score
VAT	Value added tax
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WinBUGS	Windows Bayesian inference Using Gibbs Sampling
WPAI-GH	Work Productivity and Activity Impairment Questionnaire – General Health

1. Executive summary

- Secukinumab is the first selective IL-17A inhibitor licensed for the treatment of ankylosing spondylitis (AS), a progressive and irreversible disease affecting people of working age, and therefore associated with both a significant clinical and economic burden.[1-4]
- Secukinumab is considered within this submission for the full licensed population, adult patients with active AS who have responded inadequately to conventional therapy, and evidence is presented for both the biologic naïve and biologic experienced populations.[5-8]
- The relevant comparators to secukinumab in the biologic naïve population are the currently licensed TNFα inhibitor therapies adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), and infliximab (Remicade®) including any licensed biosimilar products.[9-13] In the biologic experienced population, conventional care i.e. NSAIDs and physiotherapy, is considered as the comparator due to a lack of data on currently licensed alternative biologics.
- Two large Phase III randomised controlled trials, MEASURE 2 and MEASURE 1, provide an evidence base for the efficacy and safety of secukinumab across 590 patients with active AS; across both the MEASURE 2 and MEASURE 1 trials, secukinumab 150 mg demonstrated a rapid onset of efficacy. In both trials, this initial efficacy was then sustained up to 2 years across a number of outcomes, including the primary efficacy outcome Assessment of Spondyloarthritis International Society (ASAS) 20.[14-16]
- Overall, secukinumab was well tolerated, with a tolerability profile in AS consistent with that seen in other indications and no new or unexpected safety signals detected. Assessment of exposure-adjusted incidence rates over the entire treatment period in both MEASURE 2 and MEASURE 1 trials demonstrated adverse event rates similar to placebo.[15, 16] Adverse events of particular interest as detailed in the secukinumab Summary of Product Characteristics are broadly consistent with those highlighted for other biologic therapies in AS.[5, 9-13, 17, 18]
- A network meta-analysis (NMA) found secukinumab 150 mg to be associated with statistically meaningfully better results versus placebo across all outcomes assessed (ASAS20 response, ASAS40 response, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) 50 response, BASDAI change from baseline and BASFI (Bath Ankylosing Spondylitis Functional Index) change from baseline). The NMA demonstrated no statistically meaningful differences in these outcomes between secukinumab 150 mg and licensed biologic comparators across almost all comparisons. Results of sensitivity analyses were similar to those of the base case, supporting the robustness of the base case findings.
- A decision tree plus Markov economic model similar to the previously developed York model in AS was developed to evaluate the cost-effectiveness of secukinumab in both the biologic naïve population and the biologic experienced populations. In both biologic naïve and experienced populations, secukinumab 150 mg was seen to be cost-effective versus all comparators, with this finding supported by probabilistic sensitivity analysis and scenario analyses.
- The results of the base case analysis demonstrate that secukinumab represents a cost-effective treatment option compared to all TNFα inhibitor comparators in the biologic naïve population and compared to conventional care in the biologic experienced population.

- Exploratory analyses versus the TNFα inhibitors in the biologic experienced population also support the conclusion that secukinumab represents a cost-effective treatment option.
- Introduction of secukinumab 150 mg with the existing PAS is anticipated to be associated with significant cost savings to the NHS rising from [redacted] in Year 1 to [redacted] in Year 5.

Conclusions

- **Secukinumab 150 mg demonstrated superior clinical efficacy to placebo and a favourable safety profile in two phase III RCTs.**
- **In an NMA, secukinumab 150 mg demonstrated comparable efficacy compared to all TNFα inhibitor biologic therapies: adalimumab, etanercept, golimumab, certolizumab pegol and infliximab**
- **Economic analysis found secukinumab 150 mg to be cost effective versus all TNFα inhibitor comparator therapies in the biologic naïve population, and dominant in a number of cases. In the biologic experienced population, secukinumab was compared to conventional care and found to be cost-effective with an ICER of £2,245.**
- **Over the course of five years, the introduction of secukinumab150 mg is expected to result in substantial cost savings for the NHS of [redacted].**

1.1. Statement of decision problem

This submission addresses the clinical efficacy and safety, the comparative effectiveness and the cost-effectiveness of secukinumab 150 mg in adult patients with AS for whom conventional therapy, or TNFα inhibitors, have been inadequately effective or not tolerated. Consistent with the NICE MTA for TNFα inhibitors in the treatment of AS, conventional therapy is considered to include non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy.[19] The decision problem addressed is consistent with the final NICE scope for this appraisal, as outlined in Table 1.The decision problem

Table 1. Summary of the decision problem.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active ankylosing spondylitis for whom non-steroidal anti-inflammatory drugs, or TNFα inhibitors have been inadequately effective or not tolerated.	This submission considers the population of adult patients with active AS for whom conventional care has not been effective (biologic naïve population) or for whom conventional care and TNFα inhibitors have not been effective (biologic inadequate responder [IR] population)	NA
Intervention	Secukinumab	Secukinumab 150 mg	NA
Comparator(s)	TNFα inhibitors For people whose disease has responded inadequately to, or who are intolerant to TNFα inhibitors: • Established clinical management without secukinumab	Biologic naïve population: TNFα inhibitors Biologic experienced population: • Conventional care (base case): i.e. having discontinued their first biologic, patients move to conventional care • TNFα inhibitors and conventional care (exploratory analysis): i.e. having discontinued their first biologic, patients can move to either conventional care or a TNFα inhibitor	There are no formal guidelines on sequencing of biologics (i.e. administering a second biologic following discontinuation of an initial biologic therapy), and there is a lack of robust clinical data to support use of the TNFα inhibitors in the biologic experienced population, as acknowledged by the Assessment Group as part of the NICE MTA in AS and supported by the systematic literature review in Section 4.1.[19, 20] Therefore, for the

			biologic experienced population conventional care is considered to represent established clinical management. Comparison to biologics in this population is included as an exploratory analysis.
Outcomes	• Disease activity • Functional capacity • Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • Adverse effects of treatment • Health-related quality of life.	• Disease activity (ASAS20; ASAS40; BASDAI 50; BASDAI change from baseline; ASAS 5/6; ASAS partial remission; ASDAS-CRP [major improvement]; hsCRP change from baseline; patient's global assessment of disease activity) • Functional capacity (BASFI change from baseline; BASMI linear change from baseline) • Disease progression (mSASSS; MRI outcomes) • Pain (as captured by ASAS and BASDAI criteria) • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) (MASES) • Symptoms of extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis (captured under safety reporting) • Adverse effects of treatment • Health-related quality of life (ASQoL, EQ-5D, SF-36 PCS and MCS, FACIT-Fatigue) • Impairment in work and activities (WPAI-GH)	NA
Economic analysis	• Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being	• Cost effectiveness analysis results expressed as incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY • Lifetime time horizon: a lifetime time horizon is consistent with previous models in AS, including the recent MTA of biologic therapies.[19] AS is a chronic, progressive life-long condition for which there is no cure. The mean age of patients entering the model is 42.37; a 58-year time	NA

	compared. • NHS and Personal Social Services (PSS) perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	horizon is therefore appropriate to capture the lifetime of patients, as all patients within the model are assumed to die by age 101. This assumption is consistent with the fact that only 0.02% of the overall UK population survive to reach centenarian status.[21] • The perspective of the NHS and PSS is used • Patient access schemes for secukinumab, certolizumab pegol and golimumab 100 mg are taken into account	
Other considerations	If evidence allows, the appraisal should consider people who have or have not had TNFα inhibitors	The decision problem addressed by the economic analysis considers both the population of patients who are biologic naïve and the population of patients who are biologic experienced	NA

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; EQ-5D, EuroQol 5D questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; (hs)CRP, (high sensitivity) C-reactive protein; ICER, incremental cost-effectiveness ratio; IR, inadequate responder; SF-36 PCS, Short Form 36 Physical Component Summary; MCS, Mental Component Summary; MRI, magnetic resonance imaging; mSASSS, Modified Stoke Ankylosing Spondylitis Spinal Score; MTA, Multiple Technology Appraisal; NA, not applicable; NHS, National Health Service; PSS, Personal Social Services; QALY, quality-adjusted life year; TNFα, Tumour necrosis factor alpha; WPAI-GH, Work Productivity and Activity Impairment Questionnaire – General Health.

1.2. Description of the technology being appraised

A description of the technology being appraised (secukinumab [Cosentyx®]) is provided in Table 2 below.

Table 2: Summary of secukinumab.

UK approved name and brand name	Secukinumab (Cosentyx®)
Marketing authorisation/CE mark status	Secukinumab holds a marketing authorisation with the European Medicines Agency (EMA) and is therefore licensed for marketing in the European Union.
Indications and any restriction(s) as described in the summary of product characteristics	Secukinumab is indicated for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. Note: secukinumab also holds marketing authorisations in other indications that are not the subject of this submission (please see below).
Method of administration and dosage	Subcutaneous (s.c.) injection with a SensoReady Autoinjector pen or pre-filled syringe. Patients may self-inject following initial training and if a healthcare professional determines that this is appropriate. The recommended dose is 150 mg by s.c. injection with initial dosing at Baseline, Weeks 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4.

Abbreviations: EMA, European Medicines Agency; s.c., subcutaneous.
Source: EMA Cosentyx® Summary of Product Characteristics[5].

1.3. Summary of the clinical effectiveness analysis

The evidence base for the clinical efficacy of secukinumab 150 mg in the treatment of AS in adults with an inadequate response to conventional care consists of three randomised controlled trials (RCTs), as identified by a systematic literature review (SLR): MEASURE 2, MEASURE 1 and A2209. MEASURE 2 and MEASURE 1 are Phase III RCTs comprise the main evidence base for the clinical efficacy and safety of secukinumab presented in this submission; the A2209 trial is a small, Phase II proof-of-concept study that provides supportive data, including radiographic outcomes.[14, 22]

Together, MEASURE 2 and MEASURE 1 included 590 patients with moderate to severe AS and a previous history of active AS despite current or previous treatment with NSAIDs, DMARDs and/or TNFα inhibitor therapy.[14] Both trials included pre-specified sub-groups; firstly, patients naïve to prior TNFα inhibitor treatment and secondly patients who had either experienced an inadequate response to prior TNFα inhibitor treatment or who had been intolerant to at least one administration of a TNFα inhibitor agent: referred to hereafter as the TNFα inadequate responder (IR) population.[14]

Across both trials a large number of outcomes were investigated, spanning disease activity, physical function, radiographic outcomes, disease progression and social functioning. The primary outcome of both MEASURE 2 and MEASURE 1 was response to treatment according to the ASAS20 criteria at Week 16, a composite measure encompassing disease activity, pain, physical function and inflammation.[14] ASAS20 is a common primary efficacy outcome used in clinical trials and NICE technology appraisals for AS and is recommended by both the British Society for Rheumatology (BSR) and EMA AS guidelines. Secondary efficacy outcomes

assessed disease activity, physical function, disease progression, quality of life and social functioning. MEASURE 2 randomised patients to secukinumab 150 mg (licensed strength; results presented), secukinumab 75 mg (unlicensed strength; results not presented) or placebo, and administered secukinumab with a s.c. loading dose, followed by s.c. maintenance dosing. MEASURE 1 had a similar study design although employed an unlicensed intravenous (i.v.) loading dose. However, the MEASURE 1 study employed s.c. maintenance dosing, and included a trial arm in which the maintenance dose was secukinumab 150 mg, reflecting the licensed maintenance dosing (referred to hereafter as the secukinumab 150 mg arm for clarity of exposition).[14] MEASURE 1 is therefore also considered to be an important part of the evidence base for this submission, in particular providing evidence for radiographic outcomes.

Across both MEASURE 2 and MEASURE 1 trials, secukinumab 150 mg demonstrated a rapid onset of efficacy. This initial efficacy was seen to be sustained for up to two years across a number of outcomes.

- In both trials, patients in the secukinumab 150 mg arm experienced results superior to placebo for all primary and secondary endpoints (with the exception of ASAS partial remission in MEASURE 2) when assessed at Week 16. Responses with secukinumab were subsequently sustained up to Week 104.[14]
- Regarding the primary efficacy variable, ASAS20, the secukinumab 150 mg treatment arm demonstrated response rates of 61.1% and 60.8% at Week 16 in MEASURE 2 and MEASURE 1 respectively, which was significantly higher than the respective placebo control arms (28.4%, $p<0.0001$ and 28.7%, $p<0.0001$).[14] This significant benefit versus placebo was also seen when considering the more stringent measure of ASAS40 response. On both the ASAS20 and ASAS40 outcomes, secukinumab 150 mg demonstrated a rapid onset of efficacy (as early as Week 1) and sustained responses up to Week 104.[14, 23]
- Additional outcome measures including BASDAI change from baseline, BASDAI 50 response, and BASFI change from baseline confirmed the clinical efficacy of secukinumab across measures of disease activity and physical function. Secukinumab 150 mg demonstrated significant benefit versus placebo across these measures at Week 16, with a rapid onset of action in both cases.[14] For example, in terms of BASDAI change from baseline, efficacy was shown as early as Week 1 in both the MEASURE 2 and MEASURE 1 trials. As with ASAS20 and ASAS40, patients treated with secukinumab 150 mg were seen to maintain BASDAI response up to Week 104.[23]
- The AS quality of life measure, ASQoL, demonstrated that the secukinumab 150 mg arm experienced significant improvements in quality of life compared to placebo controls in both trials; a mean change of -4.00 vs. -1.37 in the placebo arm ($p=0.001$) in MEASURE 2 and -3.58 vs. -1.04 in the placebo arm, ($p<0.0001$) in MEASURE 1.[14] Furthermore, statistically significant improvements could be detected as early as Week 4 in MEASURE 1 and Week 8 in MEASURE 2 demonstrating the rapid onset of action.[24, 25]

In addition to evidence of a significant clinical benefit of secukinumab 150 mg in terms of disease activity and physical function, MEASURE 1 also provided results for radiographic outcomes, highlighting the efficacy of secukinumab on a further clinically relevant and important aspect of the disease. In MEASURE 1, no radiographic progression was observed in approximately 80% of patients randomised to secukinumab at baseline (mSASSS change ≤0).[26]

In addition to the results presented above in the whole trial populations, in both the MEASURE 2 and MEASURE 1 trials patients were stratified at randomisation according to TNFα naïve and TNFα-IR status. The efficacy of secukinumab was then assessed separately in each subgroup as part of pre-specified subgroup analyses. These analyses found secukinumab 150 mg to provide significant improvements versus placebo in the primary outcome of ASAS20 across both subgroups. Furthermore, secukinumab demonstrated efficacy across both subgroups in secondary efficacy measures within both trials.[27, 28]

Taken together, the results of MEASURE 2 and MEASURE 1 demonstrate the clinical efficacy of secukinumab treatment when assessed across a variety of outcome measures in two large trials. These trials also show that the clinical benefit demonstrated by secukinumab, regardless of TNFα inhibitor treatment status, is maintained for up to two years.

Comparative Effectiveness: Network Meta-analysis

Relevant clinical comparators to secukinumab in the treatment of active AS with an inadequate response to conventional therapy are the currently licensed biologic therapies etanercept, adalimumab, infliximab, golimumab and certolizumab pegol. All of these currently licensed biologics are TNFα inhibitors.[9-13] In contrast, secukinumab provides a novel mechanism of action by targeting IL-17A.

There is no head-to-head trial evidence directly comparing secukinumab 150 mg to the relevant biologic comparators and therefore relative effectiveness was estimated by conducting a Bayesian network meta-analysis (NMA). The NMA evaluated a number of outcomes considered most clinically relevant and important: ASAS20, ASAS40 and BASDAI 50 response as binomial outcomes, and BASDAI change from baseline and BASFI change from baseline as continuous outcomes. Amongst the trials included in the NMA, some studied mixed populations of biologic naïve and biologic experienced patients; whilst others included biologic naïve patients only. NMA was therefore conducted both in the “whole population”, including all trials, and in the biologic naïve population only. Insufficient data was available to conduct an NMA in the biologic-experienced only population; outside of the MEASURE 1 and MEASURE 2 studies there is no reported data for TNFα inhibitors in the biologic-experienced population.

The base case NMA was conducted at the Week 12-16 timepoint (taking each respective trial’s primary endpoint) for all comparators and conducted in both the “whole population” and the biologic naïve population only. Additional sensitivity analyses were performed considering results from Week 12 only, to reflect the timepoint of response assessment in clinical practice, and also exploring the exclusion of MEASURE 1 from the analysis. The MEASURE 1 study is considered relevant to the decision problem as it collected relevant outcomes, in a relevant population, and patients received maintenance dosing at the licensed 150 mg strength. However, as this study used an intravenous loading regimen as opposed to the licensed subcutaneous loading regimen, it was considered appropriate to explore its exclusion from the analysis in a sensitivity analysis. Both fixed effects (FE) and random effects (RE) NMAs were considered. The assessment of model fit by Deviance Information Criterion (DIC) indicated no strong preference for either the FE or RE models in any of the analyses where both model types were possible. Furthermore, for some analyses in the biologic naïve population RE models were not mathematically feasible to conduct. Given this, combined with the low number of trials reporting in each arm and the fact that no strong evidence of heterogeneity was observed in trial baseline characteristics, FE models were chosen.

The base case NMA identified statistically meaningfully higher efficacy of secukinumab 150 mg versus placebo across all outcomes analysed and for both the whole population and biologic naïve population, demonstrating that secukinumab 150 mg can improve the proportion of patients achieving ASAS20 response, ASAS40 response and 50% improvement in BASDAI, as well as mean BASDAI and BASFI changes from baseline. The base case NMA also demonstrated no statistically meaningful differences between secukinumab 150 mg and any biologic comparator in either population and across all outcomes, with the sole exception of the comparison to infliximab 5 mg/kg for the BASDAI change from baseline outcome. In interpreting the comparison to infliximab it should be noted that the infliximab trial used observed data, compared to the more conservative non-responder imputation (NRI) reported for the secukinumab studies. Additionally, in the BASDAI change from baseline analysis, amongst others, the data inputs to the NMA for infliximab were from a single study (Giardina *et al.*) that compared infliximab to etanercept (rather than placebo) in an open-label study design.[29] This may therefore limit the reliability of the comparison between secukinumab and infliximab. Sensitivity analyses reinforced statistically meaningful results for secukinumab 150 mg versus placebo and no statistically meaningful differences versus biologic comparators across almost all analyses.

Overall, the results of the NMA suggest that secukinumab 150 mg is of comparable efficacy to other biologic comparators considered across a range of the most clinically relevant outcomes.

Safety

The overall safety and tolerability of secukinumab 150 mg were assessed as secondary outcomes in both MEASURE 2 and MEASURE 1 and neither trial showed any new or unexpected signs with regards to the safety profile of secukinumab versus the large body of safety evidence for secukinumab in other autoimmune indications, notably psoriasis. The overall incidence of treatment emergent adverse events (AEs) up to Week 16 in MEASURE 2 was comparable between the secukinumab 150 mg group (65.3%) and the placebo group (63.5%). In MEASURE 1 there was a higher rate of treatment emergent AEs in the secukinumab 150 mg group compared with placebo (69.6% vs. 55.7%). In both trials, the majority of adverse events were mild or moderate in severity. The most frequently reported AE in both trials was nasopharyngitis.

A total of 3 deaths were reported across the MEASURE 2 and MEASURE 1 trials; two in patients receiving secukinumab and one in a patient receiving placebo. None of the deaths were considered by the investigator to be related to study treatment.

1.4. Summary of the cost-effectiveness analysis

Population and comparators

A decision analytic model was developed to evaluate the cost-effectiveness of secukinumab 150 mg in the population with active AS, as defined by the Modified New York criteria, and for whom conventional therapy (i.e. NSAIDs alongside physiotherapy), or prior biologic therapy, has been inadequately effective or not tolerated. The model evaluated two distinct sub-populations within this:

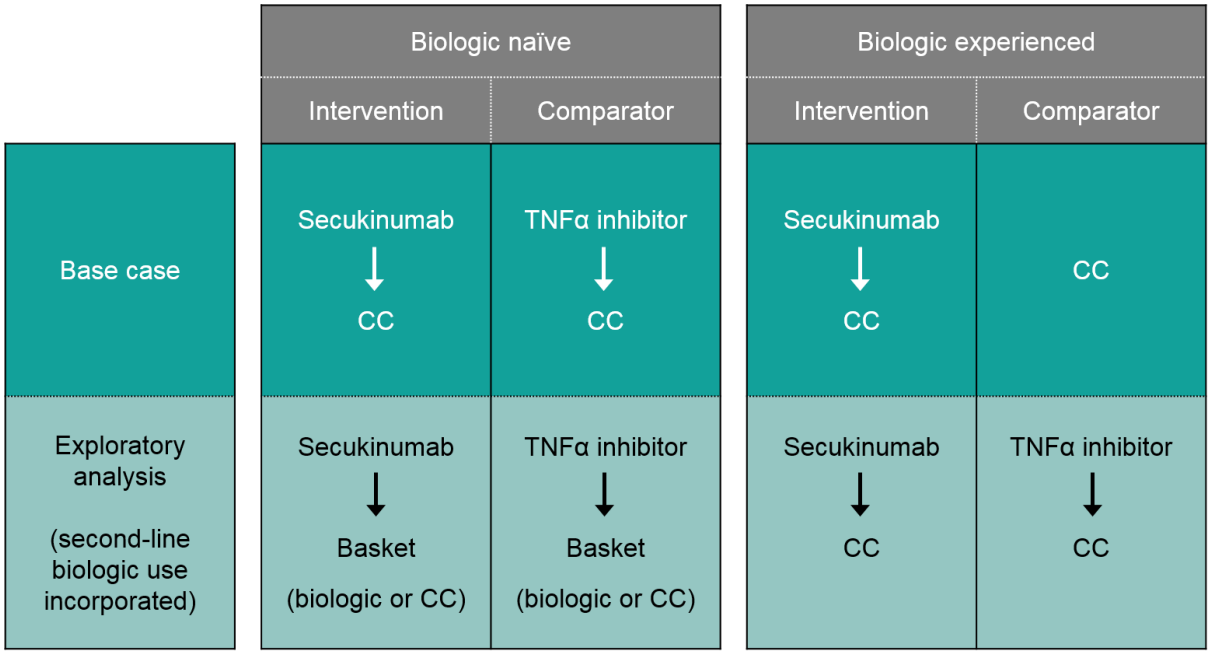
- The population of patients for whom conventional therapy has been inadequately effective or not tolerated but in whom biologic treatment has not yet been administered (biologic naïve population).

- The population of patients who have previously received one or more biologic therapies (biologic experienced patients).

In the biologic naïve population, the relevant comparators consisted of TNFα inhibitor therapies; all TNFα inhibitor therapies included in the recent MTA of such therapies in AS were included.[19] For this population, evidence for the relative effectiveness of secukinumab came from the results of the NMA in biologic naïve patients. In the biologic experienced population the only treatment with robust placebo-controlled data is secukinumab. As such, the only reliable comparison possible in this population was against conventional care. For this comparison relative effectiveness data from the subgroup of TNFα-inadequate responders in the MEASURE 2 and MEASURE 1 studies was employed.

Although there are no guidelines or recommendations on specific sequencing of biologic therapies and, as noted above, there is a lack of robust data for comparators in the biologic experienced population, two exploratory analyses were conducted assuming the same relative efficacy reduction for the TNFα inhibitors when used second line as was observed in the MEASURE 1 and MEASURE 2 studies. Amongst the biologic naïve population this enabled modelling of two lines of biologic therapy before patients revert to conventional care. For the biologic naïve population, the assumption enabled an exploratory comparison versus TNFα inhibitors as well as conventional care. Figure 1 summarises how the comparators and treatment sequencing differed between the base case analysis (no biologic sequencing) and the exploratory analysis (with biologic sequencing).

Figure 1. Summary of comparators and therapy sequencing in the base case and exploratory analyses



Abbreviations: CC, conventional care; TNFα, Tumour necrosis factor alpha.
Arrows indicate movement from active treatment to CC (or basket) after discontinuation of first line treatment in the model.

Model structure

Overall, the model structure closely reflected that of the York model in AS developed as part of the MTA of TNFα inhibitors in AS.[19] The model consisted of a decision tree model for the first 3 months of treatment, with response to biologic therapy assessed as proportion of patients

achieving a BASDAI 50 response at 12 weeks. Following this, patients entered a Markov model consisting of health states for maintenance biologic therapy, conventional care or death, for a lifetime (58 year) time horizon. Over this period the model tracked short-term changes in BASDAI and BASFI, as measures of disease activity and physical function. In addition, long-term changes in BASFI were modelled as independently related to disease activity (BASDAI) and the rate of radiographic progression (mSASSS). Patients could also experience adverse events of tuberculosis reactivation or other serious infection and risk of mortality was modelled via a gender-specific relative risk of AS-related mortality as reported in the literature. As per the NICE reference case, the outputs of the model were costs and QALYs, both discounted at 3.5%, and the perspective of the model was that of the NHS and PSS.

Utilities and costs

Benefits within the model were measured as quality-adjusted life years (QALYs), taking account of both length of life and utility of patients over the course of that life. Utility within the model was informed by a linear mapping algorithm that linked utility to covariates of BASDAI, BASFI, gender and age. The parameters for this linear model were based on EQ-5D data collected in the MEASURE 2 and MEASURE 1 trials in the base case; other published linear algorithms were explored in scenario analyses. The EQ-5D data set was valued with a UK tariff and is therefore appropriate to the NICE reference case (please see Section 5.4.1).

Costs included in the model were drug acquisition and administration costs, costs for medical visits and laboratory tests, and adverse event costs (tuberculosis and other serious infection). The secukinumab acquisition costs took account of the Patient Access Scheme (PAS) available for secukinumab, which represents a simple discount that provides secukinumab 150 mg at [redacted] per pack of two 150 mg SensoReady® pens/ pre-filled syringes. In addition, health state costs were modelled as disease management costs based on an exponential BASFI regression model, consistent with the York model in AS. Where possible, costs were informed by NHS Reference Costs 2014-15 and the PSSRU 2015. A cost year of 2015 was used for the analysis.

Results of the health economic evaluation

The base case results of the economic evaluation for the biologic naïve and biologic experienced population are presented as a fully incremental analysis in Table 3 and Table 4, respectively. In the fully incremental analysis in the biologic naïve population, all comparator biologics to secukinumab were either dominated, extendedly dominated or associated with ICERs versus secukinumab that were considerably above the conventional NICE threshold of £20,000-£30,000 per QALY. Therefore, secukinumab was found to be cost-effective versus all comparators. In the biologic experienced population, the incremental cost-effectiveness ratio (ICER) for secukinumab 150 mg versus conventional care was calculated as £2,245, also demonstrating cost-effectiveness of secukinumab in the biologic experienced population.

Table 3: Summary base case results – biologic naïve population.

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£114,847	9.328	-	-	-	-
Etanercept	£115,779	8.566	£932	-0.762	Dominated	Dominated
Certolizumab	£124,557	9.111	£9,710	-0.216	Dominated	Extendedly

pegol						dominated
Adalimumab	£127,919	9.153	£13,072	-0.175	Dominated	Extendedly dominated
Golimumab	£131,157	9.369	£16,310	0.041	£397,064	Extendedly dominated
Infliximab biosimilar	£136,095	9.420	£21,248	0.092	£230,769	£96,824
Infliximab	£139,598	9.420	£24,751	0.092	£268,811	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 4: Summary base case results – biologic experienced population.

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,417	8.105	-	-	-
Secukinumab	£109,164	8.883	£1,747	0.778	£2,245

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Summary of budget impact

Introduction of secukinumab 150 mg with the offered PAS is anticipated to be associated with a significant negative budget impact resulting in a cost saving each year rising from [redacted] in Year 1 to [redacted] in Year 5.

2. The technology

2.1. Description of the technology

Brand name: Cosentyx®

UK approved name: Secukinumab

Therapeutic class: Monoclonal antibody selective for interleukin-17A

Mechanism of action:

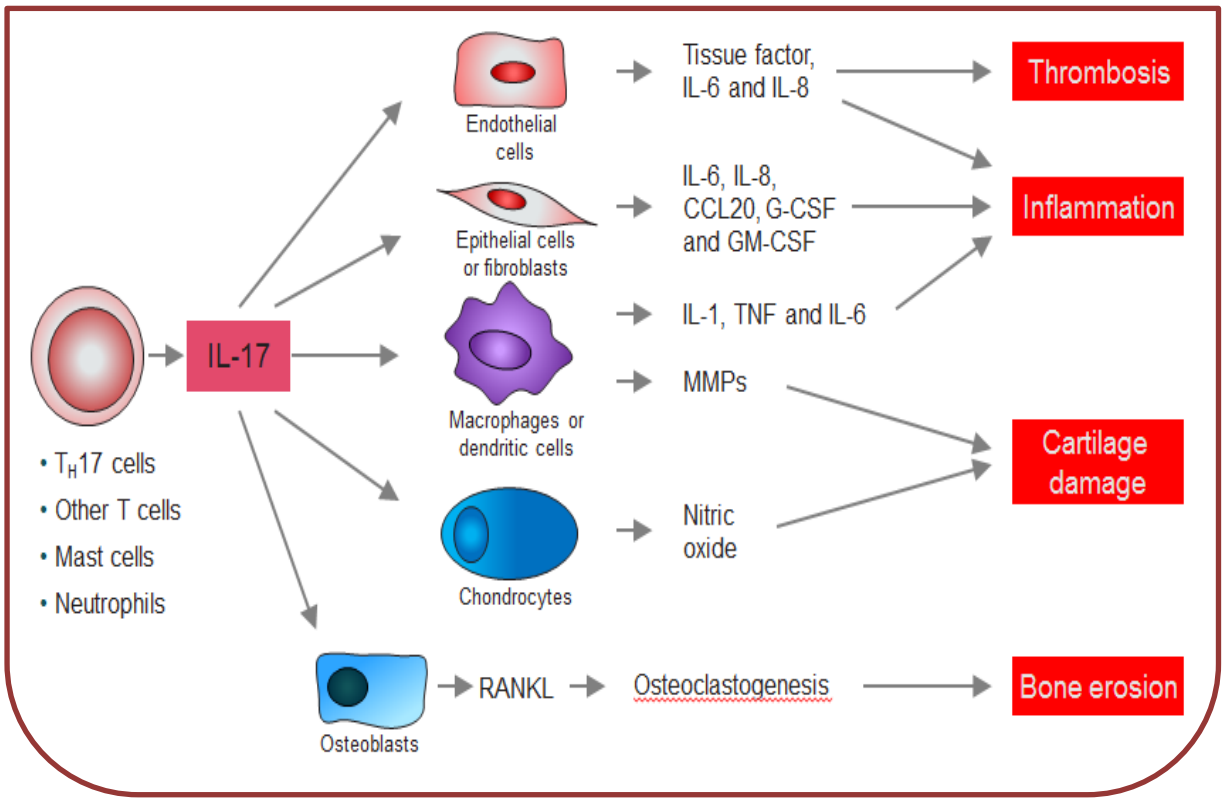
Secukinumab offers a new, alternative mode of action in the treatment of AS. Secukinumab is a first-in-class, recombinant, high-affinity, fully human monoclonal anti-human antibody of the IgG1/kappa isotype. Secukinumab selectively targets the pro-inflammatory cytokine interleukin-17A (IL-17A), an important mediator in the pathophysiology of AS and other autoimmune diseases, and is the first selective IL-17A inhibitor licensed for the treatment of active AS.[5-8]

Spondyloarthritic diseases, also known as spondyloarthropathies, represent a group of immune-mediated inflammatory diseases that exhibit overlapping clinical, genetic and pathogenic features.[30, 31] IL-17A has been implicated in processes that occur in the early phases of spondyloarthritic diseases, including tissue inflammation and enthesitis.[30] In addition, IL-17A-producing T helper (Th17) cells have been detected at a significantly higher frequency in AS patients compared with healthy control subjects.[5, 32]

By inhibiting the interaction between IL-17A and its receptor, secukinumab inhibits the production and release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A mediated contributions to autoimmune and chronic inflammatory disease.[5] Preclinical studies have demonstrated that blockade of IL-17A ligand-receptor interactions reduces levels of biomarkers that are associated with changes in bone mineral density and radiographic changes in patients with AS, which are in turn representative of changes in disease activity.[33] Ultimately, inhibition of IL-17A with secukinumab is believed to reduce bone erosion and joint inflammation, hence leading to an improvement of symptoms and physical abilities in patients with active AS.

Targeting IL-17A represents a novel mechanism of action that is more specific and selective than the inhibition of TNFα – the target of many other therapies currently licensed for AS.[6, 7, 9-13, 34] The mode of action of secukinumab is summarised in Figure 2.

Figure 2. Secukinumab mechanism of action and selective targeting through inhibition of IL-



17A

Abbreviations: CCL, chemokine (C-C motif) ligand; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; MMPs, matrix metalloproteinases; RANKL, Receptor activator of nuclear factor kappa-B ligand; Th, helper T cells; TNF, tumour necrosis factor.
Source: Adapted from Miossec *et al.* 2012.[35]

2.2. Marketing authorisation/CE marking and health technology assessment

European marketing authorisation

Secukinumab (Cosentyx®) received a marketing authorisation from the EMA for the treatment of active AS in adult patients who have responded inadequately to conventional therapy on 23rd November 2015.[5]

A link to the Summary of Product Characteristics (SmPC) can be found in Appendix A and the European Public Assessment Report (EPAR) in Appendix B.

It should be noted that secukinumab has also been licensed for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy since 15th January 2015. Secukinumab also received a marketing authorisation, alone or in combination with methotrexate (MTX), for the treatment of active psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. This marketing authorisation was granted at the same time as the marketing authorisation in AS.

There are no special conditions, exceptional circumstances or conditions attached to the marketing authorisation for secukinumab.

Anticipated launch date (UK)

Secukinumab is already available in the UK for the treatment of plaque psoriasis.

Non-EU regulatory approval

Secukinumab was approved for use in AS in the United States in January 2016. Secukinumab has also be approved for use in AS in the Philippines, Ecuador and Bangladesh and is currently pending approval in Switzerland, Canada, Australia and a number of countries across South America and Asia.

Health technology assessment (UK)

Secukinumab was submitted for assessment by the Scottish Medicines Consortium (SMC) in the AS indication in January 2016.

Secukinumab has also been recommended by NICE for the treatment of adults with plaque psoriasis, receiving a positive recommendation for use on the NHS in England and Wales in July 2015.[36] This recommendation was contingent upon the provision of the PAS agreed with the Department of Health. This same PAS, which represents a simple discount, is applied in this submission for the AS indication. Secukinumab was also issued with positive advice by the SMC in June 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Additionally, the process for appraisal by NICE of secukinumab in another spondyloarthropathy, psoriatic arthritis has been initiated. This will take the form of a multiple technology appraisal commencing in April 2016. Secukinumab was submitted to the SMC in this indication in February 2016.

2.3. Administration and costs of the technology

Details of the treatment regimen, including the method of administration, healthcare resource use and costs associated with the technology are provided in Table 5.

Table 5: Unit costs of technology being appraised

Pharmaceutical formulation	Cosentyx® 150 mg solution for injection in pre-filled SensoReady® pen x 2 Cosentyx® 150 mg solution for injection in pre-filled syringe x 2
Acquisition cost (excluding VAT) *	**List price** Cosentyx® 150 mg solution for injection pre-filled SensoReady® pen x 2: £1,218.78 Cosentyx® 150 mg solution for injection pre-filled syringe x 2: £1,218.78 **Patient Access Scheme (PAS)** Cosentyx® 150 mg solution for injection pre-filled SensoReady® pen x 2: [redacted] Cosentyx® 150 mg solution for injection pre filled syringe x 2: [redacted]
Method of administration	Cosentyx® is administered by s.c. injection
Doses	The recommended dose of secukinumab in AS is 150 mg
Dosing frequency	Initial dosing at Baseline, Weeks 1, 2 and 3 followed by monthly maintenance dosing starting at Week 4
Average length of a course of treatment	Treatment continues for as long as patients are responding to treatment.

Average cost of a course of treatment	Annual maintenance treatment at 150 mg: [redacted] and £7,312.68 (list price). Estimate is based on 12 doses administered in a year and a cost per dose of [redacted] and £609.39 (list price).
Anticipated average interval between courses of treatments	NA – Continuous treatment
Anticipated number of repeat courses of treatments	NA – Continuous treatment
Dose adjustments	None
Anticipated care setting	Secukinumab treatment should be initiated and supervised by an experienced physician/rheumatologist. It is anticipated that secukinumab maintenance treatment would be taken in the home care setting, with self-administration of monthly maintenance injections.

*Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.
Abbreviations: NA, not applicable; PAS, patient access scheme; s.c., subcutaneous; VAT, value-added tax.

2.4. Changes in service provision and management

Changes to service provision and management are not expected.

This submission relates to use of secukinumab for adult patients with active AS who have responded inadequately to conventional therapy. Conventional therapy for AS and non-radiographic axial spondyloarthritis includes non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy.[37-39] This positioning is equivalent to that considered for the other biologics licensed for the treatment of AS in the recent NICE MTA of these therapies.[19] As with the other licensed biologics, the main resource use with secukinumab is associated with treatment, administration and monitoring. Non-drug costs are in line with other subcutaneously administered comparators: initial training on self-injection for most patients and monitoring costs are similar across comparators—see Section 5.5.4 for further details. The homecare service for patients is funded by Novartis and is included in the price of the drug, as is the case for the biologic comparators.

No additional monitoring of patients receiving secukinumab is required over and above the current standard of care. Secukinumab requires less frequent administration than some of the comparator TNFα inhibitors, being administered only once every month via s.c. injection following the initial induction period, rather than weekly or two-weekly as with etanercept or adalimumab, respectively. As a s.c. injection, compared to infliximab secukinumab also avoids the need for i.v. administration, thereby reducing the administration costs compared to this therapy. Secukinumab may therefore have a positive impact in terms of reducing the patient burden with regards to frequency of injections, or requirements for i.v. administration, compared to some comparators.

No additional tests or investigations are required, either prior to or during secukinumab treatment, compared to other available biologic therapies for AS. A current requirement of clinical practice with TNFα inhibitor therapies is evaluation for tuberculosis infection prior to initiation of therapy. There is no requirement in the SmPC of secukinumab that patients should be evaluated

for tuberculosis infection prior to initiation of secukinumab therapy, which therefore presents a potential source of reduced resource burden with secukinumab. However, it is anticipated that clinicians will continue to test for tuberculosis infection prior to treating patients with secukinumab as this is a routine test for all existing biologics.

2.5. Innovation

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and has been linked to the pathogenesis of multiple autoimmune diseases.[5, 40] Increasing clinical and laboratory evidence has linked IL-17A to the pathogenesis of AS and other forms of spondyloarthritis.[22, 41-50] For example, the frequency of IL-17A-producing cells has been shown to be significantly higher in the subchondral bone marrow of facet joints from patients with AS.[5] Secukinumab is a first in class, selective IL-17A inhibitor that offers patients an alternative and more targeted mode of action to other biologics currently recommended for the treatment of AS. This more targeted mode of action delivers rapid, clinically significant and sustained improvements in signs and symptoms of AS, with associated improvements in physical function and quality of life (see Section 4.7).[33, 37]

There is a rapid onset of efficacy with secukinumab, with a significant difference from placebo in efficacy outcomes such as ASAS20 response as early as Week 1.[33, 37] This early response gives patients the benefit of symptom relief very early in their course of secukinumab treatment, giving reassurance that the treatment is working, which may motivate patients to continue treatment.

Importantly, data support that the efficacy of secukinumab seen at Week 1 is then sustained, with response rates continuing to increase before being maintained.[39, 51] In the MEASURE 2 study, the high rates of ASAS20 response observed with secukinumab 150 mg compared to placebo were sustained at all timepoints from Week 2 to Week 16, and the same was true of the ASAS40 outcome (see Section 4.7). Similarly, in the MEASURE 1 study higher and sustained ASAS20 and ASAS40 responses were observed in the study arm treated with secukinumab 150 mg following i.v. loading doses than the study arm treated with placebo, from Week 1 through to Week 24.

Furthermore, analysis up to 104 weeks in the MEASURE 2 and MEASURE 1 studies found the rates of ASAS20 and ASAS40 response observed for the secukinumab 150 mg groups at the Week 16 primary endpoint in these trials were sustained through to Week 104 (see Section 4.7).

In the NICE appraisal of secukinumab in the treatment of psoriasis, the Committee similarly recognised the innovative value of secukinumab in providing a different mechanism of action to the other biological treatments recommended by NICE. The Committee also noted that severe psoriasis can be associated with a stigma that might mean it is a condition meriting extra weight in its evaluation. Stigmatisation has also been reported as a psychosocial consequence of AS and so may also be a relevant consideration in this appraisal.[52]

Finally, secukinumab is licensed for use with a SensoReady® pen, which has received positive feedback from both healthcare professionals and patients; results from the JUNCTURE trial, in which the administration of secukinumab by autoinjector pen in patients with moderate to severe plaque psoriasis was assessed, found high subject acceptability of the autoinjector pen throughout 12 weeks.[53] This autoinjector has the potential to be more acceptable for patients with needle phobia, as well as a potential for a reduced risk of needle stick injuries (see Equity considerations in Section 3.6).

3. Health condition and position of the technology in the treatment pathway

Summary

AS is a progressive arthritic disease that afflicts patients of working age, causing pain and severe physical impairments that negatively impact on quality of life and social functioning.

Prevalence and symptoms

- AS is a seronegative spondyloarthropathy that is principally characterised by inflammation of the sacroiliac joint at the base of the spine (sacroiliitis).[54]
- The prevalence of AS in Europe is estimated to be 23.8 cases per 10,000.[51]
- Age of onset is typically between the ages of 17–35 but symptoms often present years before a formal diagnosis - which requires radiographic evidence of sacroiliitis.[55-57]
- Clinical features associated with AS include inflammatory back pain, inflammation of spinal joints (sacroiliitis and enthesitis), peripheral arthritis and restricted spinal flexibility as a result of joint fusion (ankylosis) The large peripheral joints (hips, shoulders and knees) may also be involved, and the eyes and cardiovascular system can also be affected.[58-60]
- Disease damage is progressive and irreversible; with spinal mobility impairment being more influenced by spinal inflammation in early disease, and structural damage in later disease.[4]

Burden of disease

- The clinical, humanistic and economic burden of AS increases with disease progression.[61-63]
- Pain and restricted mobility are highly debilitating for patients and affect their ability to carry out routine tasks, with considerable impact on patient-reported quality of life.[64-67]
- Given the age of onset, AS is also associated with a considerable economic burden and has negative impact on employment status.[1-3]
- AS is a life-long condition that utilises NHS resources at all disease stages, from diagnosis to treatment and rehabilitation.[63]

Treatment pathway

- Current treatments for patients with active AS with an inadequate response to conventional therapy are the licensed biologic therapies etanercept, adalimumab, infliximab, golimumab and certolizumab pegol, all of which are TNFα inhibitors.[37, 38] There is uncertainty in clinical practice regarding the efficacy of biologic therapies in patients with an inadequate response to prior biologic therapy, and the specific sequencing of biologic treatments.
- **Secukinumab represents the first alternative biologic therapy to the TNFα inhibitors for treating ankylosing spondylitis, offering a novel mechanism of action and providing patients, clinicians and the NHS with an important new treatment option for both the biologic naïve and biologic experienced populations of patients with active AS.**

AS is a progressive, irreversible arthritic disease belonging to a group of conditions known as seronegative spondyloarthropathies.[68] The disease is characterised by inflammation of the sacroiliac joint at the base of the spine (sacroiliitis).[54] The back pain and stiffness that results from chronic inflammation along the spine places a considerable burden on patients with AS in terms of physical impairment, pain, quality of life and social functioning.[69] No validated molecular biomarkers have been identified as being associated with AS diagnosis or disease activity, but there is evidence to suggest a key role for pro-inflammatory cytokines such as IL-17A in AS pathophysiology.[70, 71]

3.1. Prevalence

The exact prevalence of AS in the UK is not known. In Europe the prevalence is estimated to be 23.8 cases per 10,000; and according to 2006 data from the Department of Health an estimated 200,000 cases of AS have been diagnosed in the UK.[51, 72] An alternative estimate from the NICE Biologics Commissioning Guide (2012) estimates 70,000 cases of AS in England, based on AS prevalence estimates provided by the BSR guidelines in 2004 – from 500 to 1,000 cases in a community of 500,000 adults.[25, 39] The Commissioning Guide estimates that there are approximately 20,000 patients with AS in England eligible for treatment with biologic treatment.[39] However, it is believed that these figures may underestimate the real prevalence of AS, in part due to a mean diagnostic delay of 8.57 years.[73, 74] In order to reduce this delay, a UK best practice model for diagnosis and treatment of axial spondyloarthritis has been developed, using a care pathway in conjunction with an educational campaign. This approach has shown promising results in 222 patients with early inflammatory back pain, with a mean time between the onset of back pain and diagnosis of 5.7 years.[75]

In 90–95% of cases, patients with AS are diagnosed before the age of 45, with a typical age of onset of between 17–35 years of age.[19, 55, 57] Patients with AS are of working age and essential contributors to the workforce and the economy. AS is three times more common in men than in women, and men are also more likely to have more severe disease.[76]

3.2. Signs and symptoms

AS is formally diagnosed *via* fulfilment of the modified New York criteria which comprises both clinical and radiologic criteria, as follows:

- At least one of: inflammatory back pain, limitation of lumbar spine or restriction of chest expansion; *and*,
- Bilaterally grade 2 or unilateral grade 3–4 sacroiliitis[77]

The onset of AS is insidious and associated with significant delays in diagnosis as shown by a UK based study which found a mean diagnostic delay of 8.57 years between onset of symptoms, such as inflammatory back pain, and a formal diagnosis of AS being made.[674] Recent efforts to introduce an Early Inflammatory Back Pain Service alongside an educational campaign in the UK, have demonstrated reduced delays in the diagnosis of axial spondyloarthritis (AxSpA), with median duration from the first onset of back symptoms to the diagnosis of AxSpA generally of 3.1 years and of radiographic AxSpA of 4.0 years.[75] Other clinical features common in patients with AS include inflammation of the entheses (enthesitis), peripheral arthritis and extra-articular manifestations such as uveitis, psoriasis, inflammatory bowel disease and cardiovascular and pulmonary complications.[58-60] Notably, between 10-25% of patients with AS have concomitant psoriasis lesions, which are themselves effectively treated by secukinumab.[58, 78]

The fusion of spinal joints (ankylosis) can occur following enthesitis, as a result of new bone formation and severe restriction of spinal flexibility affects up to 40% of AS patients. [79] Spinal deformities arising from the fusion of joints typically occur 10 years after onset of the disease.[76] This can be highly disabling for patients, restricting their mobility and impairing their ease of breathing.[76] Patients with AS are also at an increased risk of developing osteoporosis and experiencing vertebral fractures.[80, 81]

3.3. Clinical and economic burden, quality of life and social functioning

AS is a life-long, progressive condition that can lead to irreversible spinal deformities and to a reduced quality of life in patients who would otherwise be in their prime of life.[510]

Inflammatory back pain is an inherent clinical feature of AS and severe pain is reported in around 25% patients suffering from AS.[66] Joint pain is often exacerbated at night, and fatigue resulting from disturbed sleep is also reported by patients with AS.[14]

The debilitating clinical features of AS can restrict the ability of those affected to carry out everyday activities, with more than 50% reporting difficulties in performing routine tasks including driving, shopping and having energy for social activities.[15] Due to the fact that the onset and progression of disease often coincides with the most productive years of a patient's life, AS is associated with a negative impact on work productivity, resulting in issues of absenteeism and presenteeism and therefore considerable indirect costs incurred through loss of productivity and permanent work disability.[18-20]

Total work-related cost of AS has been estimated to be as high as £11,943 per patient per year in the UK.[13, 51, 52] The contribution of indirect costs to the total cost of the condition is highlighted by a cross-sectional postal survey study of 1,000 patients with AS from registries at 10 secondary care rheumatology centres in the UK.[53] This study found direct healthcare costs to contribute just 15% of total costs, with unemployment, absenteeism from work and reduced productivity at work accounting for 63.2%, 1.4% and 19.0%, respectively. One of the important goals of treatment is to help patients remain in employment.[45] In addition, the symptoms of AS may have further social impact beyond direct workplace productivity, interfering with education, social relationships and job prospects at a critical and formative period in patients' lives.[50]

Due to the chronic and debilitating nature of the disease, AS utilises substantial healthcare resources for the diagnosis, treatment and rehabilitation of patients with AS.[11] Major reported direct costs associated with AS include physiotherapy, hospitalisation and medication costs, and these costs constitute a considerable economic burden when considering the substantial prevalence of the disease in the UK.[11]

The severity of disease affects both the clinical and economic burden of AS, with both higher healthcare and work-related costs associated with higher disease activity.[12, 13] Physical function and disease severity have both been identified as predictors of total costs for patients with AS with one study finding costs to be over three times higher for patients with BASDAI >6 than those with BASDAI <4.[82] As such, new and effective interventions to alleviate symptoms, inhibit progressive structural damage and improve quality of life are of real value to patients with AS.

3.4. Life expectancy and estimated eligible population

Life expectancy for patients with AS is reduced relative to the general population, with a standardised mortality rate of 1.63 and 1.38 for males and females respectively.[83] The lead cause of excess mortality in patients with AS is cardiovascular disease, with reduced survival related to disease severity and duration; the higher incidence of fractures in AS patients also contributes to increased mortality.[39, 83]

The NICE Commissioning Guide on biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology estimates the number of adult patients with AS in England at 70,000, of which an estimated 20,000 are expected to be eligible to receive biologic therapy.[39] "Estimates for the rate of uptake amongst those eligible vary between 30-70%: the NICE Commissioning Guide reports an estimate of 30% in England and Wales, while the clinical expert opinion of [redacted] reported a figure of 60-70% in Western Europe."[84, 85] Therefore, there are currently a minimum of 6,800 patients receiving biologic treatment for AS representing a rate of treatment with biologics for AS of approximately 17 per 100,000 adults per year.[39]

As previously noted, it is believed that these figures underestimate the real prevalence of AS and, consequently, the number of AS patients that are eligible and that receive biologic treatment for the disease could be much higher.[73] With the development of out-reach programmes such as the aforementioned UK best practice model for diagnosis and treatment of AS, reduced delays to diagnosis and increased awareness will lead to greater numbers of patients receiving more effective biologic treatment.[75]

3.5. Treatment pathway and existing NICE guidelines

As conventional care in the UK, patients with AS are initially treated with NSAIDs alongside non-pharmacological interventions to help relieve pain and stiffness (e.g. physiotherapy).[39] This treatment is variably referred to as conventional therapy or conventional care; the two terms are considered interchangeable within this submission, with conventional care preferentially used except where the term conventional therapy is felt appropriate to accurately reflect wording in treatment guidelines or product licences.

Regarding this treatment, there is little evidence to suggest that long term usage of NSAIDs prevents structural progression of the disease, and furthermore, there are concerns about the long term use of NSAIDs with regards to known side effects.[39] Given that research in the UK has found mean delay from onset of symptoms to diagnosis of AS of 8.57 years, and that 96% of patients were taking NSAIDs at diagnosis, it is conceivable that some AS patients in practice are taking NSAIDs for a considerable length of time even prior to diagnosis of AS.[74, 75]

Biologic therapies for the treatment of AS have been recently appraised as part of a Multiple Technology Appraisal (MTA). The Technology Appraisal Guidance (TA383) recommends the use of the TNFα inhibitor biologic therapies (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), within their marketing authorisations, for the treatment of severe active AS in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.[19] Other treatment guidelines relevant to treatment in England and Wales include those issued by the BSR in 2005.[39] Specifically, these guidelines recommend the use of TNFα inhibitor therapy in patients who have a diagnosis of AS according to the modified New York criteria, where AS is active and patients have failed conventional treatment (2 or more NSAIDs each taken

sequentially at maximum tolerated/recommended dosage for 4 weeks). According to the BSR guidelines, active AS should be defined as:

- BASDAI≥4 cms
- And spinal pain VAS (last week)≥4 cms
- Both on 2 occasions at least 4 weeks apart without any change of treatment

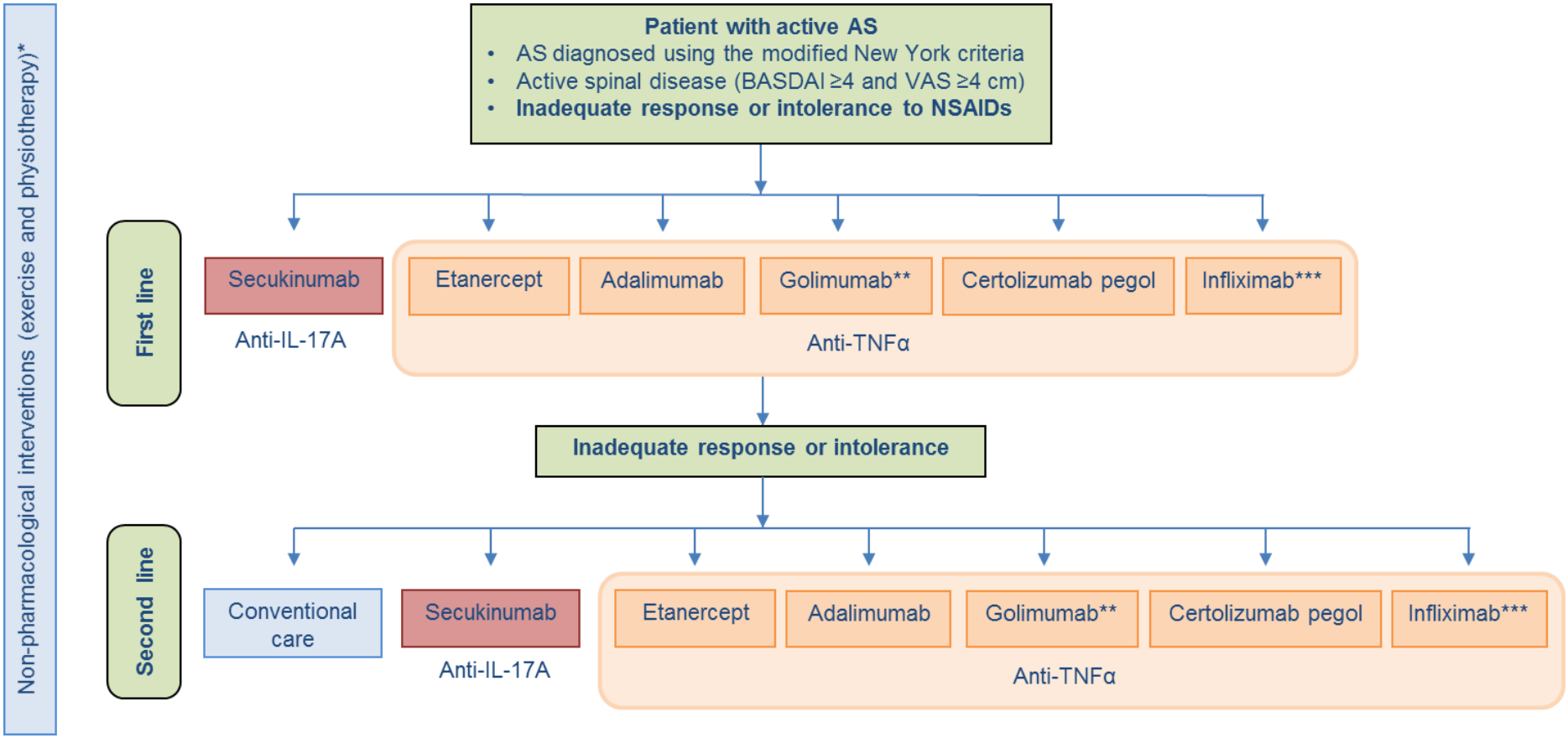
More recent published guidelines of potential relevance to England and Wales are those jointly developed by the Assessment of AS (ASAS) and European League Against Rheumatism (EULAR), which were last updated in 2010.[86] These broadly concur with the NICE guidelines for the treatment of active AS, recommending the use of TNFα inhibitors in patients with persistently high disease activity despite conventional treatment.[86]

For patients experiencing an inadequate response to, or unable to tolerate, their first-line biologic therapy, or whose disease has stopped responding after an initial response, NICE recommends treatment with another TNFα inhibitor as part of the NICE MTA in AS (TA383).[19] An adequate response is defined as a reduction of the BASDAI to 50% of the pre-treatment value, or by 2 units or more, together with a reduction of the spinal pain VAS by 2 cm or more.[19, 37] In previous appraisals it has been recognised that approximately 20% of patients receiving their first TNFα inhibitor may have an inadequate response to treatment or experience adverse events, although this figure could be as high as 40%.[38, 87] There are, however, no guidelines regarding specific sequencing of biologic therapies. Furthermore, as noted in Section 4.10.3 and by the Assessment Group as part of the MTA in AS, there is a lack of robust data to support use of TNFα inhibitors in this second-line biologic setting. The clinical trials of secukinumab presented in Section 4 provide data to support use of secukinumab in this population, and permit a comparison with a placebo arm that can be considered to reflect the conventional care that patients would receive following discontinuation of a biologic therapy as an alternative to a second-line biologic therapy.

This submission considers secukinumab in both the biologic naïve and the biologic experienced population. In the former population, secukinumab is considered as a first-line biologic for patients with active AS whose disease has responded inadequately to conventional therapy, and is therefore compared to the TNFα inhibitors. In the latter population, secukinumab is considered as an option for the population of patients who have previously received a TNFα inhibitor and is compared in the base case to conventional care based on the placebo-controlled trials of secukinumab in the absence of any robust data for TNFα inhibitors in this biologic experienced population. In considering secukinumab in both of these populations, the NICE final scope for this appraisal is addressed.

The treatment pathway within which secukinumab is being considered, based on the guidelines and the data availability discussed above, is presented in Figure 3.

Figure 3. Treatment pathway for patients with active AS



* Non-pharmacological interventions such as exercise and physiotherapy are recommended alongside pharmacological treatments.
** Recommended by NICE only when the 100 mg dose is provided at the same cost as the 50 mg dose, in accordance with the agreed patient access scheme.
*** Two biosimilar versions of the infliximab originator (Remicade®) are also available on the NHS (Inflectra®, Remsima®) NICE recommends infliximab only if treatment is commenced with the least expensive infliximab product. Note that although a biosimilar for etanercept (Benepali®) has been approved at the time of submission, a price for this biosimilar with the NHS has not been agreed and this biosimilar is therefore not available on the NHS in the UK.
Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IL, interleukin, NSAIDs, non-steroidal anti-inflammatory drugs; TNFα , tumour necrosis factor alpha; VAS, visual analogue scale.
Source: BSR Guidelines 2005,[39] NICE Technology Appraisal Guidance (TA383).[19]

3.6. Equity considerations

It is not considered that this appraisal will exclude any people protected by equality legislation, or lead to a recommendation that would have a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Two potential equity considerations were explored in the scoping exercise for this submission, relating to patient assessments and potential needle phobia. In both cases it was judged that adequate solutions are available and neither issue represents a new or major concern.

With respect to the equity consideration concerning patient assessments noted in previous technology appraisals for this indication, we consider that the conclusion reached in the previous appraisal still holds:

"When using BASDAI and spinal pain VAS scores to inform conclusions about whether or not sustained active spinal disease is present… There are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease. These are:

- where the BASDAI or spinal pain VAS score is not a clinically appropriate tool… because of a patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties
- where it is not possible to administer the BASDAI or spinal pain VAS questionnaire in a language in which the patient is sufficiently fluent… or there are similarly exceptional reasons… in that individual patient's case.

In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances." [Taken directly from TA143][37]

With respect to patients with 'needle phobia' secukinumab is licensed for use in a SensoReady® pen, which has been shown to result in high patient acceptability in studies evaluating secukinumab in patients with psoriasis.[53] The SensoReady® pen has features that may aid injection in patients with needle phobia, thereby mitigating this inequity consideration. In the SensoReady® pen, the needle is hidden and remains covered both before and after injection.

4. Clinical effectiveness

Summary of Clinical Evidence

- A systematic literature review (SLR) identified two key RCTs providing evidence for secukinumab 150 mg in the treatment of active AS for this submission. MEASURE 2 and MEASURE 1 are the first Phase III randomised-controlled trials to evaluate the effectiveness of selective IL-17A inhibition with secukinumab in the treatment of active AS. Together, MEASURE 2 and MEASURE 1 included 590 patients with moderate to severe AS, and a previous history of active AS despite current or previous treatment with NSAIDs, DMARDs and/or TNFα inhibitor therapy.
- The MEASURE 2 study used a subcutaneous loading dosing regimen with a four-weekly maintenance dosing regimen of secukinumab 150 mg, reflecting the licensed dosing regimen. MEASURE 1 used an i.v. loading dosing regimen but also used four-weekly s.c. maintenance dosing of secukinumab 150 mg. Both trials therefore provide evidence relevant to this submission.
- Both trials indicate secukinumab has a rapid onset of efficacy which is sustained for up to two years.
- In both trials, secukinumab 150 mg was superior to placebo for all primary and secondary endpoints (with the exception of ASAS partial remission in MEASURE 2) when assessed at Week 16, and the response rates with secukinumab 150 mg were subsequently sustained up to 2 years (Week 104).
- Regarding the primary efficacy variable, ASAS20, the secukinumab 150 mg treatment arm demonstrated response rates of 61.1% and 60.8% at Week 16 in MEASURE 2 and MEASURE 1 respectively, which was significantly higher than the respective placebo control groups (28.4%, $p<0.0001$ and 28.7%, $p<0.0001$). This significant benefit versus placebo was also seen when considering the more stringent measure of ASAS40 response.
- Additional outcome measures including BASDAI change from baseline, BASDAI 50 response, and BASFI change from baseline, confirmed the clinical efficacy of secukinumab across measures of disease activity and physical function, with secukinumab demonstrating significant benefit versus placebo across these measures at Week 16. Again, patients treated with secukinumab 150 mg were seen to maintain these responses up to 2 years (Week 104).
- The quality of life measure ASQoL demonstrated that the secukinumab 150 mg group experienced significantly greater improvements in quality of life compared with placebo controls in both trials; a mean change of -4.00 vs. -1.37 in the placebo arm ($p=0.001$) in MEASURE 2 and -3.58 vs. -1.04 in the placebo arm ($p<0.0001$) in MEASURE 1.
- MEASURE 1 also provided results for radiographic outcomes, highlighting the efficacy of secukinumab on a further clinically relevant and important aspect of the disease. In MEASURE 1, no radiographic progression of the disease was observed in approximately 80% of patients randomised to secukinumab at baseline after 104 weeks of treatment (mSASSS change ≤0).
- The results of MEASURE 2 and MEASURE 1 demonstrate the clinical efficacy of secukinumab treatment when assessed across a variety of outcome measures, and show that the clinical benefit conferred by secukinumab is maintained for at least two years.

4.1. Identification and selection of relevant studies

4.1.1. Systematic literature review

A clinical SLR was conducted for the purpose of identifying all relevant clinical evidence for the use of secukinumab and relevant comparators in the treatment of active AS. This SLR consisted of an original SLR and a subsequent update, as detailed below. The results of this SLR were intended to inform the clinical evidence base for secukinumab presented in this submission, as well as the NMA conducted to assess comparative effectiveness (see Section 4.10).

Additionally, a search of the Novartis Clinical Study Reports was conducted to identify non-published, more granular data of relevance to the submission from the AS clinical trial programme.[24, 25]

4.1.2. Search strategy

A predefined search strategy was used to perform searches of the following electronic databases:

- MEDLINE and MEDLINE In-Process (via PubMed platform)
- Embase (via Elsevier platform [original review] and Ovid SP [update review])
- Biosciences Information Services (BIOSIS) (via Dialog platform [original review] and Web of Science [update review])
- The Cochrane Library (via Wiley Online platform), including:
    - The Cochrane Central Register of Controlled Trials
    - The Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effectiveness

In addition, online congress abstracts (European League Against Rheumatism 2013-2015, National Ankylosing Spondylitis Society 2013-2015, American College of Rheumatology 2013-2015 and British Society of Rheumatology 2015), the EMA's European public assessment reports and clinical trial registries (ClinicalTrials.gov and the International Clinical Trials Registry Platform) were also searched.

The detailed search strategies used for online databases are provided in Appendix C. For the original review, the electronic database searches were conducted from 23rd – 27th January 2015, and no limit was placed on the publication date for electronic searches. Congress abstract searches were performed between 10th February 2015 and 5th March 2015 for the original SLR and on 3rd November 2015 for the update, and were restricted to those published in the last three years (2013-2015) as it was expected that high-quality studies presented at congresses earlier than this would have since been published. For the update to the SLR, electronic searches were performed on 14th September 2015 and searched for all articles from 1st January 2014 to this date. Results of this search were then de-duplicated against the full list of electronic records identified by the original search. The overlap in dates (1st January 2014 – 23rd January 2015) was deliberate in order to ensure that any studies published prior to the date of the original search but indexed afterwards were captured.

No language limitations were applied to either the original or update searches.

In addition to the above, hand searches of reference lists of existing, relevant SLRs and meta-analyses identified through the electronic database searches were also conducted to identify any potentially relevant records that might have been missed by the database searches.

The SLR update was designed to replicate the original SLR as closely as possible. Differences in the methodology of the original and update SLR are noted in Appendix C.

4.1.3. Study selection

Titles and abstracts were retrieved for all identified records and then independently screened by two researchers against the predefined PICOS inclusion and exclusion criteria presented below in Table 6. Any differences in decisions between researchers were resolved by consensus, or by third researcher arbitration where a consensus could not be reached. There were no limits on specific outcome requirements at the title and abstract stage.

Full-text articles of all records that met the inclusion and exclusion criteria were retrieved and subject to a second round of screening. Again, full-text articles were reviewed independently by two researchers against predefined inclusion and exclusion criteria. The criteria applied for the level 2 screen were identical to those for the level 1 screen (Table 6), with the exception of the handling of systematic reviews and meta-analyses, and the introduction of criteria relating to outcomes of interest. The inclusion and exclusion criteria for the level 2 screen are reported in Table 7. Any differences in decisions between researchers were resolved by consensus, or by third researcher arbitration where a consensus could not be reached.

Data for included articles were extracted from full-text versions of studies, when these were available, by one reviewer. Abstracts or posters were only used for extraction when these were the terminal source document. The data extracted from the relevant RCTs included the trial characteristics, patient demographics, treatment history, disease severity and interventions. Data were extracted for the following timepoints, where available: Week 12, 16, 24, 52 and outcomes reported after Week 52.

Table 6: List of criteria for the inclusion and exclusion of studies at level 1 (title and abstract) screening.

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult (≥18 years) patients with active or severe active AS • TNFα inhibitor-naïve patients as long as they had demonstrated prior intolerance or inadequate response to conventional treatments • Second-line patients who had inadequate response to prior treatments (e.g., conventional treatment with DMARDs, NSAIDs, and/or TNFα inhibitors) • Second-line patients who were intolerant to prior treatments (e.g., conventional treatment with DMARDs, NSAIDs, and/or TNFα inhibitor)	• Children • Patients with mild or early AS; if population was mixed (i.e., mild to severe), the studies were excluded if data for active or severe active AS were not reported separately • Non-radiographic axial spondyloarthritis • Treatment-naïve patients
Intervention	• Secukinumab	• Non-biologic treatments for AS (e.g., DMARDs, NSAIDs)
Comparators	• Certolizumab pegol (Cimzia®) • Etanercept (Enbrel® [biosimilars: Avent, BX2922, CHS-0214, ENIA11, Etacept, Etanar, GP2013, GP2015, HD203, LBEC0101, PRX-106, SB4, TuNEX, Yisaipu]) • Adalimumab (Humira®, Trudexa [biosimilars: ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293]) • Infliximab (Remicade® [biosimilars: CT-P13, Remsima, Inflectra]) • Golimumab (Simponi®)	• Non-biologic treatments for AS (e.g., DMARDs, NSAIDs) • Combinations of the therapies of interest
Outcomes	Any	None
Study design	• Randomised, controlled, prospective clinical trials • Long-term follow-up studies (e.g. open-label follow-up studies with continuation of treatments in their respective randomised group) • Systematic reviews, including meta-analyses[a]	• Non-randomised clinical trials • Preclinical studies • Phase I studies • Prognostic studies • Retrospective studies • Prospective observational studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews
Language	All languages	None
Date	No limit	None

Note: The inclusion criteria encompassed studies evaluating biosimilar products for etanercept, adalimumab and infliximab; The interventions of interest in this review consist of all therapy versions of the listed treatments at labelled doses.
[a]Only used for identification of primary studies that were missed in the electronic searches. Systematic reviews and meta-analyses were only included during the initial screening process and were excluded during the full-text review process (see Table 7); [b]All studies classed as Phase I were excluded according to this criteria; as such studies classed as both Phase I and Phase II were excluded.
Abbreviations: AS, ankylosing spondylitis; DMARD, disease modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; TNFα, tumour necrosis factor alpha.

Table 7: List of criteria for the inclusion and exclusion of studies at level 2 (full-text) screening.

Criteria	Inclusion criteria	Exclusion criteria
Population	As level 1	As level 1
Intervention	As level 1	As level 1
Comparators	As level 1	As level 1
Outcomes	To be included in the review, a study must report at least one of the outcomes of interest. **Efficacy measurements:** • ASAS score • Proportion of patients achieving ASAS20 response, ASAS40 response, ASAS70 response or ASAS 5/6 response • Proportion of patients achieving ASAS20 or ASAS40 response in the subgroup of patients who are TNFα inhibitor-naïve, have inadequate response to TNFα or who are TNFα intolerant • ASAS partial remission • Patient's global assessment of disease activity • Proportion of patients with inactive disease (ASDAS<1.3) • Proportion of patients with clinically important change (defined as ASDAS improvement of ≥1.1) • Proportion of patients with major improvement (defined as ASDAS improvement of ≥2.0) • BASDAI score • Spinal mobility assessed by BASMI (cervical rotation, maximal intermalleolar distance, lateral spinal flexion, lumbar flexion [modified Schober], tragus-to-wall distance), chest expansion and occiput-to-wall distance • BASFI score • 44 tender and swollen joint count • Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Serum high-sensitivity C-reactive protein • modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS): proportion of patients with a relapse • Patient assessment spinal pain **QoL measurements**: • ASQoL • EQ-5D • SF-36 • HAQ • FACIT-fatigue **Safety outcomes:** • Overall AEs • Overall serious AEs • Mortality • Treatment-related mortality • Discontinuations due to AEs	None

Criteria	Inclusion criteria	Exclusion criteria
	• Individual safety outcomes (may include serious viral upper respiratory infections, dyslipidemia, headache, gastrointestinal symptoms [nausea/pain], serious infections; TB; malignancies (including lymphoma, melanoma, and NMSC); injection site reactions; immunogenicity, uveitis flair, uveitis de novo, major adverse cardiac event, and leukopenia)	
Study design	• Randomised, controlled, prospective clinical trials • Long-term follow-up studies (e.g. open-label follow-up studies if patients continued in the group to which they were randomised)	As level 1, Systematic reviews and meta-analyses
Language	As level 1	As level 1
Date	As level 1	As level 1

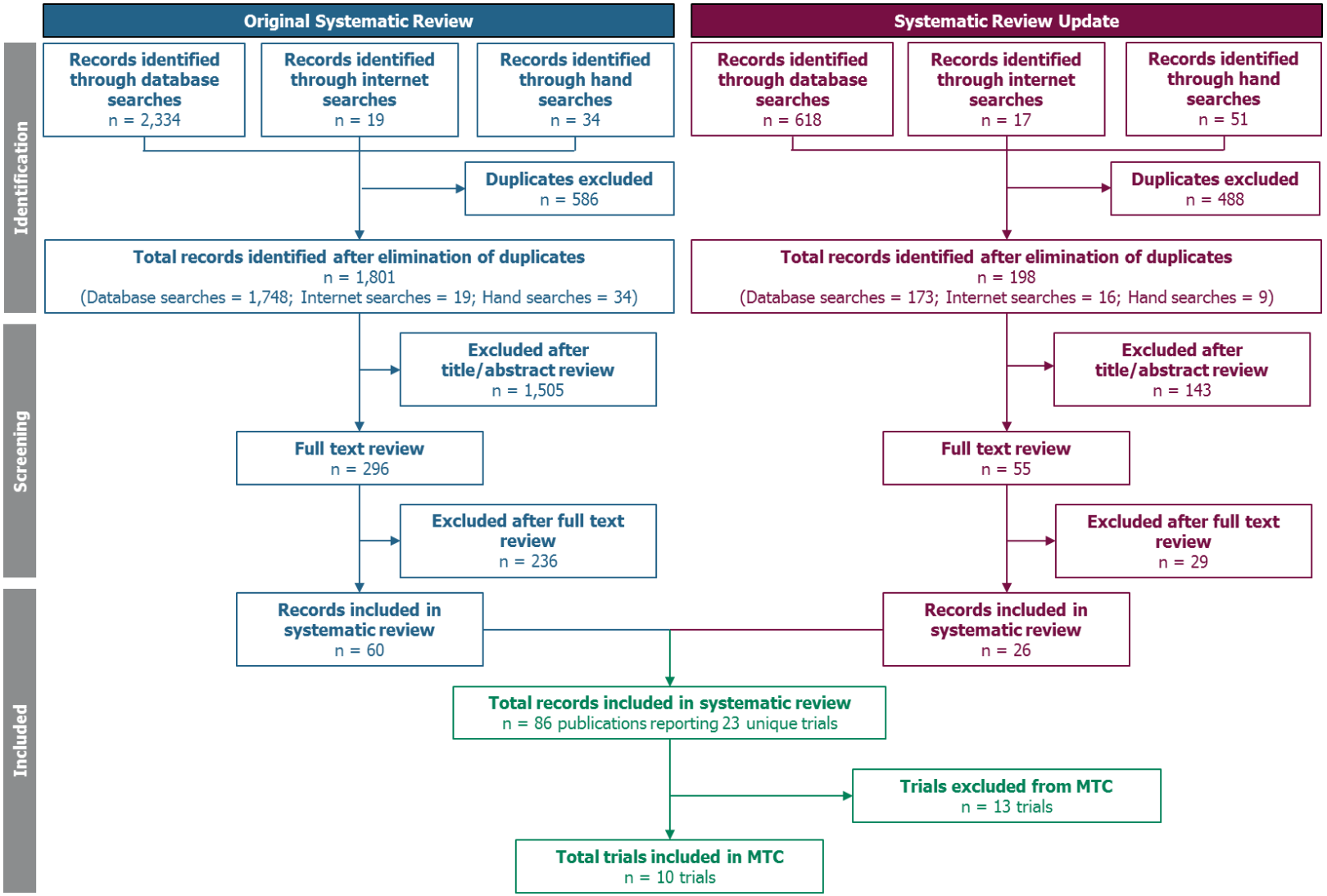
Abbreviations: AE, adverse event; ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; EQ-5D, EuroQol 5D questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ, Health Assessment Questionnaire; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; QoL, quality of life; SF-36, Short Form Health Survey; NMSC, non-melanoma skin cancer; TNFα, tumour necrosis factor alpha.

4.1.4. PRISMA flow diagram

A PRISMA flow diagram presenting the results of the original and updated SLRs is provided in Figure 4.

Overall, a total of 86 records met the inclusion criteria of the SLR, reporting on 23 unique trials. A full list of all 23 trials identified is presented in Table 8; this table also notes the primary and secondary sources for each trial and the inclusion or not of each trial in the NMA presented in Section 4.10. Of the 23 trials identified, 3 reported on secukinumab in the treatment of AS. A full list of the studies excluded at level 2 screening can be found in Appendix C.

Figure 4. PRISMA diagram for systematic literature review.



Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; MTC, mixed-treatment comparison.

Table 8: Summary of literature references for RCTs included and excluded from the NMA

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
A2209 trial	Two doses of i.v. secukinumab (10 mg/kg) given 3 weeks apart	Two doses of i.v. placebo given 3 weeks apart	30 patients aged 18-65 with moderate-to-severe AS were randomly assigned to treatment	To assess the efficacy and safety of secukinumab in treating patients with active AS	Baeten *et al.* 2013[22]	NA	No – treatment regimen is unlicensed use of secukinumab at dose of 10 mg/kg 3 weeks apart
ANSWERS	Etanercept (25 mg) s.c. once weekly	Etanercept (50 mg) s.c. once weekly	47 patients responded to etanercept (50 mg weekly) in the first phase of the trial, and were randomised to either continue on 50 mg weekly or reduce to 25 mg weekly	To evaluate maintenance of response to etanercept following dose reduction	Gaffney *et al.* 2014[88]	NA	No – dose reduction strategy not relevant
ASCEND	Etanercept (50 mg) s.c. once weekly	Sulfasalazine titrated to a maximum of 3 gm/day	566 patients, at least 18 years of age, with active AS, who had previously failed treatment with at least 1 NSAID were randomly assigned to treatment	To compare the efficacy and safety of etanercept with that of sulfasalazine after 16 weeks of treatment in patients with axial and peripheral manifestations of AS	Braun *et al.* 2011[89]	Braun *et al.* 2012[90] Moots *et al.* 2012[91]	No – sulfasalazine does not act as a comparator arm in the network and is not a treatment of interest
ASSERT	Infliximab (5 mg/kg) i.v. at Weeks 0, 2, 6, 12, and 18	Placebo at Weeks 0, 2, 6, 12, and 18	279 adult patients with AS for at least three months were randomly assigned to treatment	To evaluate the efficacy and safety of infliximab in patients with AS	van der Heijde *et al.* 2005[92]	Machado *et al.* 2010[4] Braun *et al.* 2009[93] Braun *et al.* 2006[94] Braun *et al.* 2008[95]	Yes
ATLAS	Adalimumab (40 mg) s.c.	Placebo every other week	315 patients, at least 18 years of age, with	To evaluate the safety and efficacy of	van der Heijde *et al.*	van der Heijde *et al.* 2015[97]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
	every other week		active AS, were randomly assigned to treatment	adalimumab in patients with active AS	2006[96]	Sieper *et al.* 2012[98] Maksymowych *et al.* 2010[99] van der Heijde *et al.* 2009[100] van der Heijde *et al.* 2009[101] Revicki *et al.* 2008[102] van der Heijde *et al.* 2008[103] Davis *et al.* 2007[104] Sieper *et al.* 2014[105] van der Heijde *et al.* 2008[106]	
CANDLE	Infliximab (3 mg/kg) i.v. at Weeks 0, 2, 6, 14 and every 8 weeks thereafter	Placebo at Weeks 0, 2 and 6, then infliximab at Weeks 14, 16, 22 and every 8 weeks thereafter	76 patients with active AS were randomised	To evaluate the efficacy and safety of low-dose (3 mg/kg) infliximab in the treatment of AS	Inman *et al.* 2010[107]	Maksymowych *et al.* 2010[108] Inman *et al.* 2008[109] Maksymowych *et al.* 2008[110]	No – treatment regimen is unlicensed use of infliximab at dose of 3 mg/kg
Giardina *et al.* 2010	Etanercept (50 mg) s.c. weekly	Infliximab (5 mg/kg at Week 0, 2, 6 and every 6 weeks	50 patients who were non-responders to oral NSAIDs	To compare the efficacy and safety of etanercept and infliximab	Giardina *et al.* 2010[29]	NA	Yes
GO-RAISE	Golimumab (50 mg or 100 mg) s.c. every 4 weeks	Placebo every 4 weeks	356 adult patients, with active AS, were randomly assigned to treatment	To evaluate the efficacy and safety of golimumab in patients with AS	Inman *et al.* 2008[111]	Deodhar *et al.* 2015[112] van der Heijde *et al.* 2014[113] Braun *et al.* 2014[114] van der Heijde *et al.* 2013a[115]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
						Braun *et al.* 2012b[116] Braun *et al.* 2012c[117] Deodhar *et al.* 2010[118] van der Heijde *et al.* 2013b[119] Deodhar *et al.* 2013[120] Braun *et al.* 2013[121] Deodhar *et al.* 2014a[122] Inman *et al.* 2013[123] Van Der Heijde *et al.* 2013c[124] Kay *et al.* 2015[125]	
Gorman *et al.* 2002	Etanercept (25 mg) s.c. twice a week	Placebo twice a week	40 patients with evidence of active AS despite accepted treatments	To investigate the efficacy of etanercept in patients with AS	Gorman *et al.* 2002[126]	NA	No – the study did not report any endpoints of interest
Hu *et al.* 2012	Adalimumab (40 mg) s.c. every other week during the initial 12 week double-blind period. This regimen continued throughout the ongoing open-label period	Placebo every other week during the initial 12 week double-blind period. At Week 12, all patients began receiving adalimumab (40 mg) s.c. every other week, and this regimen continued throughout the ongoing open-	46 patients who had been treated unsuccessfully (nonresponsive or lack of tolerance) with ≥ 1 NSAID	To investigate whether adalimumab is effective for active AS patients and whether it has an impact on the formation of fatty deposition lesions and serum Dickkopf homolog 1 (Dkk-1) levels in AS patients	Hu *et al.* 2012[127]	NA	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
		label period					
Huang *et al.* 2010	Etanercept (50 mg) s.c. once weekly	Placebo once weekly for 6 weeks, then etanercept (50 mg) once weekly	152 Chinese patients with active AS were randomised	To evaluate the short-term efficacy and safety of etanercept treatment in Chinese patients with active AS	Huang *et al.* 2010[128]	NA	No – there was no comparator arm after 6 weeks
Huang *et al.* 2011	Etanercept (50 mg) s.c. once weekly	Placebo once weekly for 6 weeks, then etanercept (50 mg) once weekly	381 Chinese patients completed the trial	To evaluate the efficacy and safety of etanercept 50 mg once-weekly treatment of Chinese patients with active AS	Huang *et al.* 2011[129]	NA	No – there was no comparator arm after 6 weeks
Huang *et al.* 2014	Adalimumab (40 mg) s.c. every other week	Placebo every other week	334 patients with inadequate response or intolerance to prior treatments	To evaluate the efficacy and safety of adalimumab in Chinese patients with AS	Huang *et al.* 2014[130]	NA	Yes
LOADET	Etanercept (50 mg) s.c. twice a week	Etanercept (50mg) once a week	108 patients aged 18-70 with a diagnosis of AS and who had failed treatment with at least two NSAIDs were randomly assigned to treatment	To evaluate the efficacy and safety of etanercept 100 mg vs 50 mg/ week in patients with AS	Navarro-Sarabia *et al.* 2011[131]	NA	No – comparison was to an unlicensed dose of etanercept
Marzo-Ortega *et al.* 2005	Infusions of infliximab (5 mg/kg) i.v. at Weeks 0, 2, 6, 14, and 22. In addition, all subjects were provided at Week 0 with a prescription for oral	Infusions of placebo at Weeks 0, 2, 6, 14, and 22. In addition, all subjects were provided at Week 0 with a prescription for oral methotrexate at	42 patients with persistent inflammatory back pain and CRP>10 mg/l despite treatment with NSAIDs or DMARDs	To examine the efficacy and safety of infliximab combined with methotrexate compared with methotrexate alone in the treatment of AS	Marzo-Ortega *et al.* 2005[132]	NA	No – the study did not connect to the network

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
	methotrexate at a dose of 7.5 mg with folic acid cover (5 mg twice a week), which would be eventually increased to 10 mg a week	a dose of 7.5 mg with folic acid cover (5 mg twice a week), which would be eventually increased to 10 mg a week					
MEASURE 1	Secukinumab given as i.v. loading doses (10 mg/kg) at Weeks 0, 2 and 4, followed by secukinumab (75 or 150 mg) s.c. at Week 8 and injected every 4 weeks	Placebo given i.v. at Weeks 0, 2 and 4, followed by placebo s.c. at Week 8 and 12	371 patients, at least 18 years old, with moderate to severe active AS were randomly assigned to treatment	To demonstrate the efficacy on signs and symptoms at Week 16 and to assess the long term safety, tolerability and efficacy on signs, symptoms and spine structure of secukinumab in subjects with active AS despite current or previous NSAID, DMARD and/or TNFα inhibitor therapy	Baeten *et al.* 2015[a14]	Baeten *et al.* 2014[133] Deodhar *et al.* 2014[134] Baeten *et al.* 2015[23] Baraliakos *et al.* 2015[26] Deodhar *et al.* 2015[135] Baeten *et al.* 2015[28] Baraliakos *et al.* 2015[136] Wei *et al.* 2015[137]	Yes
MEASURE 2	Secukinumab (75 mg or 150 mg) plus placebo (150 mg or 75 mg) s.c. once weekly at Weeks 0, 1, 2, 3 and 4, followed by dosing every	Placebo 75 mg and placebo 150 mg s.c. once weekly at Weeks 0, 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4	219 patients, at least 18 years of age, with moderate to severe active AS were randomly assigned to treatment	To provide 16-52 weeks efficacy, safety and tolerability data to support use of the secukinumab PFS for s.c. self-administration in patients with active AS despite current or previous NSAID, DMARD and/or TNFα inhibitor therapy	Baeten *et al.* 2015[a14]	Sieper *et al.* 2014[138] Baeten *et al.* 2015[28] Braun *et al.* 2015[139] Braun *et al.* 2015[140] Deodhar *et al.* 2015[135] Deodhar *et al.* 2015[141] Sieper *et al.* 2015[27] Sieper *et al.* 2015[142]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
	four weeks starting at Week 4						
M03-606 Canadian AS Study	Adalimumab (40 mg) s.c. every other week for 24 weeks, then open label adalimumab	Placebo every other week for 24 weeks, then open label adalimumab	82 patients with active AS who had inadequate response, or were intolerant to >1 NSAID; and had no prior exposure to anti-TNF therapy	To compare the progression of structural damage in the spine in patients with AS treated with adalimumab for up to 2 years versus patients who had not received TNF antagonist therapy	Lambert *et al.* 2007[143]	Sieper *et al.* 2014[105] Van der Heijde *et al.* 2009[144]	No – the study did not report any endpoints of interest
RAPID-axSpA	Certolizumab pegol (200 mg) s.c. every 2 weeks or certolizumab pegol (400 mg) s.c. every 4 weeks	Placebo	325 patients, at least 18 years of age, with active axial spondyloarthritis including patients with AS and non-radiographic axial spondyloarthritis were randomly assigned to treatment	To evaluate the efficacy and safety of certolizumab pegol after 24 weeks in patients with axial spondylitis and non-radiographic axial spondylitis	Landewe *et al.* 2014[145]	Sieper at al. 2015[146] Landewe *et al.* 2012[147] Sieper *et al.* 2014[148] Maksymowych *et al.* 2014[149] Sieper *et al.* 2014[150] Mease *et al.* 2014[151] Van der Heijde *et al.* 2013[152] Landewe *et al.* 2013[153] Sieper *et al.* 2013[154] Sieper *et al.* 2013[155] Landewe *et al.* 2013[156] Sieper *et al.* 2014[157] Rosenbaum *et al.* 2014[158] Rudwaleit *et al.* 2014[159] Sieper *et al.* 2014[160] Sieper *et al.* 2015[161]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in NMA?
SPINE	Etanercept (50 mg) s.c. once weekly	Placebo once weekly	82 patients who were refractory to NSAIDs but biologic-naive	To evaluate the effect of etanercept in patients with advanced AS	Dougados *et al.* 2011[162]	Dougados *et al.* 2012[163]	Yes
Tam *et al.* 2014	Golimumab (50 mg) s.c. monthly	Placebo monthly	41 patients with AS who had an inadequate response to at least two NSAIDs during a 3-month period, failure of IA steroids or failure of SSZ (in patients with predominantly peripheral arthritis)	To ascertain the efficacy of golimumab compared with placebo in the prevention of atherosclerosis and arterial stiffness in AS	Tam *et al.* 2014[164]	NA	No – the study did not report any endpoints of interest
Zhang *et al.* 2009	Etanercept s.c. for 12 weeks	Placebo for 6 weeks, then etanercept for 6 weeks	86 patients with active AS were randomised	To evaluate the short-term efficacy of etanercept in patients with active AS	Zhang *et al.* 2009[165]	NA	No – there was no comparator arm after 6 weeks
Zhang *et al.* 2012	Etanercept 50 mg s.c. for 12 weeks	Placebo for 6 weeks, then etanercept for 6 weeks	127 patients with active AS were randomised	To evaluate the efficacy of etanercept in the treatment of active AS with enthesitis	Zhang *et al.* 2012[166]	NA	No – there was no comparator arm after 6 weeks

[a]Please note that subsequent to the SLR, an additional article by Baeten *et al.* was published in January 2016, which describes results from the MEASURE 1 and MEASURE 2 trials up to Week 52, and hence is considered the primary reference source for these trials.
Abbreviations: AS, ankylosing spondylitis; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; IA, intra-articular; i.v., intravenous; kg, kilograms; mg, milligrams; NA, not applicable; NSAID, non-steroidal anti-inflammatory drug; PFS; pre-filled syringe; s.c. subcutaneous; TNFα, tumour necrosis factor alpha.

4.2. List of relevant randomised controlled trials

As presented in Table 8 the clinical SLR identified three published RCTs (A2209, MEASURE 1, MEASURE 2) investigating secukinumab in the treatment of AS. Please note that subsequent to the SLR, an additional article by Baeten *et al.* was published, which describes results from the MEASURE 1 and MEASURE 2 trials up to Week 52.[14]

The A2209 trial was a small Phase II proof of concept RCT evaluating the efficacy at 6 and up to 28 weeks.[22] Part 1 of the study enrolled 30 patients, who received two infusions spaced three weeks apart of either secukinumab 10 mg/kg or placebo. In Part 2, which enrolled 30 different patients, two infusions of secukinumab spaced three weeks apart were administered at 10 mg/kg, 1.0 mg/kg or 0.1 mg/kg (please see Appendix D). Given the small, short term nature of this study, as well as the inconsistent timepoint used as the study endpoint and the absence of licensed doses being administered, the A2209 study will not be considered further in this submission, however, relevant radiographic results are presented in Appendix D. Furthermore, two large Phase III RCTs were identified, which provide the evidence for the efficacy and safety of secukinumab in AS (MEASURE 1 and MEASURE 2) presented in this submission.

Together, MEASURE 1 and MEASURE 2 are the first Phase III randomised-controlled trials to evaluate the effectiveness of selective IL-17A inhibition with secukinumab in the treatment of active AS. Both were placebo-controlled studies; no studies were identified that directly compared secukinumab to any of the active biologic comparators.

A summary of the MEASURE 2 and MEASURE 1 trials is provided in Table 9. The two studies differed only in the choice of s.c. vs. i.v. loading regimen, which was used in MEASURE 2 and MEASURE 1 respectively; primary and secondary endpoints of the two trials were the same.

In MEASURE 2, patients received initial s.c. dosing of secukinumab 150 mg at Baseline, Weeks 1, 2, and 3, followed by maintenance s.c. dosing of secukinumab 150 mg every 4 weeks, starting at Week 4. This regimen reflects the licensed monthly dosing regimen for secukinumab in AS.

The MEASURE 1 trial differed from the licensed dosing regimen of secukinumab in that secukinumab was administered intravenously during the initial loading period at a dose of 10 mg/kg at Baseline, Week 2 and Week 4. From Week 8 onwards, patients then received a maintenance dose of s.c.secukinumab 150 mg every four weeks. Importantly, the MEASURE 1 trial provides results from radiographic outcomes from X-ray, MRI and DXA scans.

Table 9: List of relevant secukinumab randomised-controlled trials

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
NCT01649375 MEASURE 2	219 randomised adult patients with moderate to severe AS fulfilling the Modified New York criteria, with prior documented radiological evidence, and previous history of active AS* despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy • 61% patients TNFα inhibitor-naïve in the randomised set • 39% patients inadequate responder to TNFα inhibitor therapy in the randomised set	Group 1: secukinumab 75 mg plus placebo 150 mg once weekly at Baseline, Weeks 1, 2, and 3 followed by dosing every four weeks starting at Week 4 (n=73) Group 2: secukinumab 150 mg plus placebo 75 mg once weekly at Baseline, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4 (n=72)	Group 3: placebo 75 mg and placebo 150 mg once weekly at Baseline, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4 (n=74) up to Week 16. Patients were then re-randomised to receive secukinumab (either 75 mg or 150 mg) every 4 weeks.	Baeten *et al.* 2015**[14]
NCT01358175 MEASURE 1	371 randomised adult patients with moderate to severe AS fulfilling the Modified New York criteria, with prior documented radiological evidence, and previous history of active AS* despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy • 73% patients TNFα inhibitor-naïve in the randomised set • 27% patients inadequate responder to TNFα inhibitor therapy in the randomised set	Group 1: secukinumab i.v. (10 mg/kg) at Baseline, Week 2 and Week 4 followed by secukinumab 75 mg s.c. every 4 weeks starting at Week 8 (n=124) Group 2: secukinumab i.v. (10 mg/kg) at Baseline, Week 2 and Week 4 followed by secukinumab 150 mg s.c. every 4 weeks starting at Week 8 (n=125)	Group 3: placebo i.v. at Baseline, Week 2 and Week 4 then placebo s.c. at Week 8 and Week 12 (n=122). Non-responders were re-randomised at Week 16 to receive secukinumab (75 mg or 150 mg) every four weeks; responders were re-randomised at Week 24.	Baeten *et al.* 2015**[14]

*BASDAI ≥4 [0-10] and spinal pain as measured by VAS ≥4 cm [0-10 cm]); **Subsequent to the SLR, an additional article by Baeten *et al.* was published in January 2016, which describes results from the MEASURE 1 and MEASURE 2 trials up to Week 52, and hence is considered the primary reference source for these trials.
Abbreviations: AS, ankylosing spondylitis; CSR, clinical study report; DMARDs, disease modifying anti-rheumatic drugs; i.v., intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; s.c., subcutaneous; TNFα , tumour necrosis factor alpha.
Source: MEASURE 2 Clinical Study Report[25], MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015.[14]

4.3. Summary of methodology of the relevant randomised controlled trials

4.3.1. MEASURE 2 study design

The primary objective of the trial was to demonstrate that the efficacy of secukinumab 75 mg or 150 mg at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS20 response.

The primary endpoint of the MEASURE 2 trial was at Week 16, with secondary endpoints also at Week 52 and 104, allowing long-term safety and efficacy data to be collected.

Prior to randomisation, enrolled patients were screened to assess their eligibility for the trial. At baseline, eligible patients were randomised in a ratio of 1:1:1 to one of the three treatment groups (please see below). At each study treatment visit two s.c. injections in the form of pre-filled syringes were administered. This was necessary in order to maintain blinding, because the identity of the study treatments as pre-filled syringes could not be disguised due to their different volume forms.

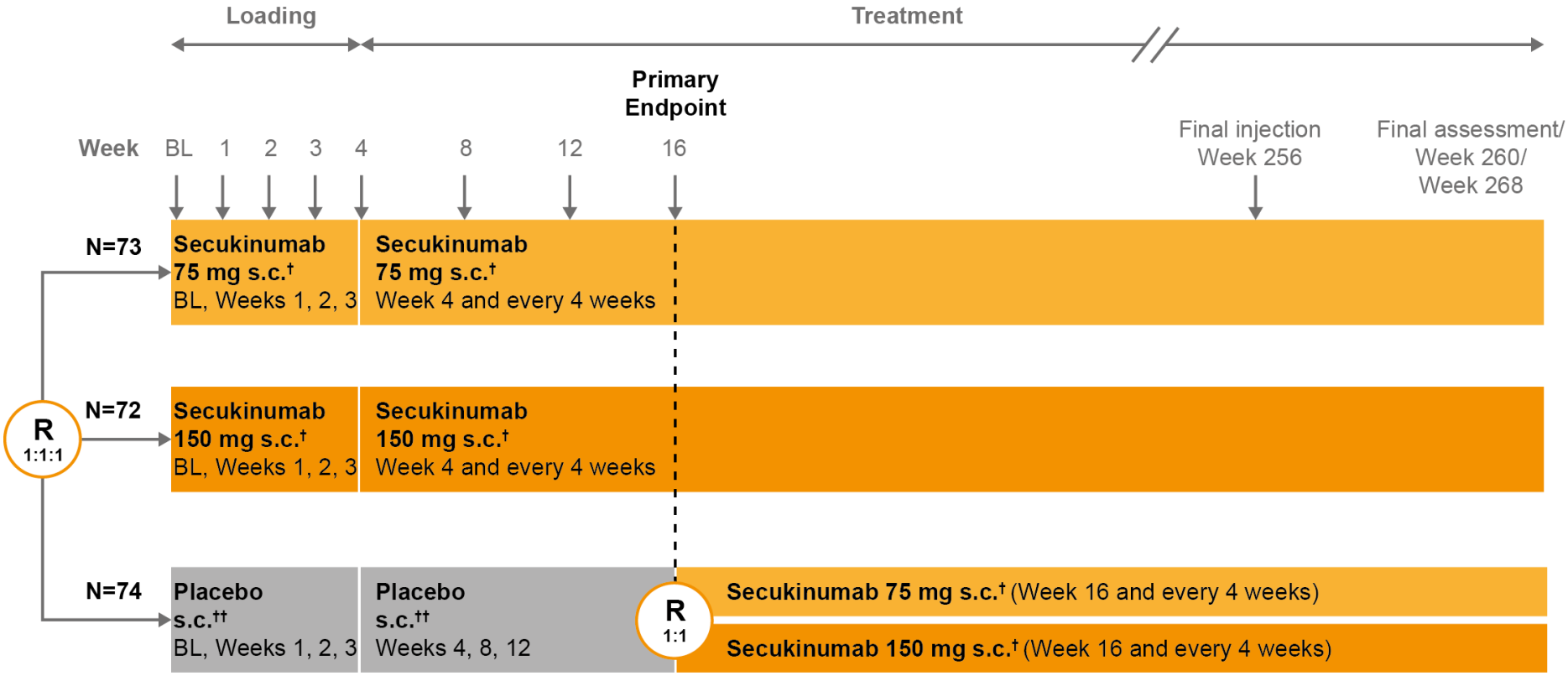
- **Group 1**: secukinumab 75 mg plus placebo 150 mg once weekly at Baseline, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4 (n=73)
- **Group 2**: secukinumab 150 mg plus placebo 75 mg once weekly at Baseline, Weeks 1, 2, and 3, followed by dosing every four weeks starting at Week 4 (n=72)
- **Group 3**: placebo 75 mg and placebo 150 mg once weekly at Baseline, Weeks 1, 2, and 3 followed by dosing every four weeks starting at Week 4 (n=74)

To minimise the time that patients with active disease spent receiving placebo treatment, at Week 16, patients who had been randomised to the placebo arm at baseline were re-randomised (1:1) to receive either 75 mg or 150 mg secukinumab every 4 weeks up to 256 weeks. The blinding was maintained beyond the primary endpoint so as to ensure reliable efficacy and safety assessments over time. Results for placebo patients who switched to secukinumab treatment should be interpreted with caution given the small sample sizes and the possible reporting bias from Week 16 onward when all patients were aware they were receiving active treatment, as per trial design.

Results from the patients that received the dosing regimen of secukinumab 150 mg are considered relevant to this submission and are presented in Section 0. Data from patients who received the unlicensed dose of 75 mg are not shown.

Full details of the MEASURE 2 trial design are shown in Figure 5, with details of the methodology summarised in Table 10.

Figure 5. MEASURE 2 Trial Design



†Secukinumab administered as 0.5 mL for 75 mg or 1 mL for 150 mg. ††Placebo administered s.c. 0.5 mL or 1 mL as per double-blind design
Abbreviations: BL, baseline; R, randomised; s.c., subcutaneous.
Source: Baeten *et al.* 2015.[14]

4.3.2. MEASURE 1 study design

The primary objective of the MEASURE 1 trial was to demonstrate that the efficacy of secukinumab at Week 16 (75 mg or 150 mg) is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS20 response.

The primary endpoint of the MEASURE 1 trial was at Week 16, with secondary endpoints also at Week 52 and 104, allowing long-term safety, efficacy and radiological data to be collected.

The MEASURE 1 trial also assessed a number of radiological secondary endpoints in a subset of patients, reporting changes from baseline for up to 2 years. Assessments included X-rays of the cervical, thoracic and lumbar spine at Week 104 analysed according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and MRI scans at Weeks 16, 52 and 104 to assess sacroiliac and spinal inflammation.

Prior to randomisation, enrolled patients were screened to assess their eligibility for the trial. At baseline, eligible patients were randomised in a ratio of 1:1:1 to one of the three treatment groups:

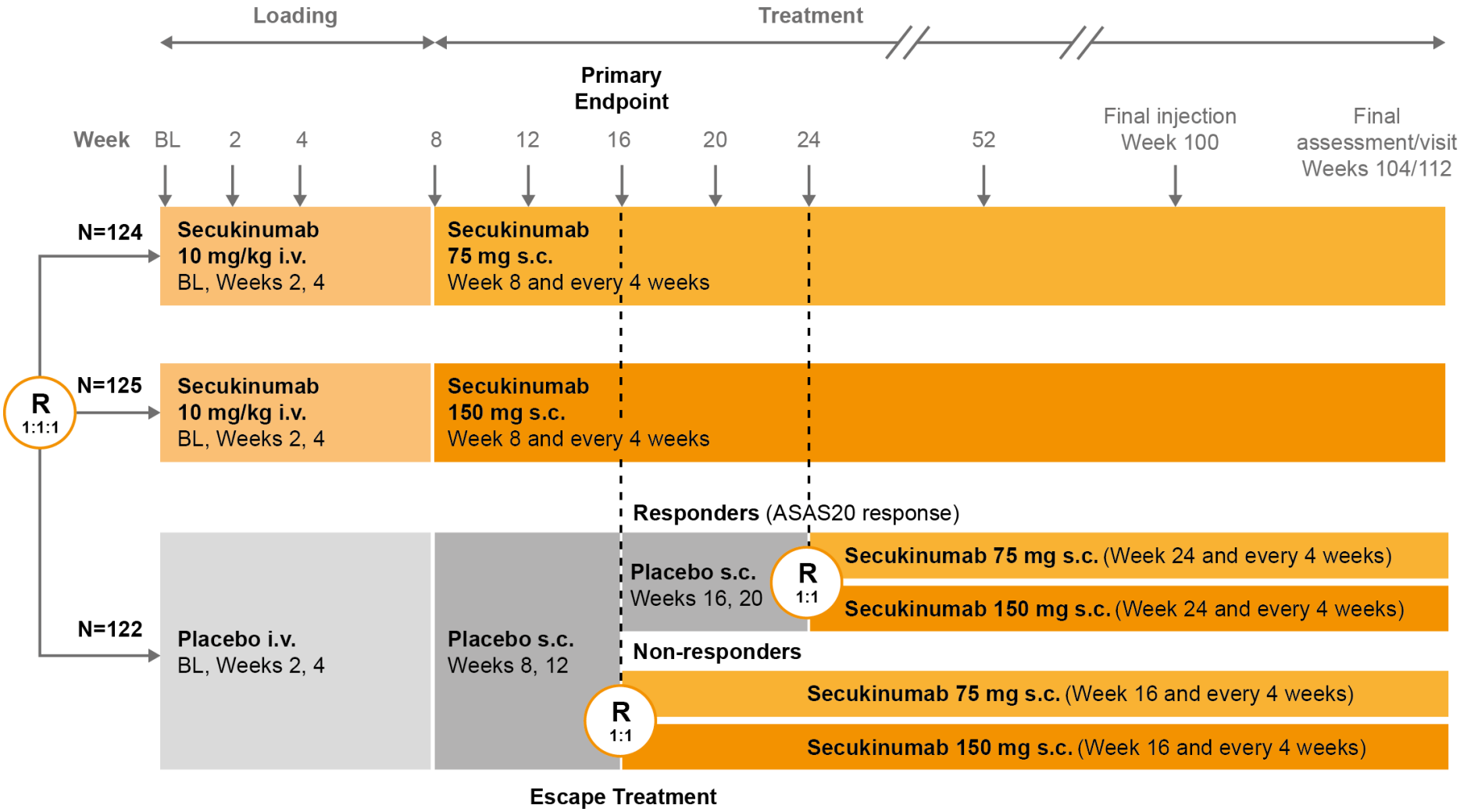
- **Group 1:** secukinumab i.v. (10 mg/kg) at Baseline, Week 2 and Week 4 then secukinumab 75 mg s.c. every four weeks starting at Week 8 (n=124)
- **Group 2**: secukinumab i.v. (10 mg/kg) at Baseline, Week 2 and Week 4 followed by secukinumab 150 mg s.c. every four weeks starting at Week 8 (n=125)
- **Group 3**: placebo i.v. at Baseline, Week 2 and Week 4 followed by placebo s.c.at Week 8 and 12 (n=122)

Similarly to MEASURE 2, the MEASURE 1 trial was designed to minimise the time that patients with active disease spent receiving placebo treatment. At Week 16, patients in the placebo arm that were classified as non-responders (based on the ASAS20 improvement criteria) were re-randomised (1:1) to receive double-blinded secukinumab 75 mg or 150 mg every 4 weeks for up to 2 years. Patients in the placebo arm classified as responders at Week 16 were re-randomised (1:1) at Week 24 to receive double-blinded secukinumab 75 mg or 150 mg (1:1) every 4 weeks for up to 2 years, regardless of responder status.

As for MEASURE 2, results from the patients that received the dosing regimen of 150 mg of secukinumab are considered relevant to this submission and are presented in Section 4.7.2. Data from patients who received the unlicensed dose of 75 mg are not shown.

Full details of the MEASURE 1 trial design are shown in Figure 6, with details of the methodology summarised in Table 10.

Figure 6. MEASURE 1 Trial Design



Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BL, baseline; R, randomised; i.v., intravenous; s.c., subcutaneous.
Source: Baeten *et al.* 2015.[14]

4.3.3. Summary of study methodologies

A comparative summary of the methodology of the MEASURE 2 and MEASURE 1 trials is summarised in Table 10.

Table 10. Summary of methodology of the relevant randomised-controlled trials

Trial Name	MEASURE 2	MEASURE 1
Location	International, multi-centre trial across 52 locations in the following countries: United States, Austria, Canada, Czech Republic, Finland, Germany, Italy, Netherlands, Russian Federation, Singapore, Spain, Switzerland, United Kingdom [redacted]/219 patients were from UK study sites.	International, multi-centre trial across 67 locations in the following countries: United States, Belgium, Bulgaria, Canada, France, Germany, Italy, Mexico, Netherlands, Peru, Russian Federation, Taiwan, Turkey, United Kingdom [redacted]/371 patients were from UK study sites.
Trial design	Randomised, double-blinded, double-dummy, parallel-group, placebo-controlled Phase III trial	Randomised, double-blinded, parallel-group, placebo-controlled Phase III trial
Inclusion and exclusion criteria for participants	Key eligibility criteria are shared across both MEASURE 2 and MEASURE 1 trials and are provided below. Full eligibility criteria and exclusion criteria are provided in Table 11. Patients must have fulfilled the following criteria: • Male or female ≥18 years • Moderate to severe AS fulfilling the Modified New York criteria for AS, with prior documented radiological evidence • Active AS, and BASDAI ≥4 (0-10) and spinal pain as measured by VAS ≥4 cm (0-10 cm) at baseline • Report active disease despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy Included patients were stratified according to being TNFα inhibitor-inadequate responders (IR) or TNFα inhibitor-naïve patients. Patients were not eligible if they fulfilled exclusion criteria such as: • Chest X-ray (or MRI in MEASURE 2 only) with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17A receptor • Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis	
Method of randomisation	In both trials, all eligible patients were randomised (1:1:1) at baseline via Interactive Response Technology (IRT) to one of the treatment arms. The IRT could be contacted via the Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS).	

	Patients were stratified at randomisation according to TNFα inhibitor-naïve patients or TNFα inhibitor inadequate responder (IR) patients:	
	• In MEASURE 2, approximately 40% of patients had to be TNFα inhibitor-IR to ensure a representative patient population for the assessment of efficacy and safety.	• In MEASURE 1, approximately 30% of patients had to be TNFα inhibitor-IR to ensure a representative patient population for the assessment of efficacy and safety.
Trial treatments	• Group 1: secukinumab 75 mg plus placebo 150 mg once weekly at Baseline, Weeks 1, 2, and 3, followed by dosing every four weeks starting at Week 4 (n=73) • Group 2: secukinumab 150 mg plus placebo 75 mg once weekly at Baseline, Weeks 1, 2, and 3, followed by dosing every four weeks starting at Week 4 (n=72) • Group 3: placebo 75 mg and placebo 150 mg once weekly at Baseline, Weeks 1, 2, and 3, followed by dosing every four weeks starting at Week 4 (n=74) [All treatments administered by s.c. injections in the form of pre-filled syringe (PFS)] At Week 16, patients who were randomised to placebo at baseline were re-randomised to receive secukinumab 75 mg plus placebo 150 mg or secukinumab 150 mg plus placebo 75 mg (1:1) every 4 weeks up to 5 years.	• Group 1 (i.v.-75 mg): secukinumab i.v. (10 mg/kg) at Baseline, Weeks 2 and Week 4 then secukinumab 75 mg s.c. every 4 weeks starting at Week 8 (n=124) • Group 2 (i.v.-150 mg): secukinumab i.v. (10 mg/kg) at Weeks 0, 2 and 4 then secukinumab 150 mg s.c. every 4 weeks starting at Week 8 (n=125) • Group 3: placebo i.v. at Baseline, Week 2 and Week 4 then placebo s.c. at Week 8 and Week 12 (n=122) At Week 16, patients who had been randomised to placebo (Group 3) at baseline were re-randomised to receive double-blind treatment up to 2 years, based on treatment response as determined by ASAS20 improvement criteria: • Placebo non-responders were re-randomised to receive secukinumab 75 mg or 150 mg s.c. (1:1) dosed every 4 weeks • Placebo responders remained on placebo s.c. at Weeks 16 and 20. At Week 24, these patients received secukinumab 75 mg s.c. or 150 mg s.c. (1:1) dosed every 4 weeks, regardless of responder status, as dictated by the re-randomisation.
Concomitant medicines	Guidelines for the use specific medications in MEASURE 2 and MEASURE 1 are provided in full in Appendix E. The list of concomitant medicines include: • Methotrexate (MTX) (7.5-25 mg/week) – stable dose for at least 4 weeks prior to randomisation and until Week 52 • Folic acid - patients on MTX had to take folic acid supplementation before randomisation and during the trial to minimise the likelihood of MTX associated toxicity. • Sulfasalazine (≤ 3 g/day) – stable dose for at least 4 weeks prior to randomisation and until Week 52 • Systemic corticosteroids – stable dose for at least 2 weeks prior to randomisation, up to a maximum daily dosage of 10 mg prednisone equivalent.	

	• NSAIDs (including COX-1 or COX-2 inhibitors) and acetaminophen/paracetamol - stable dose for at least 2 weeks prior to randomisation Medicines that were prohibited from both trials and required appropriate wash-out prior to randomisation, are listed in Appendix E. The list of prohibited medicines not allowed after the start of the washout period include: • Other biological therapies (etanercept, infliximab, adalimumab, golimumab, certolizumab)* • Unstable dose of MTX or sulfasalazine • Other DMARDs (except MTX or sulfasalazine) • Leflunomide (within 4 weeks of randomisation with cholestyramine washout or within 8 weeks of randomisation without cholestyramine washout) • Unstable dose of NSAIDs (COX-1 or COX-2 inhibitors) (until Week 20 in MEASURE 2) • Systemic corticosteroids > 10 mg prednisone equivalent • Intra-articular steroids injections (until Week 20 in MEASURE 2 and Week 16 in MEASURE 1) • Any investigational treatment or participation in any interventional trial • Analgesics other than paracetamol/acetaminophen and low strength opioids PRN • Live vaccinations (up to Week 24 in MEASURE 1)
Primary endpoint	Proportion of patients achieving ASAS20 response at Week 16
Secondary endpoint(s)	• Proportion of patients achieving ASAS40 response at Week 16 • High sensitivity C-reactive protein (hsCRP) change from baseline at Week 16 • Proportion of patients achieving ASAS 5/6 response criteria at Week 16 • BASDAI change from baseline at Week 16 • SF-36 PCS change from baseline at Week 16 • ASQoL change from baseline at Week 16 • Proportion of patients achieving ASAS partial remission criteria at Week 16 • To evaluate the overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring
Exploratory endpoints	• Primary and secondary outcome measures at timepoints other than Week 16 • Change from baseline in ASAS components including BASFI • Change from baseline in ASDAS-CRP and ASDAS-ESR • Change from baseline in nocturnal back pain** • Change from baseline BASMI linear scores and in BASMI components

	• ASDAS inactive disease (<1.3), clinically important change (≥1.1) and major improvement (≥2.0) • Change from baseline in MASES • Change from baseline in swollen or tender joint count as determined by the 44-joint assessment • Change from baseline in ESR • Work productivity (WPAI-GH), quality of life (SF-36, FACIT-FATIGUE®) and utilities (EQ-5D) • BASDAI 50 defined as a 50% improvement of the initial BASDAI • Exploration of immunogenicity against secukinumab • PK/PD relationship • Pharmacogenetic assessments • Biomarker assessments • Cumulative NSAID intake during the trial (MEASURE 2 only) In MEASURE 1, the following radiologic endpoints were also assessed (changes observed from baseline): • mSASSS; radiography scoring after 2 years of treatment • MRI of spine and sacroiliac joints at Week 16, 1 year and 2 years (in TNFα inhibitor-naïve patients and at selected clinical sites only) • BMD of the lumbar spine, total hip and femoral neck after 1 year and 2 years of treatment • Markers of cartilage and bone turnover over 2 years
Pre-planned subgroup analysis	A pre-specified subgroup analysis was performed to explore any differences in outcomes between TNFα inhibitor-IR patients and patients who were naïve to TNFα inhibitor treatment.

*These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation. **Specified as nocturnal pain in MEASURE 2

Source: MEASURE 2 Clinical Study Report;[25] MEASURE 1 Clinical Study Report[24]

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMD, Bone mineral density; COX(-1,-2), cyclooxygenase(-1,-2); DMARDs, disease modifying anti-rheumatic drugs; EQ-5D, EuroQol 5D questionnaire; ESR, Erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; (hs)CRP, (high sensitivity) C-reactive protein; IRT, interactive response technology; i.v., intravenous; IL, interleukin; IR, inadequate responder; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; mSASSS, modified stoke ankylosing spondylitis spine score; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PCS, physical component summary; PFS, pre-filled syringe; PK/PD, pharmacokinetic/pharmacodynamic; PRN, pro re nata, when necessary; s.c., subcutaneous; SF-36, Medical Outcome Short Form Survey-36; TNFα, tumour necrosis factor alpha; IR, inadequate responder; VAS, visual analogue scale; WPAI-GH, Work Productivity and Activity Impairment-General Health.

4.3.4. Study eligibility criteria

Only subjects that fulfilled all the inclusion criteria and did not meet any of the exclusion criteria were included in the MEASURE 2 and MEASURE 1 trials. The full eligibility criteria are equivalent for both studies and are provided in Table 11.

Table 11: Eligibility criteria for subjects included in MEASURE 2 and MEASURE 1

Inclusion criteria	Exclusion criteria
Patients able to understand and communicate with the investigator, comply with the requirements of the study, and give a written, signed and dated informed consent before any study assessment was performed	Chest X-ray (or MRI in MEASURE 2 only) with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician
Male or non-pregnant, non-lactating female patients ≥18 years of age	Patients with total ankylosis of the spine
Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI ≥4 (0-10) and spinal pain as measured by VAS ≥4 cm at baseline	Patients taking high potency opioid analgesics (e.g., methadone, hydromorphone, or morphine)
Patient had to be on NSAIDs at the highest recommended dose for at least 3 months with an inadequate response or failure to respond, or less than 3 months if therapy had to be withdrawn due to intolerance, toxicity or contraindications	Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17A receptor
Patients who were regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS therapy were required to be on a stable dose for at least 2 weeks before randomisation	Use of an investigational drug and/or devices within 4 weeks of randomisation, or a period of 5 half-lives of the investigational drug, whichever was longer
Patients who have been on an TNFα inhibitor agent (not more than one) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months or have been intolerant to at least one administration of an TNFα inhibitor agent	History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes
Patients who have previously been on a TNFα inhibitor were allowed entry into study after appropriate wash-out period prior to randomisation: • 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route) • 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v.infusion) • 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route) • 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days (s.c. route) • 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days (s.c. route)	Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomisation

Patients taking MTX (7.5 to 25 mg/week) or sulfasalazine (≤3 g/day) were allowed to continue their medication and must have taken it for at least 3 months and had to be on a stable dose for at least 4 weeks prior to randomisation	Any intramuscular corticosteroid injection within 2 weeks before randomisation
Patients on MTX must be on stable folic acid supplementation before randomisation	Patients previously treated with any biological immunomodulating agents except for those targeting TNFα
Patients who were on a DMARD other than MTX or sulfasalazine must have discontinued the DMARD 4 weeks prior to randomisation, except for leflunomide, which had to be discontinued for 8 weeks prior to randomisation unless a cholestyramine washout had been performed	Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
Patients taking systemic corticosteroids had to be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomisation	Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
Patients must comply with guidelines regarding concomitant medicines and washout periods as described in Appendix E.	Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment.
	Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis
	Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
	History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L)
	Screening total WBC count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or haemoglobin <8.5 g/dL (85 g/L)
	Active systemic infections during the last two weeks (exception: common cold) prior to randomisation
	History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration was measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON TB Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no

	evidence of active tuberculosis.
	Known infection with HIV, hepatitis B or hepatitis C at screening or randomisation
	History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
	Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
	Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
	Any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
	Donation or loss of 400 mL or more of blood within 8 weeks before dosing
	History or evidence of ongoing alcohol or drug abuse, within the last six months before randomisation
	Plans for administration of live vaccines during the study period or 6 weeks prior to randomisation
	Patients who fail to comply with guidelines regarding concomitant and prohibited medicines as described in Appendix E.

Abbreviations: AS, ankylosing spondylitis; BASDAI; Bath Ankylosing Spondylitis Disease Activity Score; COX(-1,-2), cyclooxygenase(-1,-2); DMARDs, disease modifying anti-rheumatic drugs; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; IL, interleukin; MRI, magnetic resonance imaging; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PPD, purified protein derivative; TB, tuberculosis; TNFα, tumour necrosis factor alpha; VAS, visual analogue scale; WBC, white blood cell.
Source: MEASURE 2 Clinical Study Report,[25] MEASURE 1 Clinical Study Report.[24]

4.3.5. Study outcomes: definitions

The definition of the ASAS Response Criteria and associated measures are presented in Table 12 below. Definitions of all other outcomes reported in the MEASURE 2 and MEASURE 1 trials, including ASAS components, are presented below in Table 13.

Table 12: ASAS Response Criteria

Trial outcome	Definition
ASAS response criteria[167]	
	The ASAS response measures consist of four main assessment domains, the so-called ASAS components: 1. Patient's global assessment of disease activity measured on a VAS scale 2. Patient's assessment of inflammatory back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale 3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale 4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale In addition, ASAS response measures includes two additional assessment domains: 5. Spinal mobility represented by the BASMI lateral spinal flexion assessment 6. C reactive protein (acute phase reactant) For further details of specific outcomes used within the ASAS response criteria, please see Table 13 below.
Measures of ASAS response criteria	
ASAS20/40	An improvement of at least 20% or 40% and absolute improvement of at least 1 or 2 units on a 0-10 cm scale in at least 3 of the main assessment domains (1 to 4), with no worsening in the remaining domain.
ASAS 5/6	An improvement of at least 20% in at least five of all six assessment domains.
ASAS partial remission	Defined as a value not above 2 units in each of the main assessment domains (1 to 4) on a scale of 10.

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; VAS, visual analogue scale.

Table 13: Additional efficacy outcomes and definitions

Study outcome	Definition
ASDAS-ESR, ASDAS-CRP and ASDAS response[168]	The ASDAS-ESR and ASDAS-CRP scores were utilised to assess AS disease activity status. Parameters used for ASDAS include: total back pain (BASDAI question 2), the patient global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 5) and C-reactive protein (CRP) in mg/litre or erythrocyte sedimentation rate (ESR). Disease activity states included: inactive disease, moderate disease activity, high disease activity and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and moderate disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cut-offs for improvement scores were a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement".
ASQoL[169]	A patient reported outcome measure designed to assess QoL in adult patients with AS. It consists of an 18 item questionnaire with dichotomous yes/no response options. A single point is assigned for each 'yes' response and zero points are assigned for a 'no' response. A lower score indicates better QoL. The purpose of the ASQoL in these studies was to assess disease specific QoL.
BASDAI	Consists of a 0 through 10 scale (1 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS: 1. Fatigue 2. Spinal pain 3. Joint pain / swelling 4. Areas of localised tenderness (called enthesitis, or inflammation of tendons and ligaments) 5. Morning stiffness duration 6. Morning stiffness severity To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness was taken. The resulting 0 to 10 score was added to the score for questions 1 through 4. The resulting 0 to 50 score was divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrolment in clinical trials evaluating new drug therapies directed at AS.
BASDAI 50 - measure of BASDAI	An improvement i.e. decrease of at least 50% in the BASDAI score compared to baseline.[170]
BASFI	Set of 10 questions designed (with input from patients with AS) to determine the degree of functional limitation in AS patients. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 0 through 10 scale captured as a continuous VAS) is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.
BASMI	Validated instrument that uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters included were: lateral spinal flexion; tragus to wall distance; lumbar flexion (modified

	Schober); maximal intermalleolar distance and cervical rotation angle. Assessments were also taken of chest expansion and occiput-to-wall distance.
ESR	Changes from baseline in ESR. Helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy.
EQ-5D[171]	The measure is divided into two distinct sections. The first section includes a questionnaire addressing five dimensions of quality of life (mobility, self-care, usual activity, pain/discomfort and anxiety/depression). The second section measures self-rated global health status utilising a vertically oriented visual analogue scale (VAS), where 100 represents the "best possible health state" and 0 represents the "worst possible health state". The EQ-5D is designed to assess health status in terms of a single index value, which is obtained by transforming the responses to the questionnaire into a scale utility score. Overall scores typically range from 0 to 1, with lower scores representing a higher level of dysfunction.
FACIT-Fatigue[172,173]	The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue© in these studies was to assess the impact of fatigue on patients with AS.
hs-CRP levels	hsCRP levels were measured to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Changes from baseline in hsCRP were expressed as a ratio of post-baseline to baseline values. With the ratio normalised to 1.0 at baseline, ratios less than 1.0 represent decreased post-baseline values, whereas ratios greater than 1.0 represent increased post-baseline values.
MASES (Expanded)[174]	Measure of enthesitis, including assessment of 13 enthesitis sites.
mSASSS[175]	Radiographic scoring method which assesses cervical, thoracic and lumbar spine regions for damage associated with AS.
Patient's global assessment of disease activity (VAS)	Patient self-assessment performed using a 100 mm VAS ranging from not severe to very severe, after the question "How active was your disease on average during the last week?"
SF-36	Widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health The purpose of the SF-36 in these studies was to assess the HRQoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, was used
WPAI-GH	The WPAI-GH questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as impairments in unpaid activity because of health problems during the past seven days.
44-joint count	Forty four pre-specified joints were assessed for tenderness and swelling.

Abbreviations: AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; EQ-5D, EuroQol-5D; ESR, erythrocyte sedimentation rate; FACIT, Functional Assessment of Chronic Illness Therapy; (HR)QoL, (health-related) quality of life; hs-CRP, high-sensitivity C-reactive protein; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; SF-36, Medical Outcome Short Form Survey-36; VAS, visual analogue scale; WPAI-GH, Work Productivity and Activity Impairment - General Health.

In both MEASURE 2 and MEASURE 1 the overall safety and tolerability of secukinumab was assessed as a secondary outcome. All blood draws and safety assessments were done prior to trial treatment administration. Appropriate safety assessments (e.g. evaluation of adverse events (AEs) and serious AEs (SAEs)) were repeated after the dose was administered. Further details of the safety assessments used in both trials are presented in Appendix E.

As part of the safety assessments the following laboratory parameters were analysed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, haemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG).

4.4. Statistical analysis and definition of study groups in the relevant randomised controlled trials

Four analysis sets, with identical definitions, were used both in MEASURE 2 and MEASURE 1 trials, as described below:

- **Randomised set**. The randomised set comprised all patients that were randomised. Mis-randomised patients were excluded from the randomised set. Mis-randomised patients were defined as those patients who were mistakenly randomised into the interactive voice response (IVR) prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomised patients were treated as screen failures.
- **Full analysis set (FAS)**. The FAS comprised of all patients from the randomised set to whom study treatment was assigned. Following the intention to treat (ITT) principle, patients were evaluated according to the treatment assigned at randomisation.
- **Safety set**. The safety set included all patients who took at least one dose of study treatment during the treatment period. Patients were evaluated according to treatment received.
- **Per-protocol set**. The per-protocol set included all patients who completed the study without a major protocol deviation. The set of criteria which excluded patients from the per-protocol set is described below:
    - Patient not exposed to any study drug at any visit
    - Patient does not meet the BASDAI criteria at baseline
    - Patient with previous exposure to secukinumab or biologic directly targeting IL-17A or IL-17A receptor
    - Incorrect study medication pack given
    - Methotrexate dose not stable during the study up to Week 16
    - Blind broken without safety issue
    - Study treatment administered to patient by unblinded site personnel (reported for MEASURE 1)

The details of the statistical tests used in the primary analysis in both MEASURE 2 and MEASURE 1 are shown in Table 14.

Table 14: Summary of statistical analyses of the primary outcome in MEASURE 2 and MEASURE 1

	MEASURE 2	MEASURE 1
Hypothesis objective	• The analysis of the primary efficacy variable was based on the FAS patients. • The statistical hypothesis for ASAS20 being tested was as follows: there was no difference in the proportion of patients fulfilling the ASAS20 criteria at Week 16 in any of the secukinumab regimens versus placebo regimen.	
Statistical analysis	• The primary analysis was conducted via logistic regression with treatment and TNFα inhibitor status as factors and baseline weight as a covariate. Odds ratios and 95% CI were presented comparing each secukinumab regimen to placebo. • In order to support the robustness of the results obtained by the logistic regression model, the primary endpoint was also evaluated using a non-parametric ANCOVA model with the same independent variables as the logistic regression model. • Interactions between treatment and selected baseline demographics and disease characteristics were explored. • The impact of missing data on the analysis results of ASAS20 response was assessed by repeating the logistic regression model using different ways to handle missing data, including multiple imputation and observed data analysis.	
Sample size, power calculation	An overall type I error (2-sided) 5% was used to control type I error. Since two secukinumab doses were tested versus placebo with respect to the primary endpoint, the type I error was split to 2.5% two-sided for each comparison. For 90% power and assuming a response rate of 20% in the placebo group, at least 39 patients per group were needed to show a response rate of 60% in the secukinumab groups based on Fisher's exact test.	
	In order to collect additional safety information on the use of secukinumab in this population, 222 patients were equally allocated to three treatment groups (74 patients in each treatment group), stratifying for prior treatment or not with TNFα inhibitor. The trial had at least 60% TNFα inhibitor treatment naive patients. The power of the test for the primary endpoint based on 74 patients per group was over 99%.	In order to collect additional safety information on the use of secukinumab in this population, 348 patients were planned to be equally allocated to 3 treatment groups (116 patients in each treatment group), stratifying for prior treatment or not with TNFα inhibitor. The trial was planned to have at least 70% TNFα inhibitor-naïve patients. The power of the test for the primary endpoint was 99%.
Data management, patient withdrawals	• Missing data for ASAS20 (as well as for ASAS40 response and other binary efficacy variables) was handled based on a three tiered approach of drop-outs, complete missing data and partial missing data. Data up to Week 52 were handled as follows: ○ Patients who dropped out of the trial for any reason were considered non-responders from the time they drop out through Week 52. ○ Patients who did not have the required data to compute response (e.g. ASAS components) at baseline and at the specific timepoint were classified as non-responders. • Patients who were unblinded prior to the scheduled timepoint were considered non-responders from the time of unblinding up to Week 16 in MEASURE 2, and up to Week 24 in MEASURE 1. The primary analysis used the non-responder imputation, which considers patients that discontinue the trial to be non-responders and in doing so provides a conservative estimate of the response. • Continuous variables (e.g. ASAS components) were analysed using a mixed-effects model repeated measures (MMRM) which was valid under the missing at random (MAR) assumption. For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed and this subject was removed from the analysis of the corresponding variable, i.e. it	

	might be that the number of patients providing data to an analysis was smaller than the number of patients in the FAS. • Data reported during the long-term treatment phase of the studies (i.e. beyond Week 52) were reported as 'observed' data, i.e. using all available data from patients at each timepoint.

Abbreviations: ASAS, Assessments in Spondyloarthritis International Society; CI, confidence interval; FAS, full analysis set; MAR, missing at random; MMRM, mixed-effects model repeated measures; TNFα, tumour necrosis factor alpha.
Source: MEASURE 2 Clinical Study Report[25], MEASURE 1 Clinical Study Report[24].

4.5. Participant flow in the relevant randomised controlled trials

CONSORT diagrams for participant flow through the MEASURE 2 and MEASURE 1 studies are presented in Figure 7 and Figure 9, respectively.

4.5.1. Study treatment discontinuation

In both MEASURE 2 and MEASURE 1, study treatment was discontinued if the investigator determined that continuation of study treatment would result in a significant safety risk for a subject. Study treatment discontinuation was required upon withdrawal of informed consent, emergence of specified adverse events, laboratory abnormalities, pregnancy, use of biologic immunomodulating agents (other than secukinumab) or protocol deviations presenting a risk to the patient's safety.

In addition to these requirements for study treatment discontinuation, the investigator was required to discontinue study treatment for a given subject if there was a lack of improvement or worsening of their symptoms, or if on balance, he/she thought that continuation would be detrimental to the subject's well-being.

Patients could also voluntarily withdraw from the trial for any reason at any time. They were considered withdrawn if they stated an intention to withdraw, failed to return for visits, or became lost to follow-up for any other reason.

4.5.2. Treatment arm crossover

In both studies, subjects in the placebo arm were reassigned to receive active treatment after reaching the primary endpoint at Week 16.

In MEASURE 2, subjects randomised to the placebo arm at baseline were re-randomised at Week 16 in a ratio of 1:1 to receive either 75 mg secukinumab plus 150 mg placebo or 150 mg secukinumab plus 75 mg placebo, every 4 weeks up to 256 weeks.

In MEASURE 1, subjects were assessed for efficacy using the ASAS20 improvement criteria at Week 16 and re-randomised as follows:

- Subjects in the placebo arm who failed to show a response based on ASAS20 (non-responders) were re-randomised in a ratio of 1:1 to receive either 75 or 150 mg secukinumab, every 4 weeks.
- Subjects in the placebo arm who demonstrated an ASAS20 response at Week 16 (responders) remained on placebo at Weeks 16 and 20. At Week 24, these subjects were re-randomised in a 1:1 ratio to receive either 75 or 150 mg secukinumab, every 4 weeks, regardless of responder status.

4.5.3. MEASURE 2 patient flow

In MEASURE 2, a total of 219 out of 253 patients completed the screening phase and were randomised in a ratio of 1:1:1 to the three treatment arms: secukinumab 75 mg n=73; secukinumab 150 mg n=72; placebo n=74.

Of those randomised to receive 75 mg and 150 mg secukinumab, 68/73 (93.2%) and 66/72 (91.7%) of patients, respectively, completed study treatment to the primary endpoint at Week 16. In the placebo arm, 66/74 (89.2%) of patients completed to Week 16. The most common reason

for premature discontinuation of the 19 patients between Week 1 and Week 16 was the occurrence of adverse events, which were reported with a similar frequency in placebo [4/74 (5.4%)] and secukinumab arms [pooled] [7/145 (4.8%)].

At Week 16, the 66 patients that completed placebo arm treatment up to Week 16 were re-randomised in a ratio of 1:1 to receive either 75 mg secukinumab (n=32) or 150 mg secukinumab (n=34), every 4 weeks.

A total of 181 patients out of the 219 (82.6%) that were originally randomised at baseline completed treatment up to Week 52, of which 174 patients completed up to Week 104. Of those patients originally randomised to received secukinumab 75 mg and 150 mg, 60/73 (82.2%) and 61/72 (84.7%) completed study treatment to Week 52, respectively. By Week 104, 57/73 (78.1%) and 60/72 (83.3%) of patients assigned to receive secukinumab 75 mg and 150 mg had completed. For those patients originally assigned to receive placebo, 60/74 (89.2%) completed to Week 52 and 57/74 (77.0%) completed to Week 104.

Discontinuations were reported at a similar frequency in each treatment arm: 13/73 (17.8%), 11/72 (15.3%) and 14/74 (18.9%) in the 75 mg secukinumab, 150 mg secukinumab and placebo arms, respectively. The most common reason for premature discontinuation between Week 1 and Week 52 was the occurrence of adverse events, which occurred at a similar frequency in the placebo [4/74 (5.4%)] arms and the secukinumab arms [pooled] [9/145 (6.2%)]. Between Week 52 and Week 104, 16/73 (21.9%) and 12/72 (16.7%) of patients assigned to secukinumab 75 mg and 150 mg discontinued treatment respectively, with the most common reasons for discontinuation being subject guardian decision [7/73 (9.6%)] in the secukinumab 75 mg arm and adverse events [6/774 (8.3%)] in the secukinumab 150 mg arm.

Full details of patient flow, including reasons for discontinuation, are provided in Figure 7 below.

Figure 7. CONSORT 2010 participant flow diagram for MEASURE 2

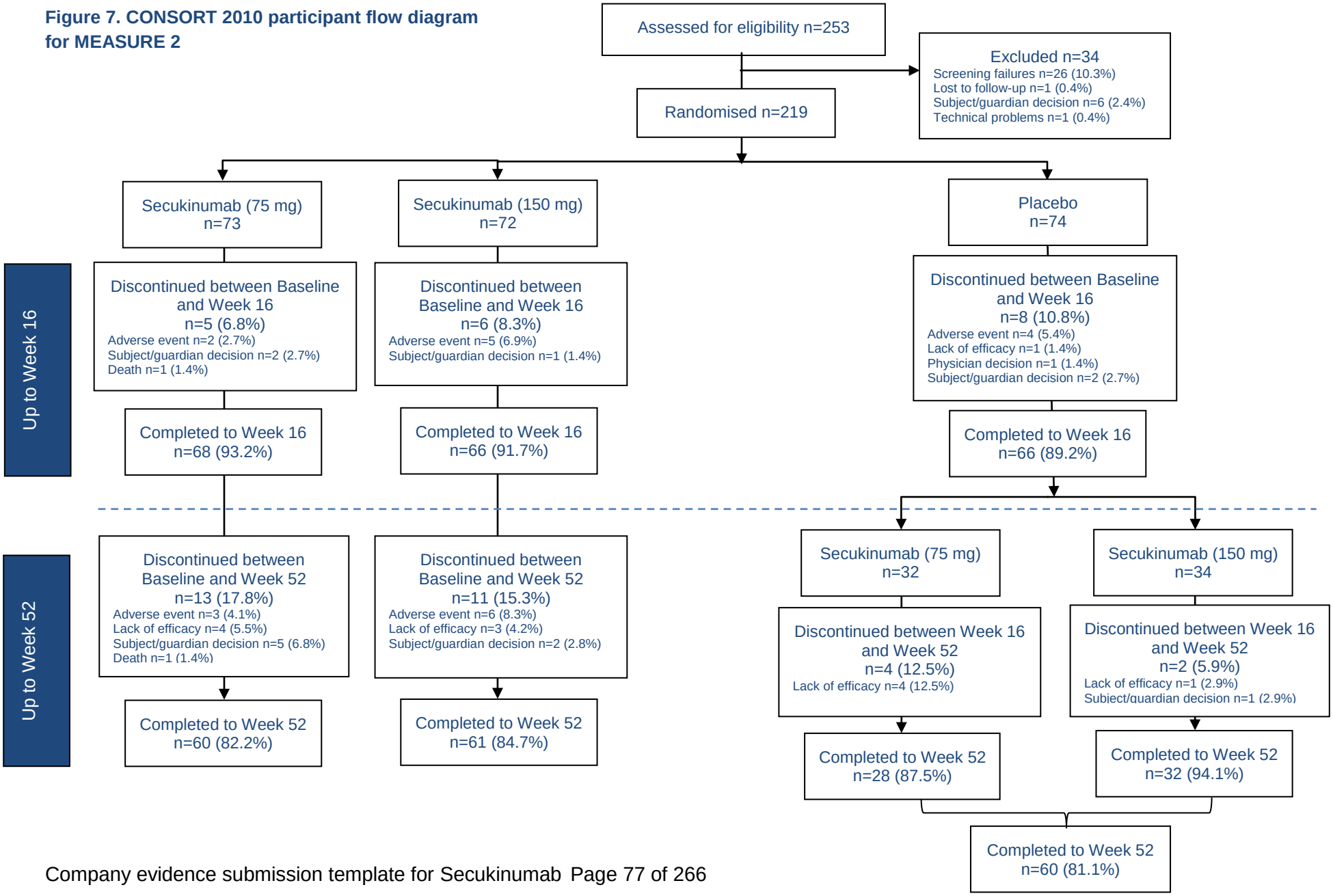
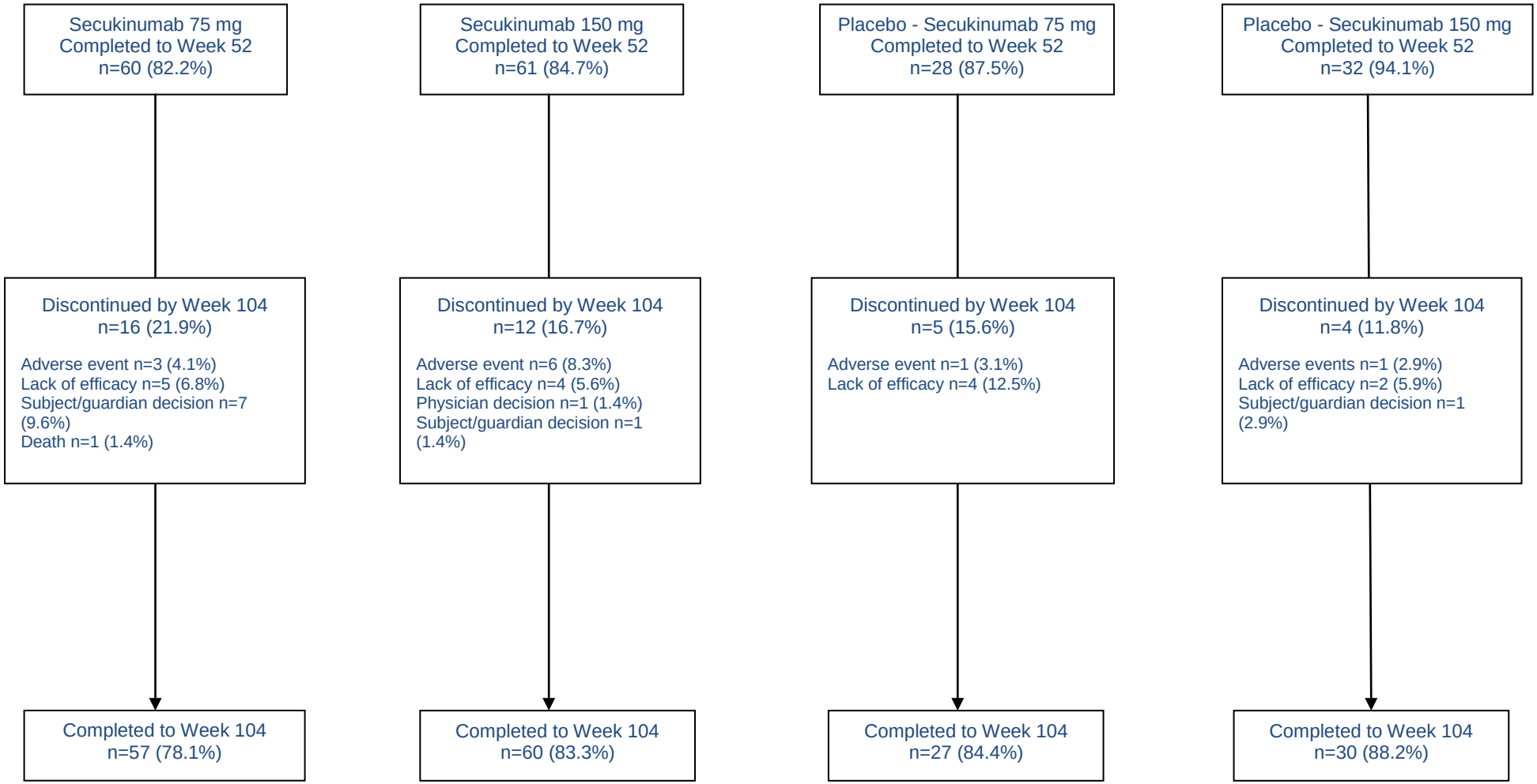


Figure 8. CONSORT 2010 participant flow diagram for MEASURE 2 - Week 52 to Week 104



4.5.4. MEASURE 1 patient flow

In MEASURE 1, a total of 371 out of 448 patients completed the screening phase and were randomised in a ratio of 1:1:1 to the three treatment arms: secukinumab 75 mg n=124; secukinumab 150 mg n=125; placebo n=122.

Of the 122 patients randomised to the placebo arm at baseline, 10 discontinued prior to Week 16 whilst on placebo treatment. Following the Week 16 primary endpoint, 77 patients in the placebo arm were classified as non-responders and were re-randomised 1:1 to receive either secukinumab 75 mg (n=39) or secukinumab 150 mg (n=38). The 35 patients in the placebo arm classified as responders at Week 16 remained on placebo treatment up to Week 24 at which point they were re-randomised 1:1 to receive either secukinumab 75 mg (n=17) or secukinumab 150 mg (n=18), regardless of responder status.

A total of 319 patients out of the 371 that were originally randomised at baseline completed treatment up to Week 52, of which 290 then completed treatment up to Week 104. Of those randomised to receive secukinumab 75 mg and 150 mg, 111/124 (89.5%) and 106/125 (84.8%) of patients, respectively, completed study treatment to Week 52; 103/124 (83.1%) of secukinumab 75 mg patients and 97/125 (77.6%) of secukinumab 150 mg patients completed treatment to Week 104. Of those originally randomised to the placebo arm at baseline, 102/122 (83.6%) of patients completed the trial up to Week 52 and 90/122 (73.8%) completed study treatment until Week 104.

Of the 77 non-responders in the placebo arm re-randomised at Week 16, 9/77 (11.7%) patients (5 receiving secukinumab 75 mg and 4 receiving secukinumab 150 mg) discontinued between Weeks 16 and 52; 19/77 (24.6%) patients (7 secukinumab 75 mg and 12 secukinumab 150 mg) had discontinued by Week 104. In the placebo-responder arm (n=35), one subject discontinued whilst on placebo at Week 20, and, following re-randomisation at Week 24, 2/35 (5.7%) patients discontinued between Week 24 and Week 104, one from each of the secukinumab 75 mg and 150 mg groups.

The most common reason for premature discontinuation was the occurrence of adverse events, which were reported at a similar frequency in the placebo arm [11/122 (9.0%)], secukinumab 75 mg arm [6/124 (4.8%)] and secukinumab 150 mg arm [11/125 (8.8%)] by Week 104. The proportion of discontinuations due to the lack of efficacy or due to subject/guardian decision were also comparable across treatment groups.

Full details of patient flow, including reasons for discontinuation, are provided in Figure 9 below.

Figure 9. CONSORT 2010 participant flow diagram for MEASURE 1

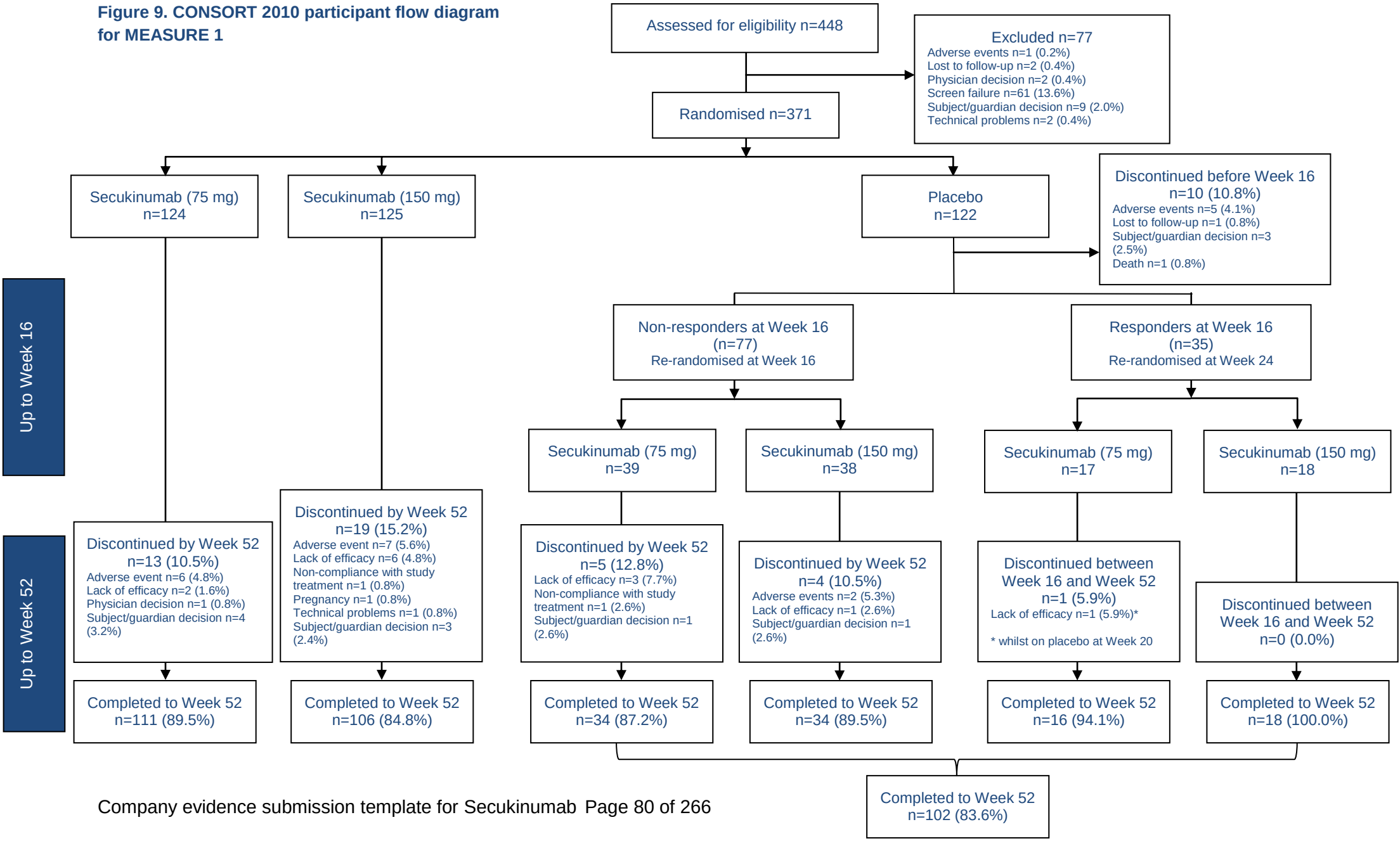
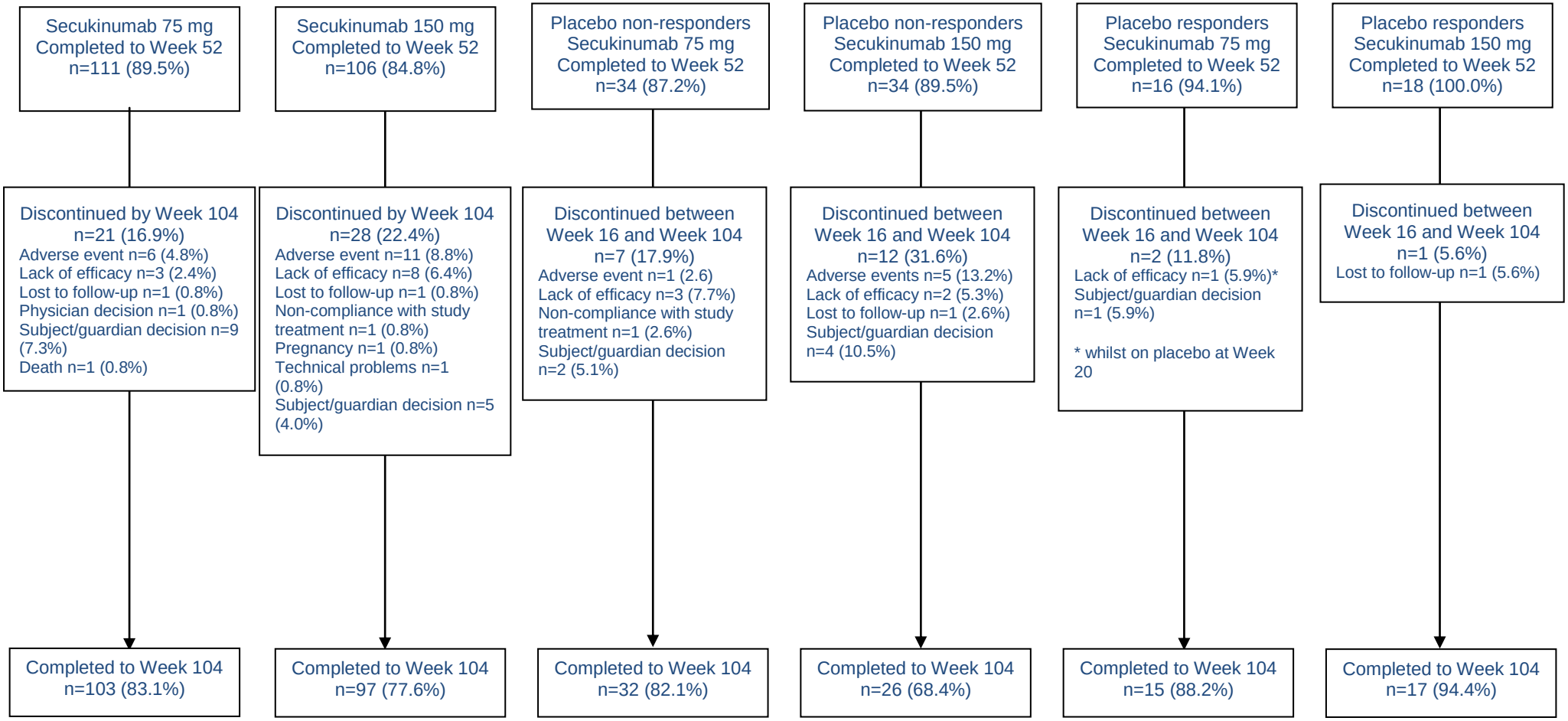


Figure 10. CONSORT 2010 participant flow diagram for MEASURE 1 - Week 52 to Week 104



4.5.5. Baseline characteristics

Key baseline characteristics of eligible subjects (in the randomised set) who participated in MEASURE 2 and MEASURE 1 trials are presented in Table 15. Within the respective trials, treatment groups were broadly similar across baseline characteristics and were representative of populations with active AS.

Additional baseline characteristics are presented in Appendix E.

Table 15: Baseline characteristics of participants in MEASURE 2 and MEASURE 1 across treatment groups

Baseline characteristic	MEASURE 2		MEASURE 1	
	Secukinumab 150 mg (N=72)[a]	Placebo (N=74)[a]	Secukinumab 150 mg (N=125)[a]	Placebo (N=122)[a]
Age (Years)				
Mean	41.9	43.6	40.1	43.1
SD	12.48	13.17	11.61	12.44
Gender, n (%)				
Female	26 (36.1)	18 (24.3)	41 (32.8)	37 (30.3)
Male	46 (63.9)	56 (75.7)	84 (67.2)	85 (69.7)
Race, n (%)				
White	69 (95.8)	70 (94.6)	69 (55.2)	81 (66.4)
Black or African American	NR	NR	0 (0.0)	1 (0.8)
Asian	2 (2.8)	4 (5.4)	21 (16.8)	19 (15.6)
American Indian or Alaska Native	1 (1.4)	0 (0.0)	8 (6.4)	3 (2.5)
Native Hawaiian or other Pacific Islander	NR	NR	0 (0.0)	1 (0.8)
Other	NR	NR	27 (21.6)	17 (13.9)
Height (cm)				
N	72	73	125	122
Mean	173.36	172.13	168.11	170.21
SD	8.840	9.294	9.575	8.811
Weight (kg)				
Mean	82.3	80.3	74.65	76.69
SD	18.0	15.2	16.156	14.409
Current smoker at baseline, n (%)				
No	51 (70.8)	44 (59.5)	90 (72.0)	91 (74.6)
Yes	21 (29.2)	30 (40.5)	35 (28.0)	31 (25.4)
Patient's global assessment of disease activity (0-100 mm)				
Mean	67.5	70.5	64.0	66.3
SD	16.84	15.75	19.42	18.59
Total back pain (0-100 mm)				
Mean	66.2	69.2	64.0	66.7
SD	16.7	18.8	18.56	16.45

Nocturnal back pain (0-100 mm)				
Mean	65.9	64.0	60.8	65.3
SD	17.15	21.76	20.04	18.30
BASFI				
N	72	73	125	122
Mean	6.22	6.10	5.64	5.82
SD	2.133	2.007	2.211	2.034
BASDAI				
Mean	6.6	6.8	6.4	6.5
SD	1.5	1.3	1.576	1.533
BASMI (linear)				
N	71	70	120	119
Mean	3.61	3.91	3.91	4.07
SD	1.937	1.622	1.785	1.579
MASES				
N	72	74	125	122
Mean	4.04	3.70	4.02	4.17
SD	4.085	3.659	4.029	4.109
hs C-reactive protein (mg/L)				
N	72	74	125	121
Mean	25.80	15.71	17.04	16.91
SD	50.088	18.498	22.246	22.305
Erythrocyte sedimentation rate (mm/h)				
N	72	74	124	121
Mean	33.9	29.5	33.7	31.2
SD	24.76	17.76	26.02	24.25
HLA-B27				
Negative	12 (16.7)	11 (14.9)	32 (25.6)	21 (17.2)
Positive	57 (79.2)	58 (78.4)	86 (68.8)	90 (73.8)
Intermediate	NR	NR	2 (1.6)	0 (0.0)
Missing	3 (4.2)	5 (6.8)	5 (4.0)	11 (9.0)
Naïve to TNFα inhibitors				
No	28 (38.9)	29 (39.2)	33 (26.4)	33 (27.0)
Yes	44 (61.1)	45 (60.8)	92 (73.6)	89 (73.0)
Number of prior TNFα inhibitors				
=0	44 (61.1)	45 (60.8)	92 (73.6)	89 (73.0)
=1	27 (37.5)	29 (39.2)	30 (24.0)	33 (27.0)
≥2	1 (1.4)	0 (0.0)	3 (2.4)	0 (0.0)
Time since first diagnosis of AS (years)				
N	70	73	125	122
Mean	7.0	6.4	6.538	8.339
SD	8.2	8.9	6.9313	8.8589
Median	3.781	2.779	4.090	5.844

Min – Max	0.00 - 32.70	0.00 - 37.89	0.00 - 32.65	0.00 - 47.18
Methotrexate use at randomisation				
No	64 (88.9)	65 (87.8)	108 (86.4)	106 (86.9)
Yes	8 (11.1)	9 (12.2)	17 (13.6)	16 (13.1)
Sulfasalazine use at randomisation				
No	62 (86.1)	65 (87.8)	83 (66.4)	80 (65.6)
Yes	10 (13.9)	9 (12.2)	42 (33.6)	42 (34.4)
Corticosteroid use at randomisation				
No	68 (94.4)	67 (90.5)	106 (84.8)	106 (86.9)
Yes	4 (5.6)	7 (9.5)	19 (15.2)	16 (13.1)
NSAID intake, n (%)				
Number of patients with NSAID score >0	63 (87.5)	64 (86.5)	NR	NR
NSAID score				
Mean	81.68	66.64	NR	NR
SD	49.624	42.307	NR	NR

* Corticosteroid doses are presented in prednisone equivalent doses; aUnless otherwise stated, N corresponds to the total N numbers provide in the table header row.
Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; HLA(-B27), human leukocyte antigen(-B27); hs (C reactive protein), high-sensitivity (C reactive protein); MASES, Maastricht ankylosing spondylitis enthesitis score; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; TNF, tumour necrosis factor
Source: MEASURE 2 Clinical Study Report[25] and MEASURE 1 Clinical Study Report[24]

4.6. Quality assessment of the relevant randomised controlled trials

An overview of the quality assessment of the MEASURE 2 and MEASURE 1 trials is provided in Table 16. Full quality assessments of MEASURE 2 and MEASURE 1 are provided in Appendix C.

Table 16: Quality assessment results for MEASURE 2 and MEASURE 1

	MEASURE 2	MEASURE 1
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

4.7. Clinical effectiveness results of the relevant randomised controlled trials

The primary outcome objective of both MEASURE 2 and MEASURE 1 was response to treatment according to the ASAS20 criteria at the primary endpoint of Week 16.[31, 32] As a secondary outcome, ASAS20 response was subsequently monitored at the secondary endpoints of Week 52 and Week 104.

In both MEASURE 2 and MEASURE 1 trials, subjects in the placebo arm were reassigned to receive active treatment after reaching the primary endpoint at Week 16. For further details please see Section 4.5.2.

Both trials also assessed the clinical efficacy of secukinumab 150 mg using a number of additional secondary and exploratory outcomes, as described in Section 4.3.3. In addition to ASAS20, the following outcomes are considered of particular clinical relevance and are presented in the main body of this submission:

- Proportion of patients achieving ASAS40 response
- BASDAI change from baseline
- Proportion of patients achieving BASDAI 50 response
- BASFI change from baseline
- ASQoL change from baseline
- Radiographic outcomes (MEASURE 1 only):
    - Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS; radiography scoring) after 2 years of treatment
    - MRI of spine and sacroiliac joints at Week 16, 1 year and 2 years (in TNFα inhibitor naïve patients and at selected clinical sites only)

The results of additional efficacy and quality of life outcomes are presented in Appendix F (MEASURE 2) and Appendix G (MEASURE 1).

Results from patients in the MEASURE 2 and MEASURE 1 trials who received the maintenance dosing regimen of secukinumab 150 mg are considered relevant to this submission and thus are presented below. Data from patients who received the lower unlicensed dose of 75 mg are not shown.

4.7.1. MEASURE 2

4.7.1.1. Primary outcome: ASAS20

ASAS20 is a common primary efficacy outcome in both AS clinical trials and NICE technology appraisals.[19, 37, 38] Furthermore, ASAS20 is recommended by both BSR and EMA guidelines, while the ASAS criteria more broadly are the recommended method of disease monitoring in AS according to ASAS/EULAR guidelines.[39, 86, 176] ASAS20 captures multiple aspects of AS, such as physical function and spinal pain, and is therefore relevant to the way the disease is treated in clinical practice.[39, 167]

Secukinumab 150 mg was statistically superior to placebo in the primary outcome of ASAS20 response at Week 16

In MEASURE 2, secukinumab 150 mg was statistically superior to placebo in the proportion of patients achieving an ASAS20 response at Week 16 and as such, the primary outcome objective was met. The results presented in Table 17 below are based on the FAS using non-responder imputation, which provides a conservative estimate of the response (please see Section 4.4).

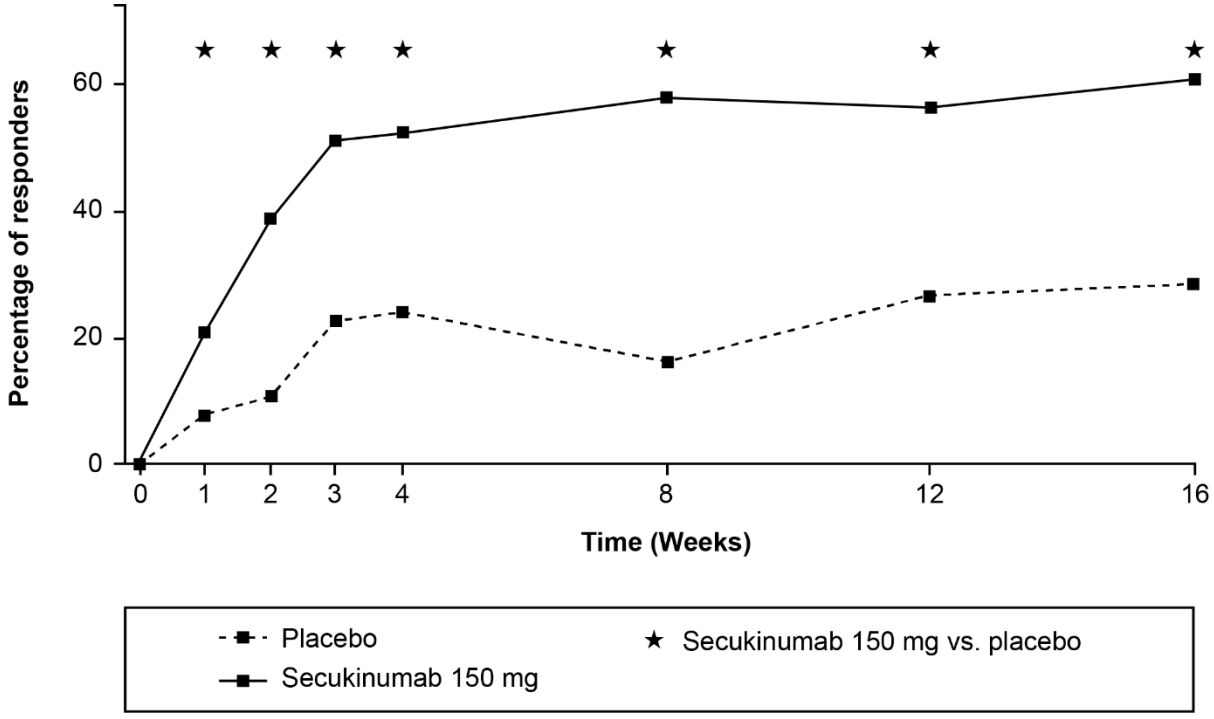
Table 17: ASAS20 response at Week 16 using non-responder imputation (full analysis set)

Treatment group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted
Secukinumab 150 mg (N=72)	44/72 (61.1)	Placebo	4.38	(2.14, 8.96)	<0.0001*
Placebo (N=74)	21/74 (28.4)	NA	NA	NA	NA

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders); *p<0.05.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015[14], Secukinumab European Public Assessment Report.[178]

The ASAS20 response was achieved rapidly with clinically meaningful and statistically significant differences demonstrated between placebo and secukinumab 150 mg as early as Week 1 and sustained up until the primary endpoint at Week 16 (Figure 11).

Figure 11. ASAS20 response up to Week 16 using non-responder imputation (full analysis set)

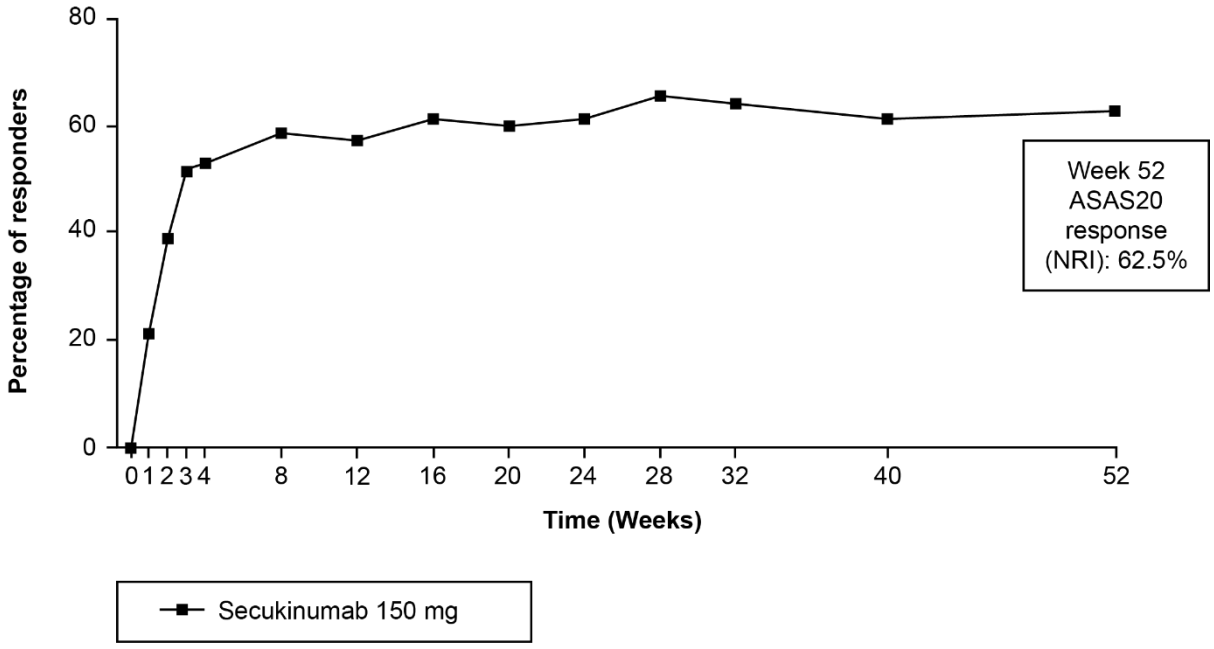


*p<0.05, unadjusted.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

Proportion of patients achieving ASAS20 at longer term follow-up: Week 52 and 104

In order to assess the long term ASAS20 response to secukinumab 150 mg, patients were monitored up to Week 104 and assessed at the secondary endpoints of Week 52 and 104. Non-responder imputation was used to assess data up to Week 52 and is presented in Figure 12 below. Importantly, the high rates of ASAS20 response observed for secukinumab 150 mg at Week 16 were consistently sustained through to Week 52.

Figure 12. ASAS20 response up to Week 52 using non-responder imputation (full analysis set)



Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

The data reported at Week 52 and Week 104 were reported as observed data, i.e. using all available data from patients at each timepoint, and the results are presented in Table 18 below.

Table 18: ASAS20 response at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104
	n/M (%)	n/M (%)
Secukinumab 150 mg (N=72)	45/61 (73.8)	[redacted]
Placebo - secukinumab 150 mg (N=34)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[15, 25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

4.7.1.2. Additional outcomes of particular clinical relevance

ASAS40

ASAS40 is more stringent than ASAS20, with the same requirements but the exception that the improvement in at least three of the main assessment domains must be at least 40%. ASAS40 is increasingly being recognised as a common outcome measure for AS. Furthermore, EMA guidelines note that ASAS40 has been already used in several trials and may be considered an appropriate primary efficacy endpoint to assess major clinical response.[176] The assessment of

ASAS40 in both MEASURE 2 and MEASURE 1 as a secondary outcome is therefore highly relevant to clinical practice and current treatment approaches, as confirmed by expert clinical opinion.[43]

Secukinumab 150 mg was statistically superior to placebo achieving an ASAS40 response at Week 16

The proportion of patients achieving an ASAS40 response at Week 16 in the secukinumab 150 mg arm was statistically superior compared with placebo (Table 19).

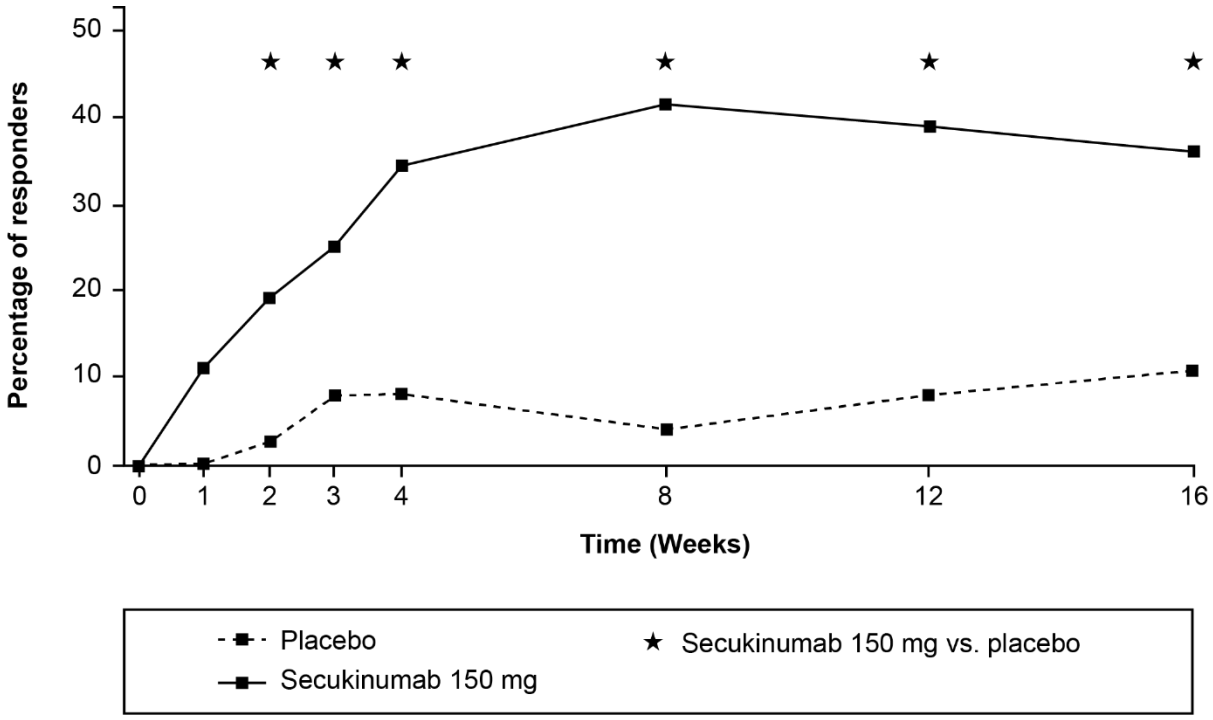
Table 19: ASAS40 response at Week 16 using non-responder imputation (full analysis set)

Treatment group	n/M (%)	p-value, adjusted
Secukinumab 150 mg (N=72)	26/72 (36.1)	<0.001
Placebo (N=74)	8/74 (10.8)	NA

M=Number of patients in each treatment group; n=Number of ASAS40 responders (missing ASAS responses were considered non-responders); *p<0.05
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

There was a statistically superior ASAS40 response in the secukinumab 150 mg arm compared with placebo observed from Week 2, with a rapid onset of action seen as early as Week 1 (Figure 13). Moreover, this statistically higher response rate was sustained through to Week 16 (all p<0.05).

Figure 13. ASAS40 response up to Week 16 using non-responder imputation (full analysis set)

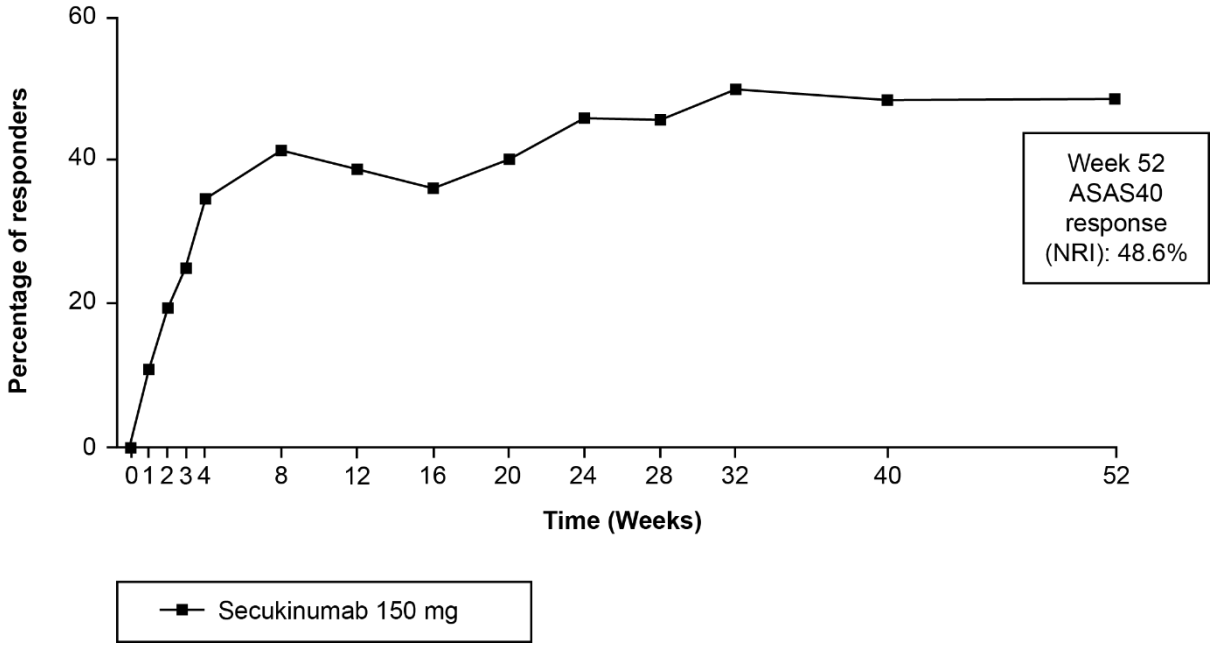


*p<0.05, unadjusted
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

Proportion of patients achieving ASAS40 at longer term follow up: Week 52 and Week 104

In order to assess the long term ASAS40 response to secukinumab 150 mg, patients were monitored up to Week 104 and assessed at the secondary endpoints of Week 52 and 104. Non-responder imputation was used to assess data up to Week 52. The ASAS40 response rates achieved for the secukinumab 150 mg group at the Week 16 endpoint were further improved and sustained through to Week 52, as shown in Figure 14 below.

Figure 14. ASAS40 response up to Week 52 using non-responder imputation (full analysis set)



Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

The data at Week 52 and Week 104 were reported as observed data, i.e. using all available data from patients at each timepoint, and the results are presented in Table 20 below.

Table 20. ASAS40 response at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104
	n/M (%)	n/M (%)
Secukinumab 150 mg (N=72)	35/61 (57.4)	[redacted]
Placebo – secukinumab 150 mg (N=34)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of ASAS40 responders
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 2 Clinical Study Report,[15, 25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

BASDAI

As discussed in Section 4.3.5, BASDAI is a composite index that includes the assessment by patients of their symptoms of pain, discomfort, stiffness and fatigue.[179] It is a widely used measure of disease activity and its changes with treatment should be assessed.[39] Furthermore, BASDAI has been shown to have excellent content validity, whilst still being easy for patients to complete.[179, 180] Results for mean change in BASDAI score from baseline were evaluated using mixed-effect model repeat measures (MMRM).

Secukinumab 150 mg demonstrated statistically superior improvements in BASDAI score from baseline to Week 16 compared with placebo

The mean change in BASDAI score from baseline to Week 16 was statistically superior in the secukinumab 150 mg arm compared with the placebo arm (see Table 21). Secukinumab 150 mg had greater improvements than placebo at all timepoints from Weeks 2 to 16 (all unadjusted p values <0.05), with a rapid onset of action seen by Week 1.

Table 21. BASDAI change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value, adjusted
Secukinumab 150 mg (N=72)	67	-2.19 (0.248)	<0.001*
Placebo (N=74)	64	-0.85 (0.252)	NA

n=Number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error,
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015[14], Secukinumab European Public Assessment Report.[178]

The mean changes in BASDAI score from baseline to Week 52 and Week 104 using observed data are shown in Table 22 below and demonstrate the maintained efficacy of secukinumab throughout the two-year time period.

Table 22. BASDAI change from baseline to Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52		Week 104	
	n	LS mean change (SD)	n	LS mean change (SD)
Secukinumab 150 mg (N=72)	61	-3.14 (2.110)	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=34)	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients with measurements at both baseline and post-baseline visit
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; LS, least squares; SD, standard deviation.
Source: MEASURE 2 Clinical Study Report,[15, 25] Sieper *et al.* 2015,[177] Baeten *et al.* 2015.[14]

BASDAI 50

The BASDAI 50 measure, a 50% reduction in BASDAI score, was suggested as an appropriate treatment outcome by the Assessments in Ankylosing Spondylitis (ASAS) working group.[181] Furthermore, expert clinical opinion has confirmed that BASDAI 50 is increasingly used in clinical practice, and thus these results are highly relevant to current treatment approaches.[43] Thus the percentage of patients achieving BASDAI 50 is considered useful to judge the clinical benefit of a treatments for AS.[180]

Secukinumab 150 mg was statistically superior to placebo in achieving a BASDAI 50 response at Week 16

The proportion of patients achieving a BASDAI 50 response at Week 16 was statistically superior with secukinumab 150 mg compared with placebo (Table 23).

Table 23. BASDAI 50 response at Week 16 using non-responder imputation (full analysis set)

Treatment group	n/M (%)	p-value, unadjusted
Secukinumab 150 mg (N=72)	22/72 (30.6)	<0.01*
Placebo (N=74)	8/74 (10.8)	NA

M=Number of patients in each treatment group; n=Number of BASDAI 50 responders (missing BASDAI 50 responses were considered non-responders); *p<0.05
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable.
Source: MEASURE 2 Clinical Study Report,[25] Braun *et al.* 2015.[140]

The proportion of patients achieving a BASDAI 50 response at Week 16 was subsequently increased at Week 52 and Week 104, as shown using observed data in Table 24.

Table 24. Point estimates for BASDAI 50 at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104
	n/M (%)	n/M (%)
Secukinumab 150 mg (N=72)	30/61 (49.2)	[redacted]
Placebo – secukinumab 150 mg (N=34)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of BASDAI 50 responders
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.
Source: MEASURE 2 Clinical Study Report,[15, 25] Braun *et al.* 2015.[140]

Although the pre-defined exploratory outcome for measurement of response in the MEASURE 2 trial was BASDAI 50, alternative definitions of response may be used in clinical practice; notably, the BSR guidelines define response to treatment as a reduction of BASDAI to 50% of the pre-treatment value or a fall of ≥2 units and reduction of the spinal pain VAS in the last week by ≥2 cm. A post-hoc analysis of individual patient-level data was conducted on the MEASURE 2 trial to explore alternative definitions of response. These results are presented in Appendix H.

BASFI

The BASFI outcome is a measure of physical function and has been found to accord well with patient perception of disease severity, indicating its relevance to clinical practice.[182] Results for mean change in BASFI score from baseline were evaluated using mixed-effect model repeated measures.

Secukinumab 150 mg demonstrated statistically superior improvements in BASFI score from baseline to Week 16 compared with placebo

The mean change in BASFI score from baseline to Week 16 was statistically superior for the secukinumab 150 mg arm compared with the placebo arm, see Table 25 below.

Table 25. BASFI change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value, unadjusted
Secukinumab 150 mg (N=72)	67	-2.15 (0.23)	<0.0001*
Placebo (N=74)	64	-0.68 (0.24)	NA

n=Number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error.
Source: MEASURE 2 Clinical Study Report,[25] Braun *et al.* 2015.[140]

The mean changes in BASFI score from baseline to Week 52 using observed data are shown in Table 26 below. The improvements observed at Week 16 were sustained up to Week 52,

demonstrating the long-term efficacy of secukinumab 150 mg. Week 104 data for this outcome were not included in the interim analysis conducted in November 2015, and as such are not presented below.

Table 26. BASFI change from baseline to Week 52 using observed data (full analysis set)

Treatment group	Week 52	
	n	Mean change (SD)
Secukinumab 150 mg (N=72)	61	-2.97 (2.421)
Placebo – secukinumab 150 mg (N=34)	[redacted]	[redacted]

n=Number of patients with measurements at both baseline and post-baseline visit
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; LS, least squares; SD, standard deviation.
Source: MEASURE 2 Clinical Study Report[25], Braun *et al.* 2015 (EULAR)[140].

4.7.1.3. Quality of life measures

A number of quality of life measures were assessed in MEASURE 2: ASQoL, SF-36, EQ-5D and FACIT-Fatigue. ASQoL is a disease-specific questionnaire, designed to capture the specific and unique aspects of this condition.[169] Furthermore, it has been shown to be well accepted by patients with excellent scaling and psychometric properties. As such, ASQoL is considered of particular relevance and presented below.[169] Additionally, the WPAI-GH measure of impairment in work and activities was also collected in MEASURE 2.

For results of SF-36, EQ-5D, FACIT-Fatigue and WPAI-GH, please Appendix F.

Secukinumab 150 mg demonstrated statistically significant improvements in ASQoL compared with placebo

As shown in Table 27 below, significantly greater improvement in patient quality of life, as measured by the ASQoL questionnaire, was observed with secukinumab 150 mg compared with placebo at Week 16. Thus demonstrating the efficacy of secukinumab and the benefit it confers to patients with respect to their quality of life.

Table 27. ASQoL change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value, adjusted
Secukinumab 150 mg (N=72)	66	-4.00 (0.528)	0.001*
Placebo (N=74)	66	-1.37 (0.530)	NA

n=Number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[142] Baeten *et al.* 2015,[14] Secukinumab European Public Assessment Report.[178]

Results were comparable between secukinumab 150 mg and placebo - secukinumab 150 mg arms by Week 52, as shown in Table 28, using observed data. According to protocol, ASQoL data were not measured beyond Week 52.

Table 28. ASQoL change from baseline to Week 52 using observed data full analysis set)

Treatment group	Week 52	
	n	LS mean change (SD)
Secukinumab 150 mg (N=72)	61	-5.25 (4.530)
Placebo – secukinumab 150 mg (N=34)	[redacted]	[redacted]

n=Number of patients with measurements at both baseline and post-baseline visit
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; LS, least squares; MMRM, mixed-effect model repeated measures; SD, standard deviation.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015,[142] Baeten *et al.* 2015.[14]

4.7.1.4. Overall summary of results

Secukinumab 150 mg was superior to placebo for all primary and secondary endpoints (except for ASAS partial remission) at Week 16. Furthermore, secukinumab 150 mg demonstrated sustained efficacy across all outcomes for up to two years, thus highlighting the long term benefits of this treatment option.

Regarding the primary efficacy variable of MEASURE 2, 61.1% of patients receiving secukinumab 150 mg achieved ASAS20 at Week 16, by comparison to only 28.4% of placebo patients (p<0.0001). Furthermore, the high rates of response in the secukinumab 150 mg treatment arm were sustained up to Week 104. Similar results in the secukinumab 150 mg treatment arm were shown for all other outcomes presented above, including a more stringent measure of response (ASAS40) at Week 16 (secukinumab 150 mg: 36.1%; placebo: 10.8%, p=0.0008) and a well-established measure of disease activity (BASDAI 50) at Week 16 (secukinumab 150 mg: 30.6%; placebo: 10.8%, p=0.004). In addition, the quality of life measure ASQoL indicated that the secukinumab 150 mg group showed significantly greater improvements in quality of life (mean change -4.00 vs. -1.37 in the placebo arm, p=0.001).

Together, the results from MEASURE 2 demonstrate the clinical benefit of secukinumab, both with respect to efficacy and quality of life. The continuation of these benefits when assessed up to Week 104, demonstrates the sustained efficacy across all clinical outcomes and the long term treatment benefit conferred by secukinumab.

4.7.2. MEASURE 1

4.7.2.1. Primary outcome: ASAS20

Secukinumab 150 mg was statistically superior to placebo in the percentage of patients achieving an ASAS20 response at Week 16

In MEASURE 1, secukinumab 150 mg was statistically superior to placebo in the proportion of patients who achieved an ASAS20 response at Week 16, reinforcing the efficacy of secukinumab demonstrated in MEASURE 2 above. The results for the ASAS20 response at Week 16, the primary endpoint, are presented in Table 29 below.

Results for additional efficacy outcomes for MEASURE 1 can be found in Appendix G.

Table 29. ASAS20 response at Week 16 using non-responder imputation (full analysis set)

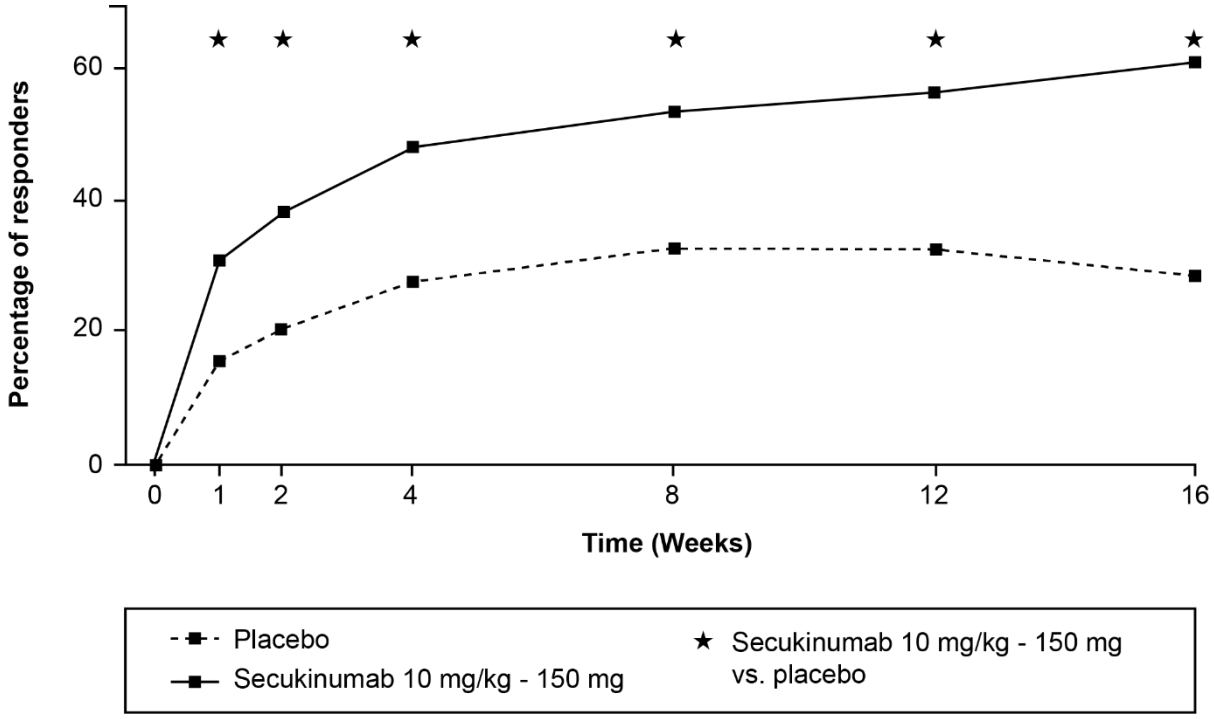
Treatment group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted
Secukinumab 150 mg (N=125)	76/125 (60.8)	Placebo	3.89	(2.28, 6.65)	<0.0001*

Placebo (N=122)	35/122 (28.7)	NA	NA	NA	NA

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders); *p<0.05
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015,[183] Baeten *et al.* 2015,[14] Secukinumab European Public Assessment Report.[178]

Higher and sustained ASAS20 response rates with secukinumab 150 mg compared to placebo were seen at all time-points from Week 1 to Week 24, with a rapid onset of action and statistically significant differences seen as early as Week 1 (Figure 15).

Figure 15. ASAS20 response using non-responder imputation up to Week 16 (full analysis set)



*p<0.05, unadjusted.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015,[183] Baeten *et al.* 2015.[14]

Proportion of patients achieving ASAS20 at longer term follow up: Week 52 and Week 104

The long term ASAS20 response was assessed at the secondary endpoints of Week 52 and 104. Non-responder imputation was used to assess data up to Week 52 and these results are presented in

below. The high rates of ASAS20 response observed for secukinumab 150 mg at Week 16 were consistently sustained through to Week 52.

[redacted]16[redacted]

[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NRI, non-responder imputation.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015,[183] Baeten *et al.* 2015.[14]

Long-term efficacy of secukinumab 150 mg was assessed up to Week 104, and the results for the ASAS20 response at Week 52 and Week 104 using observed data are shown in Table 30 below. High rates of ASAS20 response were maintained throughout this time period, demonstrating the sustained efficacy of secukinumab 150 mg as seen in MEASURE 2.

Table 30. ASAS20 response at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104

	n/M (%)	n/M (%)
Secukinumab 150 mg (N=125)	79/103 (76.7)	69/87 (79.3)
Placebo non-responder - secukinumab 150 mg (N=38)	[redacted]	[redacted]
Placebo responder - secukinumab 150 mg (N=18)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 1 Clinical Study Report[16, 24], Baeten *et al.* 2014[184], Baeten *et al.* 2015[23], Baeten *et al.* 2015[14].

4.7.2.2. Additional outcomes of particular clinical relevance

Secukinumab 150 mg was statistically superior in achieving ASAS40 at Week 16 compared with placebo

The proportion of patients achieving an ASAS40 response at Week 16 was statistically superior for secukinumab 150 mg compared with placebo, hence this secondary outcome objective was met, as shown in Table 31 below.

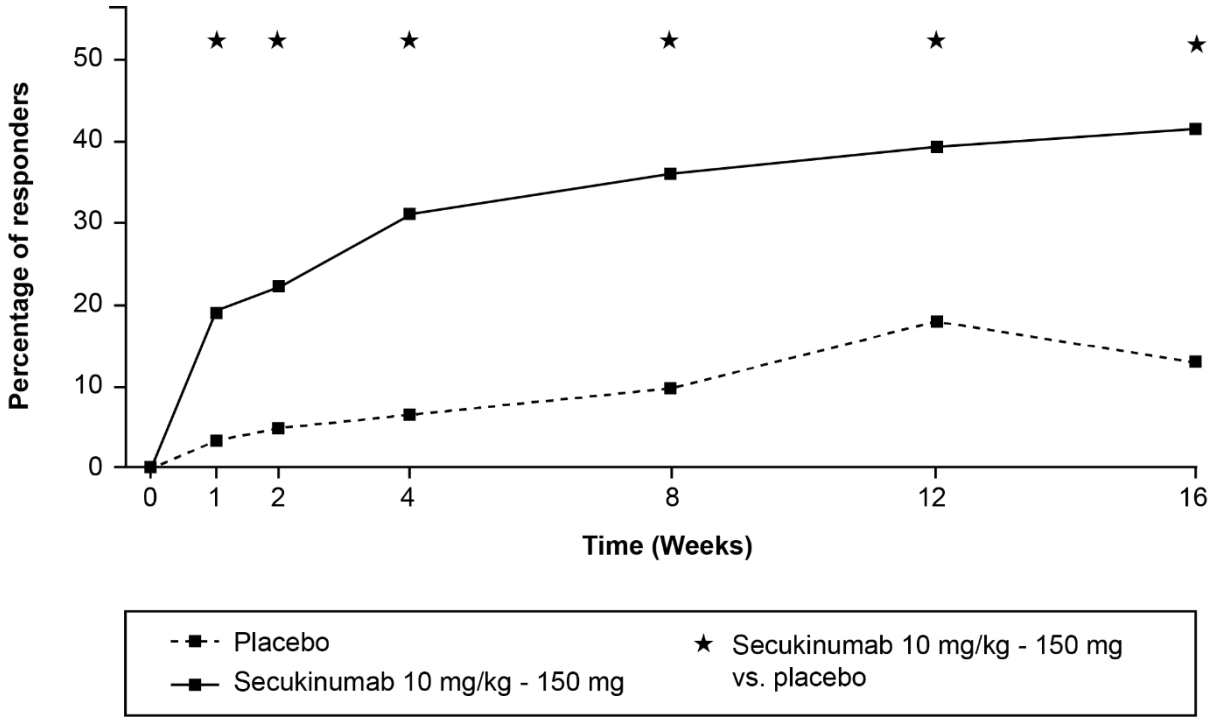
Table 31. ASAS40 response at Week 16 using non-responder imputation (full analysis set)

Treatment group	n/M (%)	p-value
Secukinumab 150 mg (N=125)	52/125 (41.6)	<0.0001*
Placebo (N=122)	16/122 (13.1)	NA

M=Number of patients in each treatment group; n=Number of ASAS40 responders (missing ASAS responses were considered non-responders); *p<0.05
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable.
Source: MEASURE 1 Clinical Study Report[24], Baeten *et al.* 2014[184], Baeten *et al.* 2015[14].

The ASAS40 response for the secukinumab 150 mg arm was superior to placebo at all time-points up to Week 24, with a rapid onset of action seen as early as Week 1 (see Figure 17).

Figure 17. ASAS40 response up to Week 16 using non-responder imputation (full analysis set)



*p<0.05, unadjusted.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2014,[184] Baeten *et al.* 2015.[14]

Proportion of patients achieving ASAS40 at longer term follow up: Week 52 and Week 104

The long term ASAS40 response was assessed at Week 52 and Week 104. Results up to Week 52 using non-responder imputation are shown xxxxxxx18.

[redacted]

[redacted]
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NRI, non-responder imputation.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015.[14]

The proportions of patients achieving an ASAS40 response rate at Week 52 and Week 104 using observed data are shown in Table 32 below, and re-emphasise the long-term efficacy of secukinumab 150 mg as demonstrated in MEASURE 2 above.

Table 32. ASAS40 response at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104
	n/M (%)	n/M (%)
Secukinumab 150 mg (N=125)	64/103 (62.1)	56/87 (64.4)
Placebo non-responder – secukinumab 150 mg (N=38)	[redacted]	[redacted]
Placebo responder – secukinumab 150 mg (N=18)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of ASAS40 responders
Abbreviations: ASAS, assessment of spondyloarthritis international society.
Source: MEASURE 1 Clinical Study Report,[16, 24] Baeten *et al.* 2014,[184] Baeten *et al.* 2015,[23] Baeten *et al.* 2015.[14]

Secukinumab 150 mg demonstrated statistically superior improvements in BASDAI change from baseline to Week 16 compared with placebo

The mean change in BASDAI score from baseline to Week 16 was statistically superior in the secukinumab 150 mg treatment arm compared with the placebo arm, as shown in Table 33 below. Secukinumab 150 mg was superior to placebo at all time-points from Weeks 1 to 16, with a rapid onset of action seen as early as Week 1.

Table 33. BASDAI change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value
Secukinumab 150 mg (N=125)	121	-2.32 (0.172)	<0.0001*
Placebo (N=122)	108	-0.59 (0.180)	NA

n=number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2014,[133] Baeten *et al.* 2015,[14] Secukinumab European Public Assessment Report.[178]

The mean changes in BASDAI score from baseline to Week 52 and Week 104 using observed data are shown in Table 34 below, again demonstrating the sustained efficacy of secukinumab 150 mg.

Table 34. BASDAI change from baseline to Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52		Week 104	
	n	LS mean change (SD)	n	LS mean change (SD)
Secukinumab 150 mg (N=125)	103	-3.19 (2.254)	87	-3.41 (2.12)
Placebo non-responder – secukinumab 150 mg (N=38)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo responder – secukinumab 150 mg (N=18)	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients with measurements at both baseline and post-baseline visit
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; LS, least squares; SD, standard deviation.
Source: MEASURE 1 Clinical Study Report,[16, 24] Baeten *et al.* 2014,[184] Baeten *et al.* 2015,[23] Baeten *et al.* 2015.[14]

Secukinumab 150 mg was statistically superior to placebo in achieving a BASDAI 50 response at Week 16

The proportion of patients achieving a BASDAI 50 response at Week 16 was statistically superior in the secukinumab 150 mg arm compared with placebo, as shown in Table 35 below.

Table 35. BASDAI 50 response at Week 16 using non-responder imputation (full analysis set)

Treatment group	n/M (%)	p-value
Secukinumab 150 mg (N=125)	[redacted]	[redacted]
Placebo (N=122)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of BASDAI 50 responders (missing BASDAI 50 responses were considered non-responders); [redacted]
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable.
Source: MEASURE 1 Clinical Study Report.[24]

The proportion of BASDAI 50 responders at Week 52 and Week 104 using observed data are shown in

Table 36 below. Secukinumab 150 mg demonstrated sustained efficacy of BASDAI 50 response over this 2 year time period.

Table 36. BASDAI 50 response at Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52	Week 104
	n/M (%)	n/M (%)
Secukinumab 150 mg (N=125)	[redacted]	[redacted]
Placebo non-responder – secukinumab 150 mg (N=38)	[redacted]	[redacted]
Placebo responder – secukinumab 150 mg (N=18)	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of BASDAI 50 responders
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.
Source: MEASURE 1 Clinical Study Report.[24]

Although the pre-defined exploratory outcome for measurement of response in the MEASURE 1 trial was BASDAI 50, alternative definitions of response may be used in clinical practice; notably, the BSR guidelines define response to treatment as a reduction of BASDAI to 50% of the pre-treatment value or a fall of ≥2 units and reduction of the spinal pain VAS in the last week by ≥2 cm. A post-hoc analysis of individual patient-level data was conducted on the MEASURE 1 trial to explore alternative definitions of response. These results are presented in Appendix G.

Secukinumab 150 mg demonstrated statistically superior improvements in BASFI change from baseline to Week 16 compared with placebo

The mean change in BASFI score from baseline to Week 16 was statistically superior for the secukinumab 150 mg arm compared with the placebo arm, as shown in Table 37 below.

Table 37. BASFI change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value
Secukinumab 150 mg (N=125)	121	-1.84 (0.17)	<0.0001*
Placebo (N=122)	108	-0.37 (0.17)	NA

n=Number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error.
Source: MEASURE 1 Clinical Study Report[24], Wei *et al.* 2015[137].

The mean changes in BASFI score from baseline to Week 52 and Week 104 are shown in Table 38 below using observed data and demonstrate the sustained effect of secukinumab 150 mg over this two-year time period.

Table 38. BASFI change from baseline to Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52		Week 104	
	n	LS mean change (SD)	n	LS mean change (SD)
Secukinumab 150 mg (N=125)	103	-2.54 (2.241)	[redacted]	[redacted]
Placebo non-responder – secukinumab 150 mg (N=38)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo responder – secukinumab 150 mg (N=18)	[redacted]	[redacted]	[redacted]	[redacted]

n=Number of patients with measurements at both baseline and post-baseline visit
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; LS, least squares; SD, standard deviation.
Source: MEASURE 1 Clinical Study Report[16, 24], Wei *et al.* 2015[137].

4.7.2.3. Quality of life measures

The results of the disease-specific quality of life measure ASQoL are presented below. For results of SF-36, EQ-5D and FACIT-Fatigue, in addition to WPAI-GH, please see Appendix G.

Secukinumab 150 mg demonstrated statistically significant improvements in ASQoL compared with placebo

As shown in Table 39 below, a significantly greater improvement in patient quality of life, as measured by the ASQoL questionnaire, was observed with secukinumab 150 mg than placebo at Week 16. Thus supporting the findings of MEASURE 2 and the benefit secukinumab confers to patients with respect to their quality of life.

Table 39. ASQoL change from baseline to Week 16 using MMRM (full analysis set)

Treatment group	n	LS mean change (SE)	p-value
Secukinumab 150 mg (N=125)	121	-3.58 (0.424)	<0.01*
Placebo (N=122)	111	-1.04 (0.437)	NA

n=Number of patients with measurements at both baseline and post-baseline visit; *p<0.05
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; LS, least squares; MMRM, mixed-effect model repeated measures; NA, not applicable; SE, standard error
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2014,[133] Baeten *et al.* 2015,[14] European Public Assessment Report.[178]

Table 40 demonstrates that improvements to ASQoL in patients treated with secukinumab 150 mg were sustained at 1 and 2 years.

Table 40. ASQoL change from baseline to Week 52 and Week 104 using observed data (full analysis set)

Treatment group	Week 52		Week 104	
	n	LS mean change (SD)	n	LS mean change (SD)
Secukinumab 150 mg (N=125)	[redacted]	[redacted]	86	-4.82 (4.83)
Placebo non-responder – secukinumab 150 mg (N=32)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo responder – secukinumab 150 mg (N=18)	[redacted]	[redacted]	[redacted]	[redacted]

n=Number of patients with measurements at both baseline and post-baseline visit
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; LS, least squares; MMRM, mixed-effect model repeated measures; SD, standard deviation.
Source: MEASURE 1 Clinical Study Report,[16, 24] Baeten *et al.* 2015,[23] Baeten *et al.* 2015.[14]

4.7.2.4. Radiographic outcomes

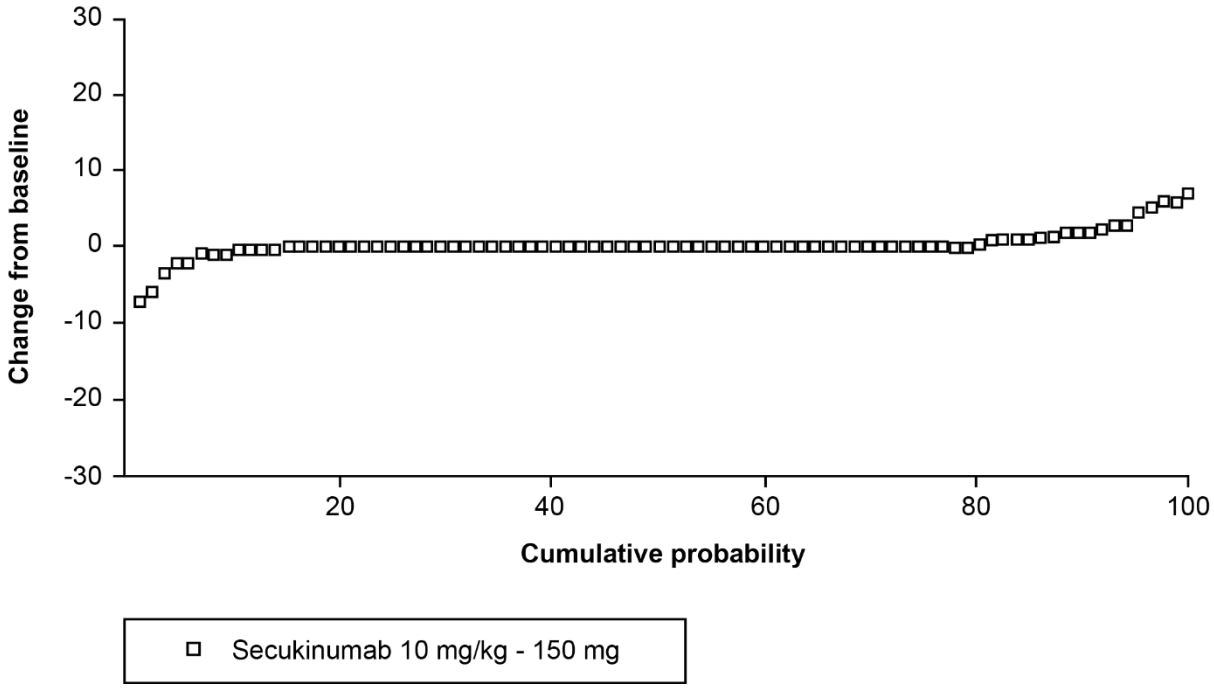
Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS; radiography scoring) after 2 years of treatment

X-rays of the cervical, thoracic and lumbar spine were performed at baseline and Week 104. There were no major differences between the secukinumab 150 mg only and the placebo - secukinumab 150 mg group in terms of mSASSS change from baseline to Week 104. The mean ± SD change in mSASSS from baseline to Week 104 was 0.30 ± 1.93 in the secukinumab 150 mg arm and [redacted] in the placebo-secukinumab 150 mg arm.[16, 183]

No radiographic progression was observed in approximately 80% of patients randomised to secukinumab at baseline (mSASSS change ≤0).[26] A probability plot of radiographic progression as measured by mSASSS is presented in Figure 19.[26]

[redacted]

Figure 19. Probability plot of radiographic progression as measured by mSASSS at 2 years (full analysis set)



Abbreviations: mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.
Source: MEASURE 1 Clinical Study Report,[16] Baraliakos *et al.* 2015.[26]

MRI of spine and sacroiliac joints at Week 16, 1 year and 2 years (in TNFα inhibitor-naïve patients and at selected clinical sites only)

MRI of the spine and sacroiliac joints was performed on a subset of TNFα inhibitor-naïve patients at selected study sites, with analysis of the following 3 MRI scoring systems: Berlin sacroiliac joint total oedema score, total ASspi-MRI-a score, and Berlin spine score.

The reduction from baseline at Week 16 for all 3 MRI scores was numerically larger for patients in the secukinumab 150 mg arm compared with placebo, and for the Berlin sacroiliac joint total oedema score, the reduction from baseline at Week 16 for secukinumab 150 mg was statistically superior to placebo (p<0.01).[184] MRI results at Week 16, Week 52 and Week 104 are shown in Table 41 to Table 43.

Table 41. MRI measurements at baseline, Week 16 and change from baseline (MRI subset of TNFα inhibitor-naïve patients only), using a non-parametric ANCOVA model

MRI variable	n	Baseline (mean ± SD)	Week 16 (mean ± SD)	Change from baseline (mean ± SD)	p-value
Berlin sacroiliac joint total oedema score					
Secukinumab 150 mg (N=38)	32	2.22 ± 3.38	0.92 ± 1.783	−1.30 ± 2.17	<0.01
Placebo (N=33)	26	2.40 ± 3.24	2.23 ± 3.238	−0.17 ± 1.23	NA
Total ASspi-MRI-a score					

Secukinumab 150 mg (N=38)	32	2.70 ± 3.80	1.58 ± 3.869	−1.13 ± 1.68	0.0790
Placebo (N=33)	28	5.73 ± 9.75	5.07 ± 8.600	−0.66 ± 2.55	NA
Berlin spine score					
Secukinumab 150 mg (N=38)	32	2.23 ± 2.83	1.16 ± 2.474	−1.08 ± 1.40	0.0570
Placebo (N=33)	28	4.50 ± 7.62	3.95 ± 6.820	−0.55 ± 2.45	NA

Abbreviations: ASspi-MRI-a, Ankylosing Spondylitis spine MRI score for Activity; MRI, magnetic resonance imagery; NA, not applicable; SD, standard deviation; TNFα, tumour necrosis factor alpha.
Source: MEASURE 1 Clinical Study Report,[24] Baraliakos *et al.* 2015.[136, 185]

Table 42. MRI measurements at baseline, Week 52 and change from baseline (MRI subset of TNFα inhibitor-naïve patients only), using observed data

MRI variable	n	Baseline (mean ± SD)	Week 52 (mean ± SD)	Change from baseline (mean ± SD)
Berlin sacroiliac joint total oedema score				
Secukinumab 150 mg (N=39)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
Total ASspi-MRI-a score				
Secukinumab 150 mg (N=39)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
Berlin spine score				
Secukinumab 150 mg (N=39)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASspi-MRI-a, Ankylosing Spondylitis spine MRI score for Activity; MRI, magnetic resonance imagery; SD, standard deviation; TNFα, tumour necrosis factor alpha.
Source: MEASURE 1 Clinical Study Report.[24]

Table 43. MRI measurements at baseline, Week 104 and change from baseline (MRI subset of TNFα inhibitor-naïve patients only), using observed data

MRI variable	n	Baseline (mean ± SD)	Week 104 (mean ± SD)	Change from baseline (mean ± SD)
Berlin sacroiliac joint total oedema score				
Secukinumab 150 mg (N=39)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
Total ASspi-MRI-a score				
Secukinumab 150 mg (N=38)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]
Berlin spine score				
Secukinumab 150 mg (N=38)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo – secukinumab 150 mg (N=16)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASspi-MRI-a, Ankylosing Spondylitis spine MRI score for Activity; MRI, magnetic resonance imagery;, standard deviation; TNFα, tumour necrosis factor alpha.
Source: MEASURE 1 Clinical Study Report.[16]

4.7.2.5. Overall summary of results

Secukinumab 150 mg was superior to placebo for all primary and secondary outcomes at Week 16 and importantly these responses were subsequently sustained until Week 104.

In MEASURE 1, 60.8% of patients receiving secukinumab 150 mg achieved ASAS20 at Week 16, by comparison to 28.7% of placebo patients ($p<0.0001$). The high rates of response in the secukinumab 150 mg treatment arm were sustained up to Week 104. Similar results in the secukinumab 150 mg treatment arm were shown for all other outcomes presented above, consistent with the results observed in MEASURE 2. At Week 16, 41.6% of patients treated with secukinumab 150 mg achieved the more stringent ASAS40 response vs. 13.1% in the placebo arm ($p<0.0001$) and 37.6% achieved BASDAI 50 vs. 8.2% in the placebo arm ($p<0.0001$). In addition, the quality of life measure ASQoL showed that the secukinumab 150 mg group showed significantly greater improvements in quality of life (mean change -3.58 vs. -1.04 in the placebo arm, $p<0.01$).

Importantly, MEASURE 1 also provided results for radiographic outcomes, highlighting the efficacy of secukinumab on a further clinically relevant and important aspect of the disease. In MEASURE 1, no radiographic progression was observed in approximately 80% of patients randomised to secukinumab at baseline (mSASSS change ≤0).

The results of the MEASURE 1 trial are consistent with the findings of MEASURE 2, emphasising the clinical efficacy of secukinumab 150 mg treatment when assessed across a variety of outcome measures and demonstrate that the benefit is maintained for up to two years.

4.8. Subgroup analysis

Pre-specified subgroup analyses were performed in both the MEASURE 1 and MEASURE 2 trials that demonstrate the efficacy of secukinumab 150 mg in patients regardless of whether or not they have received previous treatment with a TNFα inhibitor.

4.8.1. MEASURE 2

4.8.1.1. Primary outcome: ASAS20

Secukinumab 150 mg was statistically superior to placebo in TNFα inhibitor-naïve and TNFα inhibitor-inadequate responder subgroups

ASAS20 was analysed by previous TNFα inhibitor status, with patients classified as either TNFα inhibitor-inadequate responder or TNFα inhibitor-naïve. Secukinumab 150 mg achieved a statistically superior ASAS20 response rate compared with the placebo group at Week 16, regardless of previous biologic treatment status. The results of the ASAS20 response at Week 16 for these two subgroups is shown in Table 44 below.

Table 44. ASAS20 response by TNFα inhibitor status at Week 16 using non-responder imputation (full analysis set)

Treatment group	Subgroup	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted
Secukinumab 150 mg	TNFα inhibitor-naïve (N=44)	30/44 (68.2)	Placebo	4.72	(1.93, 11.56)	<0.001*
	TNFα inhibitor-inadequate responder (N=28)	14/28 (50.0)	Placebo	4.37	(1.30, 14.68)	<0.05*
Placebo	TNFα inhibitor-naïve (N=45)	14/45 (31.1)	NA	NA	NA	NA
	TNFα inhibitor-inadequate responder (N=29)	7/29 (24.1)	NA	NA	NA	NA

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders); *p<0.05
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.
Source: MEASURE 2 Clinical Study Report,[25] Sieper *et al.* 2015.[27]

ASAS20 response results for the TNFα inhibitor-naïve and TNFα inhibitor-inadequate responder subgroups at Week 52 and Week 104 are shown Appendix H.

Additional outcomes of particular clinical relevance

As a summary of the additional outcomes of particular clinical relevance within prior treatment failure sub-groups, the results at Week 16 are presented in Table 45 below. Results at Week 52 and Week 104 can be found in Appendix H.

Table 45. Secondary efficacy endpoints by TNFα inhibitor status at Week 16 (full analysis set)

Outcome	Secukinumab 150 mg		Placebo	
	TNFα inhibitor-naïve (N=44)	TNFα inhibitor-inadequate responder (N=28)	TNFα inhibitor-naïve (N=45)	TNFα inhibitor-inadequate responder (N=29)
[a]ASAS40 [n/M (%), p-value]	19/44 (43.2), <0.05*	7/28 (25.0), <0.01*	8/45 (17.8), NA	0/29 (0.0), NA
[b]BASDAI change from baseline [n, mean change (SE), p-value]	43, -2.56 (0.32), <0.01*	24, -1.60 (0.41), 0.0928	42, −1.15 (0.32), NA	22, −0.59 (0.43), NA
[a]BASDAI 50 [n/M (%), p-value]	[redacted]	[redacted]	[redacted]	[redacted]
[b]BASFI change from baseline [n, mean change (SE), p-value]	[redacted]	[redacted]	[redacted]	[redacted]
[b]ASQoL change from baseline [n, mean change (SE), p-value]	43, -5.02 (0.68),<0.01 *	23, -2.39 (0.84), 0.1184	43, -1.94 (0.68), NA	23, -0.49 (0.85), NA

M=Number of patients in each treatment group; n=Number of ASAS40 responders (missing ASAS responses were considered non-responders); *p<0.05; [a]non-responder imputation data; [b]MMRM data
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.
Source: MEASURE 2 Clinical Study Report[25], Sieper *et al.* 2015[27]

4.8.2. MEASURE 1

4.8.2.1. Primary efficacy outcome: ASAS20

Secukinumab 150 mg was statistically superior to placebo in both TNFα inhibitor-naïve and TNFα inhibitor-inadequate responder subgroups

Patients in the secukinumab 150 mg arm achieved significantly higher ASAS20 response rates compared with placebo at Week 16, regardless of TNFα inhibitor treatment status (Table 46). Consistent with the differences seen in the overall response rates, treatment differences for secukinumab 150 mg vs. placebo were also statistically significant (p<0.05) for both TNFα inhibitor-naïve and TNFα inhibitor-inadequate responder patients.

ASAS20 response results for the TNFα inhibitor-naïve and TNFα inhibitor-inadequate responder subgroups at Week 52 and Week 104 are shown in Table 46.

Table 46. ASAS20 response by TNFα inhibitor status at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted
Secukinumab 150 mg	TNFα inhibitor-naïve (N=92)	61/92 (66.3)	Placebo	4.12	(2.21, 7.66)	<0.0001*
	TNFα inhibitor-inadequate responder (N=33)	15/33 (45.5)	Placebo	3.75	(1.21,11.56)	<0.05*
Placebo	TNFα inhibitor-naïve (N=89)	29/89 (32.6)	NA	NA	NA	NA
	TNFα inhibitor-inadequate responder (N=33)	6/33 (18.2)	NA	NA	NA	NA

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders); *p<0.05
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; TNFα, tumour necrosis factor alpha.
Source: MEASURE 1 Clinical Study Report[24], Baeten *et al.* 2015.[28]

4.8.3. Additional outcomes of particular clinical relevance

As a summary of the secondary efficacy endpoints within prior treatment exposure sub-groups, the results at Week 16 are presented in Table 47 below, and the results at Week 52 and Week 104 presented in Appendix G.

Table 47. Secondary efficacy endpoints by TNFα inhibitor status at Week 16 (full analysis set)

Outcome	Secukinumab 150 mg		Placebo	
	TNFα inhibitor-naïve (N=92)	TNFα inhibitor-inadequate responder (N=33)	TNFα inhibitor-naïve (N=89)	TNFα inhibitor-inadequate responder (N=33)
[a]ASAS40 [n/M (%), p-value]	45/92 (48.9), <0.0001*	7/33 (21.2), 0.0941	14/89 (15.7), NA	2/33 (6.1), NA
[b]BASDAI change from baseline [n, mean change (SE), p-value]	89, -2.72 (0.19), <0.0001*	32, -1.72 (0.33), 0.0287*	80, -0.72 (0.20), NA	28, −0.65 (0.35), NA
[a]BASDAI 50 [n/M (%), p-value]	[redacted]	[redacted]	[redacted]	[redacted]
[b]BASFI change from baseline [n/M, Mean change, p-value]	[redacted]	[redacted]	[redacted]	[redacted]
[b]ASQoL change from baseline [n, mean change (SE), p-value]	[redacted]	[redacted]	[redacted]	[redacted]

M=Number of patients in each treatment group; n=Number of ASAS40 responders (missing ASAS responses were considered non-responders); *p<0.05; [a]non-responder imputation data; [b]MMRM data

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.
Source: MEASURE 1 Clinical Study Report,[24] Baeten *et al.* 2015.[28]

4.9. Meta-analysis

No meta-analysis of the MEASURE 2 and MEASURE 1 studies alone was performed. A network meta-analysis (NMA) was conducted to estimate the relative effectiveness of secukinumab 150 mg and relevant comparator therapies and this NMA included both the MEASURE 2 and MEASURE 1 studies in the base case analysis (see Section 4.10).

4.10. Indirect and mixed treatment comparisons

Summary of Network Meta-analysis

- Relevant comparators to secukinumab in AS were considered to include the TNFα inhibitors and conventional care, consistent with the final NICE scope for this appraisal. No direct head-to-head evidence for secukinumab versus the TNFα inhibitor therapies was identified and therefore a Bayesian network meta-analysis (NMA) was conducted to evaluate the relative effectiveness of secukinumab 150 mg and these comparators.
- The NMA was conducted with separate networks for clinically relevant outcomes of ASAS20 response, ASAS40 response, BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline. Most included trials had primary endpoints between 12-16 weeks and these were the timepoints considered for inclusion in the analysis.
- The base case analysis was based on the timepoint of the primary endpoint for each comparator between Weeks 12 and 16, and included both the MEASURE 2 and MEASURE 1 studies of secukinumab. The population considered was a mixed population of biologic naive and biologic experienced patients, though subgroup analysis was conducted in the biologic naive population only; no such analysis was possible in the biologic experienced population due to lack of evidence for comparator therapies in this population.
- Despite some potential sources of bias, the studies were considered of sufficient quality to include in the NMA without introducing undue bias. Both fixed effects (FE) and random effects (RE) models were considered and FE analyses ultimately selected based on comparable deviance information criterion (DIC) and deviance values between FE and RE models, infeasibility of RE models for some networks and the fact that no strong evidence of heterogeneity in baseline characteristics between trials was apparent.
- The base case NMA found statistically strong evidence, which was classically significant, of higher efficacy for secukinumab 150 mg versus placebo across all outcomes analysed and for both the analysis in the whole population and in the biologic naïve population. This demonstrated that secukinumab 150 mg can improve the proportion of patients achieving ASAS20 response, ASAS40 response and 50% improvement in BASDAI, as well as mean BASDAI and BASFI changes from baseline, when considering both the mixed population of biologic naïve and biologic experienced patients, and the biologic naïve population specifically.
- The base case NMA also demonstrated no statistically meaningful differences between secukinumab 150 mg and any biologic comparator in either the whole population or biologic naïve population and across all outcomes, with the sole exception of the BASDAI change from baseline outcome, for which infliximab 5mg/kg was superior.
- Sensitivity analyses exploring the assessment of all comparators at a 12 week timepoint and the exclusion of the MEASURE 1 trial also reinforced statistically meaningful results for secukinumab 150 mg versus placebo and no statistically significant results versus biologic comparators in almost all analyses.
- **Overall, secukinumab 150 mg has comparable efficacy to all TNFα inhibitor therapies, adalimumab, etanercept, certolizumab pegol, infliximab and golimumab for the treatment of ankylosing spondylitis in both the biologic naïve and biologic experienced populations of patients with active AS.**

4.10.1. Search strategy

The SLR (Section 4.1) did not identify any available direct evidence comparing secukinumab with the relevant comparators in this submission: adalimumab, etanercept, golimumab, certolizumab pegol and infliximab. Therefore, a network meta-analysis (NMA) was performed in order to assess the relative efficacy and safety of secukinumab when compared to these approved biologic treatments.

The primary objective of the NMA was to provide relative treatment-effect estimates for the efficacy and safety of secukinumab 150 mg compared with approved biologic treatments, for the treatment of active AS among patients with previous inadequate response to conventional therapy. This represents the population of relevance to the decision problem outlined in this submission.

The methodology of the systematic literature review which identified studies to potentially inform the NMA is described in Section 4.1.

4.10.2. Study selection

A total of 86 records were ultimately included in the review, reporting 23 trials (unique RCTs) to be considered for inclusion in the NMA.

For inclusion in the NMA, studies needed to enable treatments in the list below to be connected to at least one other treatment in the list via a common comparator.

- Secukinumab
- Etanercept
- Adalimumab
- Infliximab
- Golimumab
- Certolizumab pegol

Placebo was identified as a common comparator within the network.

Only studies identified by the SLR that reported useful relative efficacy estimates for licensed treatment doses were considered for inclusion in the NMA; all such studies identified by the SLR were included. Where there were multiple different licensed doses for an intervention, these were subsequently treated as separate treatments for the purposes of the analysis. In studies including both licensed and unlicensed doses, unlicensed dose arms were excluded. One study, LOADET, included both licensed and unlicensed doses of etanercept but no placebo arm, and therefore was not included in the network since it did not provide a relative efficacy estimate for the licensed dose versus the common comparator, placebo.

One identified trial – the ASCEND trial – included sulfasalazine rather than placebo as the comparator and was therefore excluded from the NMA.

The Giardina *et al.* study of infliximab did not include placebo as a comparator and was the only open-label study in the NMA. It compared infliximab and etanercept and was included since it was the only source of BASDAI and BASFI outcomes for infliximab. The potential bias introduced by the open-label design of the Giardina *et al.* study is considered in the interpretation of results informed by this study.

Outcomes considered relevant for consideration for inclusion in the NMA and presented in this submission were those listed below reported at a timepoint between Week 12 – 16 (inclusive).

- ASAS20 response
- ASAS40 response
- BASDAI 50 response
- BASDAI change from baseline
- BASFI change from baseline

In addition to these 5 outcomes, outcomes of ASAS 5/6 response and SF-36 PCS were analysed. Results for these 2 outcomes are not presented in this submission but are available on request.

As presented in the PRISMA flow diagrams in Section 4.1.4, of the 23 identified trials 13 were excluded from the NMA. A list of all 23 trials and the justification for their exclusion from the NMA is provided previously in Table 8.

4.10.3. Summary of included trials and resultant networks

4.10.3.1. Included trials

A summary of the relevant trials and the treatments and dosing schedules considered is provided in Table 48 below. Table 49 summarises the endpoints of interest (i.e. relevant outcomes between Week 12 and Week 16) available for inclusion in the NMA.

Table 48: Summary of treatments included in the NMA from identified trials

Trial	Adalimumab 40 mg (ADA40)	Certolizumab pegol 200 mg (CZP200)	Certolizumab pegol 400 mg (CZP400)	Etanercept 50 mg QW (ETN50QW)	Infliximab 5 mg/kg (INF5)	Golimumab 50 mg (GOL50)	Golimumab 100 mg (GOL100)	Secukinumab 150 mg (SEC150)	Placebo (PBO)
ATLAS	Q2W								✓
Hu (2012)	Q2W								✓
Huang (2014)	Q2W								✓
RAPID-axSpA		Weeks 0, 2, 4, then Q2W	Weeks 0, 2, 4, then Q4W						✓
Giardina (2010)				QW	Weeks 0, 2, 6, 12, 18				
SPINE				QW					✓
ASSERT					Weeks 0, 2, 6, 12, 18				✓
GO-RAISE						Q4W	Q4W		✓
MEASURE 2								s.c. at BL, Weeks 1, 2 and 3, then Q4W from Week 4	✓

Trial	Adalimumab 40 mg (ADA40)	Certolizumab pegol 200 mg (CZP200)	Certolizumab pegol 400 mg (CZP400)	Etanercept 50 mg QW (ETN50QW)	Infliximab 5 mg/kg (INF5)	Golimumab 50 mg (GOL50)	Golimumab 100 mg (GOL100)	Secukinumab 150 mg (SEC150)	Placebo (PBO)
MEASURE 1								i.v. at BL, Weeks 0, 2, 4 then s.c. Q4W from Week 8	✓

Cells with numbers indicate data availability for that treatment. In the comparators columns, a ✓ indicates data availability.
Abbreviations: ADA40, adalimumab 40 mg; BL, baseline; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50QW, etanercept 50 mg once weekly; INF5, infliximab 5 mg/kg; i.v., intravenous; NMA, network meta-analysis; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SEC150, secukinumab 150 mg; s.c., subcutaneous.

Table 49: Endpoints evaluated in the NMA

Trial	Switched/ Offered Escape[a]	ASAS20	ASAS40	BASDAI 50	BASDAI Score (Mean Change)	BASFI Score (Mean Change)
ATLAS	12	12	12	12	12	12
Hu (2012)	12	-	-	-	12	12
Huang (2014)	12	12	12	12	12	12
RAPID-axSpA	16	12	12	12	12	12
Giardina (2010)	-	12	12	-	12	12
SPINE	12	12	12	12	12	12
ASSERT	18	12	12	-	-	-
GO-RAISE	16	12,14,16	14	14	12,14,16	12,14,16
MEASURE 2	16	12,16	12,16	12,16	12,16	12,16
MEASURE 1	16	12,16	12,16	12,16	12,16	12,16

Numbers indicate the week data were collected; -=not available; [a]Any data post treatment switch would be subject to bias as either all or some placebo patients are switched to active treatment at this point, and therefore no true placebo arm is available post treatment switch. As demonstrated in the table above, the timepoints included in the NMA avoided this bias, for all endpoints.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; NMA, network meta-analysis.

The base case NMA pooled Week 12 – 16 timepoints. This period encompasses the primary endpoints of all included trials with the exception of the ASSERT study of infliximab (24 week primary endpoint). In this analysis, for each included trial the endpoint used was the primary endpoint of that trial between Week 12 and 16, with a 12 week timepoint used for ASSERT. Therefore, for a given outcome the inputs into the NMA may have differed between interventions in terms of the timepoint considered. However, use of trial primary endpoints was considered to be the most robust approach to estimating true relative treatment effects. Sensitivity analyses explored the impact of considering all outcomes at the 12 week timepoint only, to reflect the timepoint of response assessment in clinical practice. Sensitivity analyses looking only at Week 14 or Week 16 outcomes were not possible as only one treatment has primary endpoints at each of these time points (golimimab at Week 14 in GO-RAISE and secukinumab at week 16 in MEASURE 1 and MEASURE 2).

The base case NMA also included both the MEASURE 2 and MEASURE 1 studies of secukinumab. The MEASURE 1 study is considered relevant to the decision problem as it collected relevant outcomes, in a relevant population, and patients received maintenance dosing at the licensed 150 mg strength. Furthermore, including this study provides more information to inform the estimates of relevant treatment effects. Sensitivity analyses were conducted to explore the exclusion of the MEASURE 1 trial of secukinumab, as this trial used an intravenous loading dose of secukinumab as opposed to the licensed subcutaneous administration route.

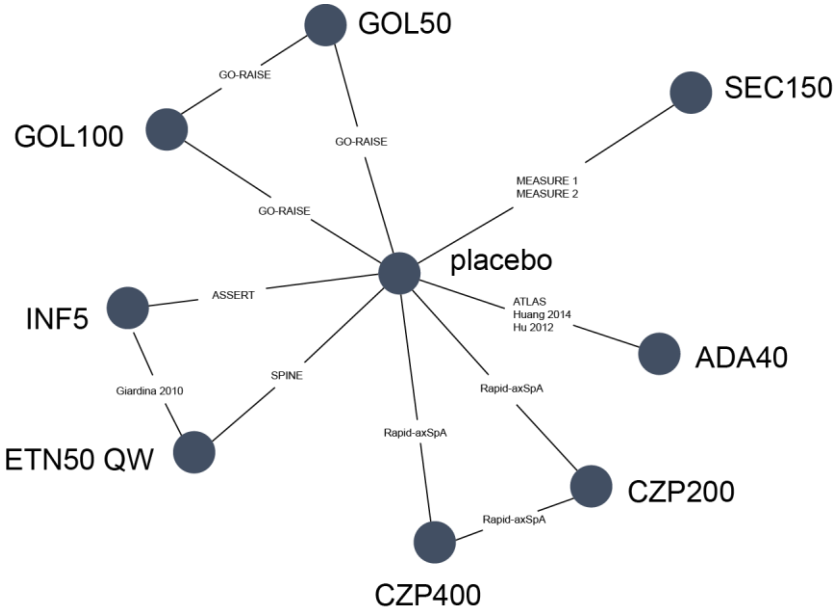
These adjustments gave rise to three sensitivity analyses:

1. Sensitivity analysis 1: Pooled Week 12-16, MEASURE 1 excluded
2. Sensitivity analysis 2: Week 12 timepoint only, both MEASURE 2 and MEASURE 1 included
3. Sensitivity analysis 3: Week 12 timepoint only, MEASURE 1 excluded

Network diagrams

The complete treatment network of the 10 RCTs is shown in the network diagram in Figure 20. Each node represents a treatment regimen included in the network and lines represent direct comparisons between nodes. The studies contributing to each comparison are also detailed along each line in the network diagrams. As discussed in more detail in Section 4.10.4, some included studies considered both biologic naïve and biologic experienced patients, whilst others considered biologic naïve patients only. As such, the NMA was conducted both for the whole population (ie. including both biologic naïve and biologic experienced patients) and for the population of biologic naïve patients only (i.e. including studies of biologic naïve patients and the pre-specified TNF-naïve sub-group of the MEASURE 1 and MEASURE 2 studies; no naïve sub-group data was available for the other study with a mixed population; RAPID-axSpA, see Appendix K). Network diagrams for the base case analysis for each outcome of interest for the whole population and biologic naïve population analyses are presented Appendix K.

Figure 20. Complete treatment network of RCTs among AS patients



Nodes in blue represent each treatment included in the network. Trial names along each edge indicate the trials with head-to-head comparisons for the corresponding treatments.
Abbreviations: ADA40, adalimumab 40 mg; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

4.10.4. Methods and outcomes of included studies

Methods

The included studies all considered patients with active AS at baseline. Relevant demographic and baseline characteristics were considered and reviewed across the identified trials. Baseline characteristics are presented in Appendix K.

The mean age and percentage of males was comparatively similar between trials, as was the duration of AS. A number of publications did not report baseline weight; for those articles that did so, baseline weight was relatively similar. The only baseline characteristic that demonstrated discernible heterogeneity across trials was the duration of AS, which was substantially higher in the Giardina (2010) trial, the only open-label study in the network. Network meta-regression analysis was explored to investigate whether potential heterogeneity in the network could be explained by differences in baseline characteristics.

Trials included in the evidence base employed different imputation strategies as reported in Table 50.

Table 50. Imputation methods employed in each trial

Trial	Treatment	Imputation method
ATLAS	Adalimumab	NRI
Hu (2012)	Adalimumab	Unclear
Huang (2014)	Adalimumab	NRI
RAPID-axSpA	Certolizumab pegol	LOCF

Giardina (2010)	Etanercept / Infliximab	Observed
SPINE	Etanercept	LOCF
ASSERT	Infliximab	LOCF
GO-RAISE	Golimumab	LOCF/NRI
MEASURE 2	Secukinumab	NRI and MMRM
MEASURE 1	Secukinumab	NRI and MMRM

Abbreviations: LOCF, last observation carried forward; MMRM, mixed-effect model repeated measures; NRI, non-responder imputation.

All secukinumab trials (MEASURE-1, MEASURE 2) employed the conservative NRI strategy for dichotomous outcomes and MMRM method for continuous outcomes. Two of the adalimumab trials (ATLAS, Huang) also used NRI. The trial reporting on golimumab (GO-RAISE) employed an LOCF strategy, unless there were no measurements, in which case NRI was employed. Infliximab and etanercept trials employed the LOCF strategy, with the exception of the Giardina *et al* study that compared these two therapies and reported observed data. However, as can be seen, there was little to no variety in the imputation method used along each edge, thus not allowing for analytical adjustments to account for this source of heterogeneity. Therefore, it should be acknowledged indirect comparisons involving edges with different imputation methods are potentially biased. Given that NRI is a more conservative approach than LOCF and observed data, estimates of efficacy of secukinumab relative to golimumab, etanercept and infliximab are potentially reduced. This should be considered throughout the interpretation of the results that follow.

Finally, it should be noted that there were some differences in the trial populations in terms of the status of the patients with regards to exposure to prior biologics. In the majority of included trials, the population considered was biologic naïve (no prior treatment with biologics). However, in the case of the MEASURE 2 and MEASURE 1 trial of secukinumab and the RAPID-axSpA trial of certolizumab pegol, the population contained a mix of biologic naïve and biologic experienced patients. In the case of RAPID-axSpA, results were not reported separately for the biologic naïve and biologic experienced sub-groups. In the Hu *et al.* study of adalimumab, reporting was insufficient to determine the status of the trial population with regards to prior biologic treatment.

As previously mentioned, subgroup analysis considering data from biologic naïve populations only was conducted in order to explore this potential source of bias. Due to data limitations it was not possible to conduct a subgroup analysis of the biologic experienced population only.

Outcomes

As previously noted, the data inputs into the base case NMA were the results from Week 12-16 representing the primary endpoint of the respective trials. The available data from these timepoints that acted as inputs into the base case NMA and sensitivity analyses are summarised in Appendix K for both the whole population and the biologic naïve population.

4.10.5. Risk of bias

Quality assessments of each trial included in the NMA were performed according to NICE guidelines and the results are presented in AppendixK.[186] Generally, all studies included in the NMA were deemed to be of sufficient quality, though the quality of included studies did vary, with trials such as Huang *et al.,* MEASURE 2 and MEASURE 1 scoring well, while others such as

Giadrina *et al.,* ATLAS and Hu *et al.* scored negatively against some criteria based on available information.

For a number of the studies there was inadequate reporting of the methods of randomisation and concealment of treatment allocation, which could represent a potential source of bias. However, for all but one study it was possible to determine that there were no unexpected drop-outs between treatment arms and therefore attrition bias does not appear to be a relevant consideration for this analysis.

A potential source of bias in the analysis is the Giardina *et al.* study. This was an open-label study of infliximab and etanercept, and therefore patients and study investigators were not blinded to treatment. Furthermore, the NMA inputs from this study were based on observed data; in comparison the MEASURE 2 and MEASURE 1 studies of secukinumab used NRI, a more conservative estimate, and hence this may bias against secukinumab in the comparison. Finally, this study was identified as an outlier from the other studies in terms of the average duration of AS of trial participants at baseline (see Section 4.10.4). For analyses of BASDAI and BASFI outcomes, the Giardina *et al.* study was the only study informing the comparison of secukinumab and infliximab. The design features of the Giardina *et al.* study therefore present a risk of bias within the comparison of secukinumab and infliximab on these outcomes.

Overall, the studies were considered to be of sufficient quality to include in the NMA without introducing undue bias.

4.10.6. Methods of analysis and presentation of results

Methods of analysis

The BASDAI 50, ASAS20 and, ASAS40 scores were modelled as binomial endpoints. For binomial data, a generalised linear model with logit link function and binomial likelihood was used.

BASFI change from baseline and BASDAI change as continuous outcomes were modelled with a normal likelihood NMA setup with an identity link function. This was consistent with the method described by Dias *et al.* in NICE DSU Technical Support Document 2.[187]

For all endpoints, Bayesian models for fixed effects (FE) and random effects (RE) were considered. FE models were selected as preferable, for the reasons outlined in Section 4.10.9 and all results presented in the main body of the submission are therefore based on FE models.

Meta-regression adjustments for specific baseline characteristics were not feasible for the baseline characteristics that were extracted. Meta-regression adjustments can also be extended to include the mean placebo effect as a covariate.[187] This captures many characteristics within a single measure, akin to the random-effects adjustments for heterogeneity. This model views the study effects themselves as effect modifiers to the treatment. The model that was applied to this end was the baseline natural history model, which is described in detail in the NICE DSU Technical Support Document 5. (NICE TSD5: Dias et *al*). Analyses using placebo-response adjustments were explored, but were often not feasible, particularly within random-effects modeling.

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS and JAGS software packages. For each model, the first 50,000 iterations from the OpenBUGS/JAGS sampler were discarded as ‘burn-in’ and the inferences

were based on an additional 50,000 iterations using two chains. Convergence of the chains was confirmed by the Gelman-Rubin statistic. All analyses were performed using R version 3.1.2 (http://www.r-project.org/) and OpenBugs/JAGS version 3.2.3 (OpenBUGS/JAGS Project Management Group).

Further statistical details, including the code used to run the NMA, can be found in K.

Presentation of results

The NMA allows comparisons to be made between each treatment in the network, and therefore allows estimation of the relative effectiveness of secukinumab 150 mg versus all relevant comparators. For each outcome, the following forms of results are presented:

- Relative effect estimates for secukinumab 150 mg versus each relevant comparator
- Predicted absolute response for each treatment

For the relative results of analysis conducted on binomial endpoints, relative risks and 95% credible intervals are shown; for relative results concerning BASFI and BASDAI change from baseline outcomes, relative differences in mean change from baseline are presented, along with 95% credible intervals.

All results shown are from FE models. The DIC values for the FE and RE models are presented in 4.10.9, along with the justification for the choice of the FE models.

Treatments with highly uncertain estimates of effect size may have high probability of being both best and worst. Rankograms are therefore recommended in favour of presenting only the probability of each treatment being the best (Dias *et al*.[187]). Rankograms are presented for the base case analysis in Appendix K.

4.10.7. Results of the NMA

4.10.7.1. Base case analysis

Overall summary

Table 51 and Table 52 provide an overall summary of the significance or not, at the 0.05 level, of the base case relative comparisons of secukinumab 150 mg versus each relevant comparator, for each evaluated outcome, in the whole population and biologic naïve population, respectively. Detailed results of the relative comparisons are then presented subsequently in Table 53 (binomial endpoints) and Table 54 (continuous endpoints).

These analyses found secukinumab 150 mg to be associated with statistically significantly better results compared to placebo for all outcomes assessed. No statistically significant differences in results were found between secukinumab 150 mg and any of the biologic comparators with the exception of one comparison that found infliximab 5 mg to be statistically significantly superior for the single outcome of BASDAI change from baseline outcome. These results were observed consistently in the whole population analysis and biologic naïve subgroup analysis. In interpreting the comparison to infliximab it should be noted that the BASDAI and BASFI data inputs to the NMA for infliximab were from a single study that compared infliximab to etanercept (rather than placebo) in an open-label study design.[29] Furthermore, the inputs from this trial are based on observed data, compared to the more conservative NRI imputation reported for the secukinumab studies, and this study was seen to be an outlier in terms of the included patients' average

duration of AS at baseline. This may introduce bias that may limit the reliability of the results of the comparison between secukinumab and infliximab.

Finally, the results of the analyses in terms of absolute response for each treatment are presented subsequently for each individual outcome in g once weekly in this population.

[redacted]

[redacted] to xxxxxxx.

In addition to the results presented here, in an initial set of NMA analyses that were similar to the final analyses presented here, a formal assessment of the probability of equivalence of secukinumab to the other biologic comparators was conducted. This found that secukinumab was associated with a high probability of being equivalent to each of the biologic comparators for both of the two outcomes on which probability of equivalence was assessed (change from baseline in BASDAI and change from baseline in BASFI).

Table 51. Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – whole population

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

Table 52. Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – biologic naive population

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	-	-	-	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

Results of comparisons of relative treatment effects

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 53.

Table 53. Relative risks for secukinumab 150 mg versus comparators on binomial endpoints

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	ASAS20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BN, biological naïve; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 54.

Table 54. Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BN, biological naïve; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Predicted absolute response for each treatment

ASAS20

As discussed in Section 4.3, the primary efficacy outcome for both MEASURE 1 and MEASURE 2 trials was ASAS20. The predicted absolute ASAS20 response for each treatment is presented in g once weekly in this population.

[redacted]

[redacted] for the whole population and xxxxxxx for the biologic naïve population. Secukinumab 150 mg was found to have higher point estimates of response than certolizumab pegol 400 mg and 200mg and etanercept 50 mg once weekly in the whole population. Certolizumab pegol did not form part of the biologic naïve network, but point estimates of response for secukinumab 150 mg were similarly higher than etanercept 50 mg once weekly in this population.

[redacted]

Abbreviations: ADA, adalimumab; ASAS, Assessment of Spondyloarthritis International Society; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; LOCF, last observation carried forward; NRI, non-respondent imputation; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SEC, secukinumab.

Abbreviations: ADA, adalimumab; ASAS, Assessment of Spondyloarthritis International Society; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; LOCF, last observation carried forward; NRI, non-respondent imputation; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SEC, secukinumab.

ASAS40

The predicted absolute ASAS40 response, the most stringent measure of response, for each treatment is presented in xxxxxxx for the whole population and xxxxxxx for the biologic naïve population. Secukinumab 150 mg was found to have higher point estimates of response than both dosing regimens of certolizumab pegol, etanercept 50 mg once weekly and golimumab 50 mg in the whole population. Point estimates of response rates versus these comparators, as well as adalimumab 40 mg, were also greater for secukinumab 150 m in the biologic naïve population.

[redacted]

Abbreviations: ADA, adalimumab; ASAS, Assessment of Spondyloarthritis International Society; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; LOCF, last observation carried forward; NRI, non-respondent imputation; PBO, placebo; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SEC, secukinumab.

[redacted]

Abbreviations: ADA, adalimumab; ASAS, Assessment of Spondyloarthritis International Society; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; Q2W, once every 2 weeks; QW, once weekly; SEC, secukinumab.

BASDAI 50

The predicted absolute BASDAI 50 response for each treatment is provided in xxxxxxx for the whole population and xxxxxxx for the biologic naïve population. In the whole population analysis, secukinumab 150 mg was found to have higher point estimates of response versus all comparators other than certolizumab pegol 200 mg and certolizumab pegol 400 mg. In the biologic naïve population neither dose of certolizumab pegol could be included in the network and the point estimate of BASDAI 50 response for secukinumab 150 mg was higher than all comparators in this population.

[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP, certolizumab pegol; ETN, etanercept; INF, infliximab; NMA, mixed-treatment comparison; PBO, placebo; QW, once weekly; SEC, secukinumab.

[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ETN, etanercept; GOL, golimumab; PBO, placebo; QW, once weekly; SEC, secukinumab.

BASDAI change from baseline

The predicted absolute change from baseline in BASDAI for each treatment is provided in xxxxxxx for the whole population and xxxxxxx for the biologic naïve population. Infliximab 5mg/kg was found to superior to etanercept 50mg, certolizumab 200mg, certolizumab 400mg, adalimumab 40mg and secukinumab 150mg. This result is informed by the biased Giardina *et al.* study. Secukinumab 150 mg was found to be numerically superior in efficacy to etanercept 50 mg once weekly, certolizumab pegol (both doses) and adalimumab 40 mg in the whole population. In the biologic naïve population, neither dose of certolizumab pegol could be included in the network and secukinumab 150 mg was found to have a numerically higher change from baseline than etanercept 50 mg once weekly and adalimumab 40 mg.

[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; SEC, secukinumab.

[redacted]

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; SEC, secukinumab.

BASFI change from baseline

The predicted absolute change from baseline for each treatment is provided in xxxxxxx for the whole population and xxxxxxx for the biologic naïve population. Secukinumab 150 mg was found to be numerically superior in efficacy to etanercept 50 mg once weekly, certolizumab pegol (both doses) and adalimumab 40 mg in the whole population. In the biologic naïve population, secukinumab 150 mg was found to be numerically superior to all analysed comparators with the exception of infliximab 5 mg in terms of BASFI change from baseline, for which it is relevant to note the potential bias introduced by the Giardina *et al.* study.

[redacted]

Abbreviations: ADA, adalimumab; BASFI, Bath Ankylosing Spondylitis Functional Index; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; SEC, secukinumab.

[redacted]

Abbreviations: ADA, adalimumab; BASFI, Bath Ankylosing Spondylitis Functional Index; BN, biological naïve; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; SEC, secukinumab.

4.10.7.2. Sensitivity analyses

As described in Section 4.10.3, in addition to the base case analysis considering pooled Week 12-16 timepoints and the inclusion of MEASURE 2 and MEASURE 1 studies of secukinumab, three sensitivity analyses were conducted to explore the effect on the analysis of considering all comparators at the same (Week 12) timepoint and the exclusion of the MEASURE 1 study, which used an intravenous loading dose:

1. Sensitivity analysis 1: Pooled Week 12-16, MEASURE 1 excluded
2. Sensitivity analysis 2: Week 12 timepoint only, MEASURE 2 and MEASURE 1 included
3. Sensitivity analysis 3: Week 12 timepoint only, MEASURE 1 excluded

As for the base case analysis, these sensitivity analyses were conducted in both the whole population and the biologic naïve population. The input data available at the 12 week timepoint is summarised in Appendix K.

Relative results from the three sensitivity analyses for binomial endpoints and continuous endpoints are summarised in Table 55 and Table 56, respectively. Absolute results from the three sensitivity analyses for binomial and continuous endpoints are summarised in Table 57 and Table 58.

Table 55. Relative risks for secukinumab 150 mg versus comparators on binomial endpoints – sensitivity analyses

Population	Binomial endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	ASAS20	1								
		2								
		3								
	ASAS40	1								
		2								
		3								
	BASDAI 50	1								
		2								
		3								
Biologic naïve population	ASAS20	1								
		2								
		3								
	ASAS40	1								
		2								
		3								
	BASDAI 50	1								

Population	Binomial endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
		2								
		3								

Green cells represent a statistically significantly meaningful result. -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 56. Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints – sensitivity analyses

Population	Continuous endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	BASDAI change from baseline	1								
		2								
		3								
	BASFI change from baseline	1								
		2								
		3								
Biologic naïve population	BASDAI change from baseline	1								
		2								
		3								
	BASFI change from baseline	1								
		2								
		3								

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 57. Absolute results for binomial endpoints – sensitivity analyses

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	ASAS20	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	ASAS20	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASDAI 50	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

-=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 58. Absolute results for continuous outcomes – sensitivity analyses

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	BASDAI change from baseline	1	[redacted]								
		2	[redacted]								
		3	[redacted]								
	BASFI change from baseline	1	[redacted]								
		2	[redacted]								
		3	[redacted]								
Biologic naïve population	BASDAI change from baseline	1	[redacted]								
		2	[redacted]								
		3	[redacted]								
	BASFI change from baseline	1	[redacted]								
		2	[redacted]								
		3	[redacted]								

-=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

4.10.8. Heterogeneity and inconsistency

Within an NMA there is a risk that the patients assigned to different trials are not comparable, such that there is an imbalance in the distribution of treatment-effect modifiers leading to bias. The level to which this is the case can be determined by assessment of heterogeneity. As in this NMA there were very few situations in which multiple trials informed a comparison, no formal assessment of heterogeneity was performed. However, a discussion of potential sources of heterogeneity is presented below.

Of note, trials included in the NMA differed in terms of the proportion of patients with prior exposure to biologics; many trials enrolled only biologic naïve patients. In addition, differing approaches to handling missing data as described in Section 4.10.4. With regards to both these sources of heterogeneity, secukinumab would be expected to be disadvantaged in the analysis. The secukinumab trials used the most conservative of the different imputation methods (NRI) and both MEASURE 1 and MEASURE 2 included a mixed population, in contrast to some comparators for which data inputs to the whole population NMA were based solely on biologic naïve patients. Based on the efficacy of secukinumab 150mg in the TNF-naïve sub-group versus the TNF-IR sub-group (see Section 4.8 Subgroup analysis), a mixed population would be expected to reduce efficacy estimates. An additional source of heterogeneity is that one non-blinded trial (Giardina *et al.* 2010) was seen to be an outlier with regards to duration of AS at baseline of the included patients.

Although there were some sources of heterogeneity the included trials were seen to be generally comparable (see Table 201). The possibility of using meta-regression to make adjustments with respect to differences in baseline characteristics was explored, but there was insufficient evidence to fit the meta-regression models, with at most one trial with a contrast relative to potential effect modifiers.

In terms of assessment of inconsistency, the base case network possessed only four closed loops, of which three represented a single trial that examined multiple drug doses. The fourth closed loop comprised of the ASSERT, SPINE and Giardina *et al.* 2010 study and assessment of the direct and indirect estimates of treatment effects in this loop found no evidence of inconsistency (NICE TSD4: Dias et *al.*).

Ultimately, although there are some limitations in the evidence synthesis in terms of the base case analysis considering mixed populations of biologic naïve and biologic experienced patients from some studies, and some differences in duration of AS between trial populations, the results of the analysis are felt to provide a robust estimate of the relative effectiveness of biologic therapies in the treatment of AS.

4.10.9. Justification of Fixed Effects Model

Bayesian models for both fixed effects (FE) and random effects (FE) were considered for all networks. The Deviance information criterion (DIC) and total residual deviance were calculated for all FE and RE networks where possible and these results are presented in Table 59. The deviance information criterion (DIC) tended to be comparable between the various models. As indicated by “NA” in Table 59, RE models were simply not mathematically feasible for some networks in the biologic naïve population. Given this, the lack of clear preference based on DIC values and the absence of strong evidence of heterogeneity in the baseline characteristics between trials and comparisons, the FE models were selected for the base case and sensitivity analyses.

Table 59. DIC and total residual deviance for the FE and RE NMAs

Outcome	Analysis	DIC Whole population (biologic naïve population)		Deviance Whole population (biologic naïve population)	
		FE	RE	FE	RE
ASAS20	Base case	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 1	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 2	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 3	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	Base case	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 1	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 2	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 3	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50	Base case	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 1	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 2	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 3	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline	Base case	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 1	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 2	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 3	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline	Base case	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 1	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 2	[redacted]	[redacted]	[redacted]	[redacted]
	Sensitivity analysis 3	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; DIC, Deviance information criterion; FE, fixed effects; RE, random effects.

4.10.10. Overall summary of NMA evidence

In summary, the base case NMA found statistically significantly higher efficacy of secukinumab 150 mg versus placebo across all outcomes analysed and for both the whole population and biologic naïve population, demonstrating that secukinumab 150 mg can improve the proportion of patients achieving ASAS20 response, ASAS40 response and 50% improvement in BASDAI, as well as mean BASDAI and BASFI changes from baseline.

The base case NMA also demonstrated no statistically meaningful differences between secukinumab 150 mg and any biologic comparator in either population and across all outcomes, with the sole exception of the comparison to infliximab 5 mg/kg for the BASDAI change from baseline outcome. As noted above, the results of the BASDAI and BASFI comparisons with infliximab should be interpreted in the context of the limitations of the Giardina *et al.* study as an open-label study that reported the less conservative observed dataset, in comparison to the NRI dataset informing inputs for secukinumab within the NMA. Sensitivity analyses exploring the assessment of all comparators at a 12 week timepoint and the exclusion of the MEASURE 1 trial also reinforced statistically meaningful results for secukinumab 150 mg versus placebo and no statistically meaningful differences versus biologic comparators in almost all analyses.

Overall, the results of the NMA suggest that secukinumab 150 mg is at least equally effective to other biologic comparators considered across all clinically relevant outcomes, in both the whole population representing a mix of biologic naïve and experienced patients, and in the biologic naïve population specifically.

4.10.11. Additional comparative analysis

In addition to the NMA performed across all comparators at their primary trial endpoint (base case) or at week 12 (sensitivity analysis), an additional matching-adjusted indirect comparison (MAIC) was conducted to explore the long-term efficacy of secukinumab compared with adalimumab by matching secukinumab trial patients to those from the ATLAS study of adalimumab. The results of this analysis, which found [redacted], are presented in Appendix J.

4.11. Non-randomised and non-controlled evidence

There is no relevant non-randomised or non-controlled evidence for presentation in this submission.

4.12. Adverse reactions

Summary of Adverse Reactions

- MEASURE 2 and MEASURE 1 assessed overall safety and tolerability compared with placebo, determined by vital signs, clinical laboratory values and adverse events (AEs), as secondary objectives.
- The overall incidence of treatment emergent AEs up to Week 16 in MEASURE 2 was comparable between the secukinumab 150 mg group (65.3%) and the placebo group (63.5%). In MEASURE 1 there was a higher rate in the secukinumab 150 mg group than placebo (69.6% vs. 55.7%).
- In both trials, the most frequently reported AE was nasopharyngitis.
    - At Week 16, this occurred in 11.1% and 13.6% of patients receiving secukinumab 150 mg treatment in MEASURE 2 and MEASURE 1, respectively; this was higher than the respective placebo groups (4.1% and 7.4%).
    - However, exposure-adjusted incidence rates per 100 patient-years over the entire-treatment period were similar to placebo: 13.6% and [redacted] in patients who had received secukinumab 150 mg at any point in MEASURE 2 and MEASURE 1, respectively, versus 14.0% and [redacted] for the placebo control groups.
- A total of 3 deaths were reported across the MEASURE 2 and MEASURE 1 trials; two in patients receiving secukinumab and one in a patient receiving placebo. None of the deaths were considered by the investigator to be related to study treatment.
- The safety results from MEASURE 2 and MEASURE 1 showed no new or unexpected safety signals associated with secukinumab in the treatment of AS in comparison to a large body of safety evidence from other autoimmune indications, notably psoriasis.
- In conclusion, the safety results of MEASURE 2 and MEASURE 1 demonstrate secukinumab is well-tolerated in patients with active AS, with a low incidence of SAEs, consistent with that which has been found previously in similar indications.

The two large secukinumab Phase III RCTs in AS (MEASURE 2 and MEASURE 1) were designed primarily to investigate efficacy outcomes for secukinumab in AS; overall safety and tolerability compared with placebo, as assessed by vital signs, clinical laboratory values and adverse events (AEs), were included as secondary objectives.

In addition, the safety of secukinumab has been assessed in the context of another similar indication (psoriasis) and these results are presented in Section 4.12.4 below.

A summary of treatment emergent adverse events up to Week 16 and exposure-adjusted treatment emergent adverse events for the entire treatment period of the MEASURE 2 and MEASURE 1 trials is presented below.

4.12.1. MEASURE 2

Treatment emergent AEs up to Week 16 in MEASURE 2 are summarised in Table 60; patients who received secukinumab at either the licensed strength of 150 mg or the unlicensed strength of 75 mg are included in the “Any secukinumab dose” (N=145) group. The overall incidence of AEs up to Week 16 was comparable in the secukinumab 150 mg group (65.3%) to the placebo group (63.5%). The majority of AEs reported up to Week 16 were mild or moderate in severity. Severe AEs were reported by 6 patients (8.3%) in the secukinumab 150 mg s.c. group, and 5 patients (6.8%) in the placebo group. The most frequently reported AEs in any secukinumab dose group were nasopharyngitis, headache, influenza, oropharyngeal pain and upper respiratory tract infection. One death was reported in the period up to Week 16, which occurred in the secukinumab 75 mg group due to cardiac disorder and was not considered by the investigator to be related to study treatment.

Table 60. Treatment emergent adverse events up to Week 16 (Safety set)

	Secukinumab 150 mg (N=72) n (%)	Any secukinumab dose (N=145) n (%)	Placebo (N=74) n (%)
Patients with any AE(s)	47 (65.3)	89 (61.4)	47 (63.5)
Patients with serious or other significant events			
Death	0 (0.0)	1 (0.7)	0 (0.0)
Non-fatal serious AE(s)	4 (5.6)	7 (4.8)	3 (4.1)
Discontinued study treatment due to any AE(s)	5 (6.9)	8 (5.5)	4 (5.4)
Common adverse events (those >2% in any secukinumab group)			
Nasopharyngitis	8 (11.1)	14 (9.7)	3 (4.1)
Headache	3 (4.2)	6 (4.1)	6 (8.1)
Influenza	3 (4.2)	6 (4.1)	0 (0.0)
Oropharyngeal pain	2 (2.8)	5 (3.4)	2 (2.7)
Upper respiratory tract infection	1 (1.4)	5 (3.4)	2 (2.7)
Viral infection	3 (4.2)	5 (3.4)	2 (2.7)
Gastroenteritis	1 (1.4)	4 (2.8)	1 (1.4)
Hypercholesterolaemia	2 (2.8)	4 (2.8)	3 (4.1)
Injection site pain	4 (5.6)	4 (2.8)	1 (1.4)
Nausea	3 (4.2)	4 (2.8)	3 (4.1)
Bronchitis	2 (2.8)	3 (2.1)	1 (1.4)
Diarrhoea	2 (2.8)	3 (2.1)	1 (1.4)
Dyspepsia	2 (2.8)	3 (2.1)	1 (1.4)
Fatigue	1 (1.4)	3 (2.1)	5 (6.8)
Hepatic enzyme increase	2 (2.8)	3 (2.1)	0 (0.0)
Hypertension	2 (2.8)	3 (2.1)	0 (0.0)
Pain in extremity	3 (4.2)	3 (2.1)	1 (1.4)

Abbreviations: AE, adverse event.
Source: MEASURE 2 Clinical Study Report.[25]

For the entire treatment period of MEASURE 2 (up to Week 104), the exposure adjusted incidence rates (IR per 100 patient-years) for treatment-emergent AEs are shown in Table 61 below. All patients who received secukinumab 150 mg either from baseline or following re-randomisation at Week 16 are included in the “Any secukinumab 150 mg” group. All patients who received secukinumab (either 150 mg or 75 mg) either from baseline or following re-randomisation at Week 16 are included in the “Any secukinumab dose” group. Treatment comparisons of secukinumab with placebo for the entire treatment period must still be interpreted with caution due to the different exposure times and potential non-constant event rates over time. The most frequently reported AEs for any secukinumab dose were nasopharyngitis, upper respiratory tract infection and headache.

A total of 12/72 (16.7%) patients in the secukinumab 150 mg arm discontinued by Week 104, of which 6/72 (8.3%) discontinued due to adverse events. A similar number of patients discontinued in the placebo arm [17/74 (30.0%)], of which 6/74 (8.1%) discontinued due to adverse events. For further details please see Section 4.5.3.

Table 61. Exposure adjusted incident rates for treatment emergent adverse events for the entire treatment period up to Week 104 (Safety set)

	Any secukinumab 150 mg (N=106), n/EX (IR)	Any secukinumab dose (N=211), n/EX (IR)	Placebo (N=74), n/EX (IR)
Any AE	[redacted]	[redacted]	[redacted]
Common adverse events (those >2% in any secukinumab group)			
Nasopharyngitis	15/110.6 (13.6)	[redacted]	3/21.4 (14.0)
Upper respiratory tract infection	7/118.7 (5.9)	[redacted]	2/21.5 (9.3)
Headache	8/115.5 (6.9)	[redacted]	6/20.3 (29.5)
Diarrhoea	8/118.6 (6.7)	[redacted]	1/21.5 (4.6)
Influenza	6/119.8 (5.0)	[redacted]	0/21.8 (0.0)
Hypertension	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Hypercholesterolaemia	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Hepatic enzyme increase	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; EX, exposure in patient years; IR, incidence rate per 100 patient years.
Source: MEASURE 2 Clinical Study Report.[15]

4.12.2. MEASURE 1

MEASURE 1 treatment emergent AEs up to Week 16 are shown in Table 62; patients who received secukinumab at either the licensed dose of 150 mg or the unlicensed dose of 75 mg are included in the “Any secukinumab dose” (N=249) group. One death was reported in the placebo arm prior to Week 16 in a patient who suffered from depression and committed suicide. An additional death was reported following the data lock at Week 52 and was due to respiratory failure secondary to pulmonary fibrosis and cardiac failure; following approximately 2 years on active treatment (please see Section 4.12.3). Nasopharyngitis, dyslipidaemia, headache, nausea and leukopenia were the most common AEs reported, with each more prevalent in the secukinumab dose groups compared with placebo.

Table 62. Treatment emergent adverse events up to Week 16 in MEASURE 1 (Safety set)

	Secukinumab 150 mg (N=125), n (%)	Any secukinumab dose (N=249), n (%)	Placebo (N=122), n (%)
Any AE	87 (69.6)	170 (68.3)	68 (55.7)
Patients with serious or other significant events			
Death	0 (0.0)	0 (0.0)	1 (0.8)
Non-fatal serious AE(s)	3 (2.4)	5 (2.0)	4 (3.3)
Discontinued study treatment due to any AE(s)	1 (0.8)	3 (1.2)	6 (4.9)
Common adverse events (those >2% in any secukinumab group)			
Nasopharyngitis	17 (13.6)	30 (12.0)	9 (7.4)
Dyslipidaemia	9 (7.2)	24 (9.6)	6 (4.9)
Headache	14 (11.2)	20 (8.0)	7 (5.7)
Nausea	6 (4.8)	11 (4.4)	2 (1.6)
Leukopenia	4 (3.2)	10 (4.0)	1 (0.8)
Oropharyngeal pain	6 (4.8)	10 (4.0)	6 (4.9)
Diarrhoea	4 (3.2)	9 (3.6)	6 (4.9)
Mouth ulceration	5 (4.0)	9 (3.6)	3 (2.5)
Upper abdominal pain	3 (2.4)	8 (3.2)	0 (0.0)
Fatigue	3 (2.4)	7 (2.8)	2 (1.6)
Arthralgia	3 (2.4)	6 (2.4)	4 (3.3)
Cough	3 (2.4)	6 (2.4)	2 (1.6)
Anaemia	3 (2.4)	5 (2.0)	1 (0.8)
Gastroenteritis	3 (2.4)	5 (2.0)	1 (0.8)
Hypertension	3 (2.4)	5 (2.0)	0 (0.0)
Pharyngitis	3 (2.4)	5 (2.0)	1 (0.8)
Upper respiratory tract infection	1 (0.8)	5 (2.0)	2 (1.6)

Source: MEASURE 1 Clinical Study Report[24]

The exposure-adjusted incidence rates of adverse events for the entire treatment period of MEASURE 1 (up to Week 104) are shown in Table 61 below. All patients who received secukinumab 150 mg either from baseline or following re-randomisation at Week 16 or Week 24 are included in the “Any secukinumab 150 mg” group. All patients who received secukinumab (either 150 mg or 75 mg) either from baseline or following re-randomisation are included in the “Any secukinumab dose” group.

A total of 28/125 (22.4%) patients in the secukinumab 150 mg arm discontinued by Week 104, of which 11/125 (8.8%) discontinued due to adverse events. A similar number of patients discontinued in the placebo arm [32/122 (26.2%)], of which 11/122 (9.0%) discontinued due to adverse events. For further details please see Section 4.5.4.

Table 63. Exposure adjusted incident rates for treatment emergent adverse events for the entire treatment period up to Week 104 (Safety set)

	Any secukinumab 150 mg (N=181), n/EX (IR)	Any secukinumab dose (N=360), n/EX (IR)	Placebo (N=122), n/EX (IR)
Any AE	[redacted]	[redacted]	[redacted]
Common adverse events (those >2% in any secukinumab group)			
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]	[redacted]
Dyslipidaemia	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]
Upper abdominal pain	[redacted]	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; EX, exposure in patient years; IR, incidence rate per 100 patient years.
Source: MEASURE 1 Clinical Study Report.[16]

Symptoms of extra-articular manifestations (EAMS), including uveitis, inflammatory bowel disease and psoriasis, were only assessed as part of the safety reporting within MEASURE 2 and MEASURE 1. The lack of new cases in either trial suggests that secukinumab is not associated with a worsening of EAMs.

The pooled analysis of the two trials has recently been published and supports the above analysis of the individual trials.[135] In conclusion, the safety results of MEASURE 2 and MEASURE 1 demonstrate secukinumab is well-tolerated in patients with active AS with a low incidence of SAEs and discontinuations due to AEs.

4.12.3. Selected adverse events

Selected adverse events of interest, as specified by the SmPC, are infections, neutropenia, hypersensitivity and immunogenicity.[5] In addition, details of major adverse cardiovascular events (MACE), malignancy and death are shown. MACE and malignancy are considered of particular clinical importance as they have been previously associated with the use of IL-12/23 and TNFα inhibitors.[188-190] The adverse events highlighted in the SmPC of secukinumab are broadly consistent with those highlighted in the SmPCs of the TNFα inhibitors licensed for use in AS.[9-13]

Infections

In the MEASURE 2 study, [redacted] of patients in the “Any secukinumab 150 mg” group and [redacted] of patients in the “Any secukinumab” group had an infection or infestation over the entire 104 week treatment period, compared to a total of [redacted] of patients in the placebo arm.[15] The exposure adjusted incidence rates for infections and infestations over the entire treatment period were [redacted] and [redacted] per 100 patient years in the “Any secukinumab 150 mg”, “Any secukinumab dose” and placebo groups respectively.[15]

In the MEASURE 1 study, adverse events of infections and infestations were observed in [redacted] of patients in the “Any secukinumab 150 mg” group and [redacted] of patients in the “Any secukinumab dose” group when assessed over the entire 104 week treatment period.[16] This was compared to [redacted] of patients in the placebo group, though due to the design of the trial this was measured up to Week 24 only for the placebo arm. The exposure adjusted incidence rates for infections and infestations over the 104 week treatment period was similar in all groups [[redacted] and [redacted] per 100 patient years in the “Any secukinumab 150 mg”, “Any secukinumab dose” and placebo groups respectively].[16]

Neutropenia

Absolute frequencies of treatment emergent neutropenia in both the MEASURE 2 and MEASURE 1 trials were low ([redacted] in the “Any secukinumab 150 mg” group and [redacted] in the “Any secukinumab dose” group in MEASURE 2; [redacted] in the “Any secukinumab 150 mg” and [redacted] in the “Any secukinumab dose” group in MEASURE 1).[15, 16]

Hypersensitivity

Exposure adjusted incidence rates of hypersensitivity were similar in both secukinumab dose groups in MEASURE 2 (up to Week 52): [redacted] in the “Any secukinumab 75 mg” group and [redacted] in the “Any secukinumab 150 mg” group. In MEASURE 1, exposure adjusted incidence rates of hypersensitivity were more frequently reported in the “Any secukinumab 150 mg” group [redacted] by comparison to the “Any secukinumab 75 mg” group [redacted] in the entire Week 104 treatment period.[15, 16]

Major adverse cardiovascular events (MACE)

In MEASURE 2, one potential case of MACE was identified for adjudication in one patient with myocardial infarction, who was receiving the unlicensed dose of secukinumab 75 mg. This event was adjudicated as a MACE event and was considered by the investigator to be unrelated to study medication. No other MACE events were reported up to Week 52.[15, 191]

In MEASURE 1, there were 3 potential cases of MACE identified for adjudication: 2 patients with myocardial infarctions and 1 patient with a stroke. There were no cardiovascular deaths. All 3 events were on secukinumab and considered to be unrelated to study medication.[16, 191]

Malignancy

Across MEASURE 2 and MEASURE 1 only one patient receiving secukinumab (either 75 mg or 150 mg) reported a malignancy during the placebo controlled period. During this time, a single patient receiving placebo treatment also reported a malignancy, and thus there was no difference between the treatment arms.[135] When assessed over the entire safety period there was a lower number of malignancies per 100 patient years in the pooled secukinumab treatment groups

(either 75 mg or 150 mg) across the two trials in comparison to patients receiving placebo treatment [0.6 (95% CI: 0.2-1.5 vs. 1.6 (95% CI: 0.0-8.8)].[135]

Death

In total, 3 deaths were reported across both MEASURE 2 and MEASURE 1 for the entire 2 year period. In both trials, one death was reported up to Week 52, which occurred prior to Week 16.[191] In MEASURE 2 in a patient receiving secukinumab 75 mg this death was due to a cardiac disorder, which was not considered by the investigator to be related to secukinumab; in MEASURE 1 this death occurred in a placebo patient who suffered from depression and committed suicide. In addition, one death was reported in MEASURE 1 after the database lock for the Week 52 analysis, which was due to respiratory failure secondary to pulmonary fibrosis and cardiac failure, following approximately two years on active treatment. This was not considered to be related to secukinumab.[191]

4.12.4. Pooled Safety Analysis – plaque psoriasis trials

In addition to the data available from the MEASURE 2 and MEASURE 1 trials, a large body of evidence from other indications, most notably plaque psoriasis, describes safety results for secukinumab, and therefore considered of relevance to this submission and discussed below. A total of 6,200 patients have been treated with Cosentyx in blinded and open-label clinical studies in various indications (plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and other autoimmune conditions).[5] Of these, 3,671 patients were exposed to secukinumab for at least one year, representing 6,267 patient years of exposure.[5]

Although not the same indication, psoriasis represents an autoimmune disease for which secukinumab has recently been approved by SMC and NICE following appraisal of a number of factors including its safety profile. In addition, 10-25% AS patients suffer from concomitant psoriasis lesions.[58] Therefore, consideration of the safety results in the psoriasis population provides additional relevant safety evidence. Although a higher dose of secukinumab, 300 mg, is recommended for the treatment of psoriasis, data from psoriasis patients on a dose of 150 mg is available and is therefore presented for comparison. A pooled analysis of the placebo-controlled plaque psoriasis studies (FIXTURE, ERASURE, JUNCTURE and FEATURE) was conducted and reported in the SmPC.[5] Results from this analysis are discussed below.

The four placebo-controlled Phase III studies in plaque psoriasis were pooled to evaluate the safety of secukinumab in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).[5]

In addition, published two year data from the FIXTURE and ERASURE trials and recently published three year data from the SCULPTURE trial has found no new or unexpected safety signals, in line with the results presented below.[192] [193]

4.12.4.1. Adverse Events

The most frequently reported single adverse events were upper respiratory tract infections (most frequently nasopharyngitis and rhinitis). Most of the events were mild or moderate in severity.

AEs from the plaque psoriasis clinical studies (Table 64) are listed with the corresponding frequency category for each adverse drug reaction, based on the following Council for International Organizations of Medical Sciences convention (CIOMS III): very common (≥1/10);

common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 64. Summary of Adverse Events in Clinical Studies

System organ Class	Frequency	Adverse reaction
Infections and infestations	Very Common	Upper Respiratory tract infections
	Common	Oral herpes
	Uncommon	Oral candidiasis
		Tinea pedis
		Otitis externa
Blood and lymphatic disorders	Uncommon	Neutropenia
Immune system disorders	Rare	Anaphylactic reactions
Eye disorders	Uncommon	Conjunctivitis
Respiratory, thoracic and mediastinal disorders	Common	Rhinorrhoea
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous disorders	Uncommon	Urticaria

Source: Secukinumab Summary of Product Characteristics.[5]

Selected adverse events of interest, as specified by the SmPC, are infections, neutropenia, hypersensitivity and immunogenicity.[5] These are discussed in more detail below.

Infections

The majority of infections reported in the psoriasis trials consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0.14% of patients treated with secukinumab and in 0.3% of patients treated with placebo.[5]

Over the entire treatment period (a total of 3,430 plaque psoriasis patients treated with secukinumab for up to 52 weeks), infections were reported in 47.5% of patients treated with secukinumab (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of patients treated with secukinumab (0.015 per patient-year of follow-up).[5]

Neutropenia

Although neutropenia was more frequently observed with secukinumab than with placebo, across the psoriasis clinical studies, most cases observed have been mild, transient and reversible.[5]

Hypersensitivity reactions

The SmPC for secukinumab notes that urticarial and anaphylactic reactions to secukinumab have been observed, however these are uncommon and rare, respectively.[5]

Immunogenicity

As noted in the SmPC for secukinumab, immunogenicity rates with secukinumab are low (<1% of patients treated with secukinumab had developed antibodies to secukinumab within 52 weeks at the time the SmPC was published). Neutralising antibodies were not associated with loss of efficacy or any pharmacokinetic abnormalities.[5]

Comparative Safety

Although no active comparator safety data is available in the AS indication, this is available for the psoriasis indication where the FIXTURE trial included an etanercept treatment arm. The results from that trial indicated that the adverse event profiles of secukinumab and etanercept were similar.[194]

4.12.5. Summary of safety results

Overall, results from MEASURE 2 and MEASURE 1 demonstrate that secukinumab was well tolerated in the AS population. The safety profile of secukinumab in both MEASURE 2 and MEASURE 1 was comparable across doses up to Week 16 and assessment of exposure-adjusted incidence rates over the entire treatment period demonstrated adverse event rates similar to placebo. Consistent with the results from plaque psoriasis trials, the most commonly reported adverse event in both trials was nasopharyngitis, which by Week 16 had occurred in 11.1% and 13.6% of patients receiving secukinumab 150 mg treatment in MEASURE 2 and MEASURE 1, respectively. Other commonly reported adverse events included headache, nausea, dyslipidaemia and influenza. The results showed no new or unexpected safety signals associated with secukinumab in MEASURE 2 and MEASURE 1 compared to a large body of safety evidence from other autoimmune indications, notably psoriasis.

4.13. Interpretation of clinical effectiveness and safety evidence

4.13.1. Clinical effectiveness

Secukinumab is a first-in-class, IL-17A inhibitor for the treatment of AS in adults who have responded inadequately to conventional therapy. The targeting of IL-17A represents a novel mechanism of action that is more specific and selective than the inhibition of TNFα, the target of most other therapies currently licensed for AS.

The clinical effectiveness of secukinumab 150 mg in the treatment of AS has been demonstrated in two international, multicentre, Phase III randomised controlled trials: MEASURE 2 and MEASURE 1. Together, MEASURE 2 and MEASURE 1 included a large cohort of 590 patients with moderate to severe AS and a previous history of active AS despite current or previous treatment with NSAIDs, DMARDs and/or TNFα inhibitor therapy. These trials were placebo-controlled studies. Given that concomitant medications such as NSAIDs and physical therapy were permitted during the trials, the placebo arms can also be considered to represent a proxy for UK conventional care.

Outcome measures

The primary outcome of MEASURE 2 and MEASURE 1 was ASAS20 response at Week 16. Secondary outcomes including ASAS40, BASDAI, and ASQoL, assessed disease activity, physical function, disease progression and quality of life. ASAS20 is recommended by both BSR and EMA guidelines, while the ASAS criteria more broadly are the recommended method of

disease monitoring in AS according to ASAS/EULAR guidelines.[39, 86, 176] ASAS40 is more stringent than ASAS20, and is increasingly being recognised as a common outcome measure for AS.[163] BASDAI is a widely used measure of disease activity that has been shown to have excellent content validity, whilst still being easy for patients to complete.[166, 167] ASQoL is a disease-specific questionnaire, designed to capture the specific and unique aspects of this condition.[169]

Primary outcome: ASAS20 response

- Both MEASURE 2 and MEASURE 1 trials provide evidence for a rapid onset of efficacy with secukinumab, which is sustained for up to two years.
- For the primary outcome, 61.1% and 60.8% of patients receiving secukinumab 150 mg achieved an ASAS20 response at Week 16 in MEASURE 2 and MEASURE 1, compared with 28.4% and 28.7% for placebo, respectively ($p<0.0001$). This significant benefit versus placebo was also seen for the more stringent measure of ASAS40.

Secondary outcomes

- Secondary outcome measures including ASAS40, BASDAI change from baseline, and BASFI change from baseline, further confirmed the clinical efficacy of secukinumab on disease activity and physical function, with secukinumab demonstrating significant benefit versus placebo across these measures at Week 16. Again, patients treated with secukinumab 150 mg were seen to maintain these responses up to 2 years (Week 104).
- MEASURE 1 also provided results for radiographic outcomes, highlighting the efficacy of secukinumab on a further clinically relevant and important aspect of the disease. In MEASURE 1, no radiographic progression was observed in approximately 80% of patients randomised to secukinumab at baseline (mSASSS change ≤0).

Subgroup analyses

- Both MEASURE 2 and MEASURE 1 trials assessed the efficacy of secukinumab separately in TNFα naïve and TNFα inadequate responder populations as part of pre-specified subgroup analyses. Secukinumab 150 mg provided significant improvements versus placebo for both primary and secondary outcomes across both subgroups.

Comparative effectiveness: indirect comparison

With no head-to-head trial evidence directly comparing secukinumab 150 mg to the relevant biologic comparators, relative effectiveness was estimated by conducting a Bayesian NMA. No statistically meaningful differences were found between secukinumab 150 mg and the relevant biologic comparators across all outcomes analysed, with the exception of the comparison to infliximab 5 mg/kg in the BASDAI change from baseline outcome; a comparison that may be considered unreliable due to the limitations of the Giardina *et al.* study. Importantly, these results were observed consistently in both the analysis of the whole population in which trials with mixed populations were considered and in the analysis of the biologic naïve population specifically. These results demonstrate the comparable efficacy of secukinumab 150 mg to other biologic comparators across the most clinically relevant outcomes.

4.13.2. Safety evidence

Secukinumab 150 mg was well tolerated and neither MEASURE 2 nor MEASURE 1 showed any new or unexpected signs with regards to the safety profile of secukinumab compared with the

large existing body of safety evidence for secukinumab in other autoimmune indications, most notably psoriasis. In both trials, the majority of adverse events were mild or moderate in severity, with the most commonly reported adverse event in both trials being nasopharyngitis. In MEASURE 2, the overall incidence of treatment-emergent AEs up to Week 16 in the secukinumab 150 mg group was comparable to the placebo group (65.3% vs 63.5%, respectively). In MEASURE 1 there was a slightly higher rate of treatment emergent AEs up to Week 16 in the secukinumab 150 mg group compared with placebo (69.6% vs. 55.7%).

4.13.3. Strengths of the evidence

Both MEASURE 2 and MEASURE 1 are international, multicentre, randomised, double-blind, placebo controlled trials and are the first Phase III trials to investigate secukinumab as a potential therapy for adults with AS who have responded inadequately to conventional therapy. The internal validity of both MEASURE 2 and MEASURE 1 is supported by the following:

- Both trials are of high-quality, undergoing full quality assessment according to the Centre for Reviews and Dissemination criteria and scoring correctly for all questions (see Section 4.6 and Appenidix C).
- All patients enrolled in both MEASURE 2 and MEASURE 1 were randomised following appropriate double-blind procedures
- A large sample size of patients were included in both trials, matching the patient population in the secukinumab marketing authorisation and reflective of the AS patient population seen in UK clinical practice. Baseline characteristics were seen to be similar across the MEASURE 2 and MEASURE 1 trials.
- A large number of outcomes were investigated, spanning disease activity, physical function, quality of life, radiographic outcomes and disease progression. The primary outcome, ASAS20, is a recommended clinical outcome by both BSR and EMA guidelines, and the secondary outcome ASAS40 is a more stringent response outcome and considered by the EMA to be an appropriate primary efficacy endpoint to assess major clinical response. [39, 86, 176]
- Both MEASURE 2 and MEASURE 1 reported consistent results, with all primary and secondary endpoints met across both trials (with the exception of ASAS partial remission in MEASURE 2)

4.13.4. Limitations of the evidence

A potential limitation of the external validity of MEASURE 1 is that patients were treated with an intravenous loading dose which is not reflective of the licensed subcutaneous loading schedule. However this is not thought to severely limit the external validity of the results of the trial. The EPAR for secukinumab recognised that ASAS20 outcomes for secukinumab in AS are similar regardless of the route of administration, suggesting that the MEASURE 1 trial should be considered relevant to the decision problem.[178] Furthermore, the impact of excluding the MEASURE 1 trial from consideration is comprehensively addressed by the NMA presented in Section 4.10 through sensitivity analyses 1 and 3, which explore the removal of MEASURE 1 from the analysis. These two sensitivity analyses were seen to provide results that were broadly similar to the base case analysis in which MEASURE 1 is included.

Both MEASURE 2 and MEASURE 1 were double-blind and placebo-controlled up to Week 16. After this point, patients allocated to placebo were re-randomised to receive secukinumab.

Double-blinding was maintained up to Week 52 after which both patients and site personnel were unblinded up to Week 104, to remove the need for placebo injections to be received by the patients. The lack of placebo-controlled results post-Week 16 does not detract from the meaningfulness of the observed efficacy of secukinumab 150 mg which was sustained up to Week 104 across all outcomes. The removal of blinding post-Week 52 would not introduce bias since all patients were receiving the study drug at this timepoint. Furthermore, unblinding of the trial due to re-randomisation of placebo patients to active treatment is similarly a feature of the trials of the TNFα inhibitor comparators in this indication.

Finally, the principal trials for the efficacy of secukinumab are limited to comparison with placebo and do not provide robust comparative evidence of the efficacy of secukinumab compared to other licensed therapies. However, a Bayesian NMA was conducted to provide comparative evidence for secukinumab versus all other licensed comparators and this found there to be no significant difference between the efficacy of secukinumab and all other treatment options.

4.14. Ongoing studies

MEASURE 2 and an extension to the MEASURE 1 study are currently ongoing. In addition, two additional trials, MEASURE 3 and MEASURE 4 are ongoing, details of which are available on clinicaltrials.gov. However, none of these trials are anticipated to provide additional evidence in the indication under review within the next 6 to 12 months.

5. Cost effectiveness

Summary of Economic Evidence

- In line with the final NICE scope for this appraisal, the cost-effectiveness of secukinumab 150 mg was evaluated in the population of patients with active AS for whom conventional therapy has been inadequately effective or not tolerated (biologic naïve population) and the population for whom TNFα inhibitors have been inadequately effective or not tolerated (biologic experienced population).
- Overall, the results of the economic base case fully incremental analysis found all comparator biologics to secukinumab were either dominated, extendedly dominated or associated with ICERs versus secukinumab that were considerably above the conventional NICE threshold of £20,000-£30,000 per QALY, indicating that secukinumab represents a cost-effective treatment option. In the biologic experienced population, secukinumab was compared to conventional care and found to be cost-effective versus this comparator with an ICER of £2,245.
- The economic evaluation was based on a decision analytic model, the structure of which aligned closely with that of the York model developed for the MTA of TNFα inhibitors in AS, and which ran over a lifetime (58 year) time horizon.[19]The model consisted of a decision tree model for the first 12 weeks of treatment, at which point response to therapy was assessed by BASDAI 50 response. Following this, patients entered a Markov model in which clinical effects of short-term changes in BASDAI and BASFI were reflected. Relative effect estimates were informed by the NMA in the biologic naïve population for the comparison to TNFα inhibitors in this population, and by the MEASURE 2 and MEASURE 1 trials for the comparison to conventional care in the biologic experienced population.
- In addition, the model considered long-term changes in BASFI as independently related to disease activity (BASDAI) and rate of radiographic progression (mSASSS). Adverse events considered were tuberculosis reactivation and other serious infections.
- Utility was based on a linear mapping algorithm that linked utility to covariates of BASDAI, BASFI, gender and age; in the base case this algorithm was informed by the MEASURE 2 and MEASURE 1 trials. Costs were included from a NHS and PSS perspective and took account of the simple PAS available for secukinumab 150 mg.
- Exploratory analyses were performed in which use of second-line biologics following discontinuation of a first biologic was considered amongst patients entering the model as biologic naive. An exploratory analysis in the biologic experienced population extended the comparators from conventional care only to TNFα inhibitors. In both these exploratory analyses assumptions of reduced efficacy for biologic comparators when used as second-line biologics were required due to a lack of comparator data in this population. These exploratory analyses similarly found secukinumab to represent a cost-effective treatment option in both the biologic naïve and biologic experienced populations.
- Results of scenario analyses confirmed that the base case findings were robust to changes in key model assumptions and input parameters.
- **Secukinumab 150 mg is a cost effective treatment versus all TNFα inhibitor comparator therapies in the biologic naïve population.**

- **Secukinumab 150 mg is a cost effective treatment versus conventional care in the biologic experienced population with an ICER of £2,245.**

5.1. Published cost-effectiveness studies

5.1.1. Identification of studies

A systematic literature review (SLR), consisting of an original SLR and an update, was conducted to identify and review evidence from economic analyses relating to the use of secukinumab and/or relevant biologic comparators in the treatment of adult patients with AS. In addition, studies that included cost or resource utilisation estimates, or reported utility data pertinent to AS and its treatment were also identified. These latter studies are discussed in more detail in the appropriate sections of this submission (Section 5.4 for utility data; and Section 5.5 for cost and resource utilisation estimates), but the methods and overall results of the SLR are described below and in the accompanying appendices.

5.1.2. Search strategy

Relevant studies were identified using a predefined search strategy, as described in full in Appendix C. The search strategy included searches of the following electronic databases:

- MEDLINE and MEDLINE In-Process (via PubMed platform)
- Embase (via Elsevier platform [original review] and Ovid SP [update review])
- EconLit (via EBSCO platform)
- The Cochrane Library (via Wiley Online platform), including:
    - The Cochrane Central Register of Controlled Trials
    - National Health Service's (NHS's) Economic Evaluation Database
    - Health Technology Assessment database
- BIOSIS (via Dialog platform [original review] and Web of Science [update review])

In addition, targeted desktop research was performed to identify relevant health technology assessment (HTA) documents from recognised sources (including NICE, SMC, International Society for Pharmacoeconomics and Outcomes Research [ISPOR], Canadian Agency for Drugs and Technologies in Health [CADTH] and Institute for Quality and Efficiency in Healthcare [IQWiG] websites). Hand searches of the bibliographies of any identified, recent, and relevant SLRs, as well as the identified HTA documents, were then conducted to identify any further studies of interest that were not captured by the database search. Systematic reviews were not included in the review in their own right.

For the original SLR, the database searches were performed from January 1999 – January 2015. This date range was selected because infliximab, as the first biologic of interest, was approved in the European Union in 1999. Although infliximab was not approved for AS at this time, this date was chosen to ensure that evidence published prior to market authorisation in AS was included. For the update to the SLR, electronic searches were performed on 14th September 2015 and searched for all articles from 1st January 2014 to this date. Results of this search were then de-duplicated against the full list of electronic records identified by the original search. The overlap

in dates (1st January 2014 – January 2015) was deliberate in order to ensure that any studies published prior to the date of the original search but indexed afterwards were captured.

Searches of congress abstracts and HTA websites were originally performed from 3rd – 16th March 2015, and update searches were conducted on 7th December 2015.

Congress abstracts more than 3 years old were excluded from the SLR because high-quality studies reported in abstract form before 2013 will be expected to have been subsequently published in a peer-reviewed journal and therefore captured by database searches.

No language or geographical restrictions were applied to searches.

5.1.3. Study selection

Titles and abstracts were retrieved for all identified records and then reviewed against the predefined inclusion and exclusion criteria presented below in Table 65. Full-text articles of all records that met the inclusion and exclusion criteria were then retrieved and subject to a second round of screening using the same criteria.

At each stage, records were double-screened by two independent researchers to determine eligibility according to the inclusion and exclusion criteria. When there was a disagreement about study relevance, the two researchers discussed their decisions; in all instances, they were able to reach a consensus without consulting a third researcher.

Table 65. List of criteria for the inclusion and exclusion of studies in economic SLR

Criteria	Inclusion criteria	Exclusion criteria
Population	• Patients with AS	• None
Interventions[a] (applied to economic evaluations only)[b]	• Secukinumab (Cosentyx) • Certolizumab pegol (Cimzia) • Etanercept (Enbrel [biosimilars: Avent, BX2922, CHS-0214, ENIA11, Etacept, Etanar, GP2013, GP2015, HD203, LBEC0101, PRX-106, SB4, TuNEX, Yisaipu]) • Adalimumab (Humira, Trudexa [biosimilars: ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293]) • Infliximab (Remicade [biosimilars: CT-P13, Remsima, Inflectra]) • Golimumab (Simponi)	• Non-biologic treatments for AS (e.g., DMARDs)

Criteria	Inclusion criteria	Exclusion criteria
Study type	• Economic analyses (cost-effectiveness, cost-utility, cost-minimisation analyses) • Utility studies (including studies where utility weights were mapped from other instruments, eg. disease-specific patient-reported outcome measures) • Prospective studies reporting costs or resource utilisation (eg. observational studies, clinical trials) • Retrospective studies reporting costs or resource utilisation (eg. cost-of-illness, cross-sectional studies) • Systematic reviews of economic analyses, utility, resource-use, or cost studies[c]	• Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews • Articles reporting cost estimates that are not based on data (eg. commentaries making general reference to cost burden)
Outcomes	**Economic Evaluation outcomes** • ICERs • QALYs **Direct costs of interest may include the following:** • Medication costs • Outpatient visits • Hospitalisation costs (ED or hospital visits) • Laboratory costs • Diagnostic costs (e.g., magnetic resonance imaging, x-rays) • Physician costs • Resource-use estimates • Cost per treatment success or per remission or per QALY **Indirect costs of interest include:** • Productivity loss costs (wages lost because of travel, wages lost because of absences from work to outpatient visits) • Out-of-pocket expenses • Travel costs for patient and carer **Utility outcomes** • EQ-5D • SF-6D • HUI • Other dermatological utility measures	• Studies reporting QoL data but not utility outcomes[d]
Language	No limit	None
Date	• Database searches: January 1999 onwards • Conference abstracts: January 2013 onwards	None

[a]Note: Interventions of interest in this review consist of all therapy versions of the listed treatments (monotherapy and combinations, including methotrexate) at labelled doses. Studies that include patients with active AS despite treatment with DMARDs, NSAIDs, and/or previous TNFα inhibitor therapy and/or previous biologic therapy will be evaluated.
[b]Utility, resource-use, and cost studies that are relevant to AS were included regardless of interventions and comparators.
[c]Systematic reviews were included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening.
[d]Studies reporting QoL data but not utility outcomes were initially included in the original systematic review. However, given that sufficient relevant utility outcomes were identified (among which the majority of studies used EQ-5D, in line with the NICE reference case) these studies were excluded from the final systematic review.
Abbreviations: AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drug; ED, emergency department; EQ-5D, EuroQol 5 Dimensions; HUI, health utilities index; ICER, incremental cost-effectiveness ratio; NSAID, non-steroidal anti-inflammatory drug; QALY, quality-adjusted life-year; SF-36, SF-36 Health Survey; TNFα , tumour necrosis factor alpha.

5.1.4. Study flow diagram for the economic SLR

The number of records included and excluded at each stage of the screening process for the original and updated SLRs is shown in the PRISMA flow diagram presented in Figure 21.

Overall, a total of 201 and 32 records were included the original systematic review and systematic review update respectively. However, 95 publications from the original systematic review reported only HRQoL data and not utility, cost or economic outcomes, and were excluded from the final set of included studies. Therefore, 138 publications were ultimately included in this systematic review.

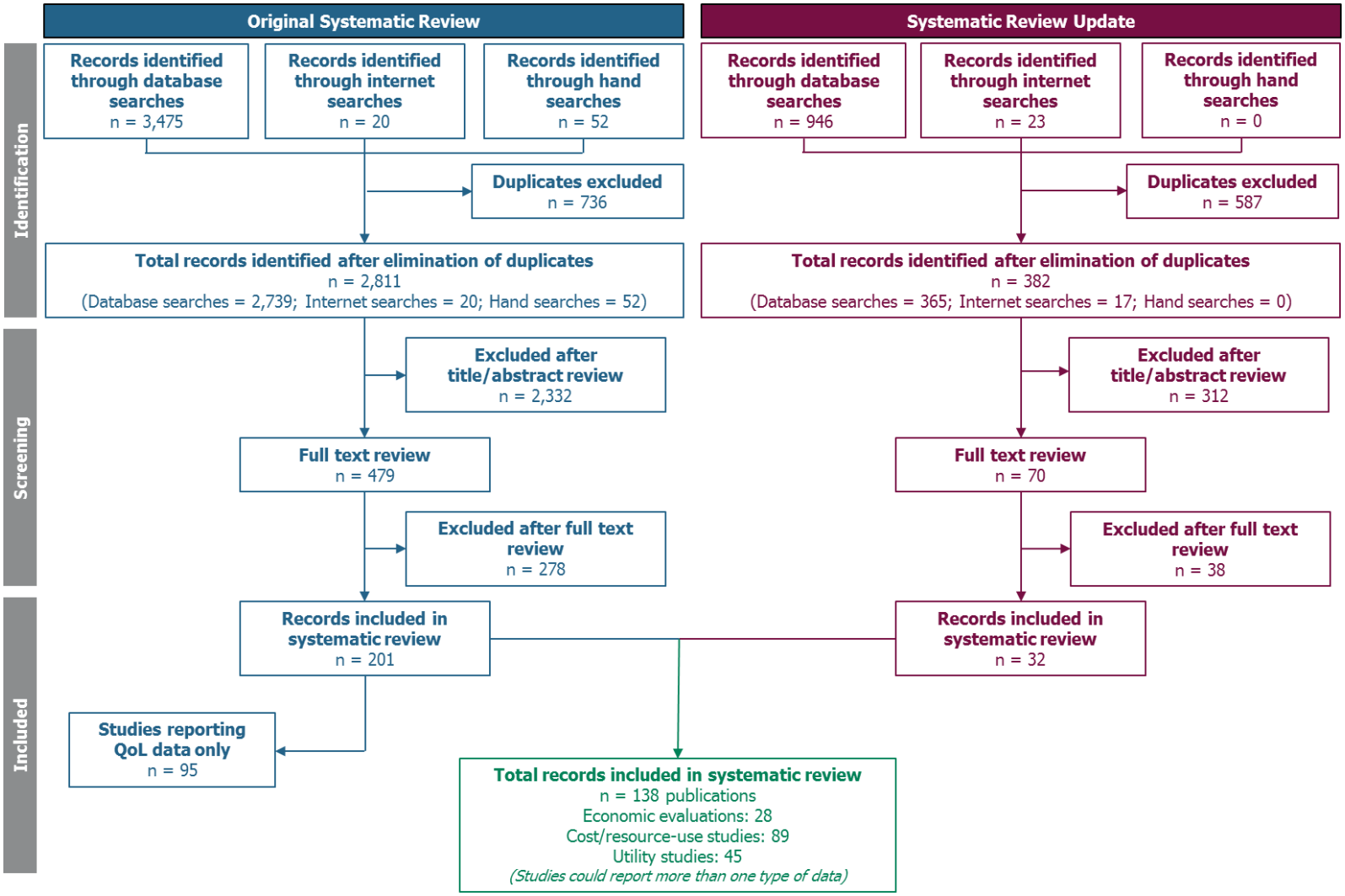
Within these 138 publications, 28 reported economic evaluations, 89 reported cost and resource use studies and 45 reported health state utility values. A number of publications reported more than one category of data.

The lists of included studies are provided in the following sections and accompanying appendices for each study type:

- For included cost-effectiveness studies see: Section 5.1.5 and Appendix M.
- For included utility studies see: Section 5.4 and Appendix N.
- For included cost and resource use studies see: Section 5.5 and Appendix O

The full list of excluded studies is presented in Appendix O.

Figure 21. PRISMA diagram for economic SLR



Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses; QoL, quality of life; SLR, systematic literature review.

5.1.5. Description of identified cost-effectiveness studies

Of the 138 records identified in the SLR, 28 consisted of economic evaluations that met the eligibility criteria specified in Table 65. Twelve analyses were conducted in the UK, with the remainder performed in the Netherlands (3); Spain (3); and 1 economic evaluation from each of the following countries: Brazil, the Czech Republic (two publications), Canada, France, Germany, Greece, Romania, Russia and Turkey.

No studies were identified that conducted an economic analysis including the use of secukinumab.

A summary list of UK-based and non-UK-based cost-effectiveness studies and HTA reports related to AS is presented in Table 66 and Appendix M, respectively.

Quality assessment was performed for each of the included UK economic evaluations, using the NICE methodology checklist for economic evaluations, which is based on the format described by Drummond and Jefferson (1996).[195] Quality assessments are presented Appendix Q

Table 66. Summary list of UK-based economic evaluations and HTA reports identified in the systematic literature review

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
Ara (2007)[196]	UK; NR	Mathematical model using patient-level data from phase 3 RCTs to inform clinical effectiveness and HRQoL changes in the model.	This study aimed to provide evidence on the potential costs and benefits associated with long-term (25-year) etanercept treatment for patients with severe AS in the UK in accordance with the BSR guidelines.	25 years	All patients had active AS and were assumed to have tried and failed to respond to at least two consecutive NSAIDs and have a BASDAI measurement ≥40 (scale 0–100) prior to entering the model. The mean age of patients in these studies ranged from 39.5 to 42 years.	**Breakdown of costs and time horizons incurred for a cohort of 1,000 patients over 4 time periods**			
						2 years			
						Etanercept plus NSAIDs	£13,041,740	1,185	**£27,594**
						NSAIDs alone	£2,889,706	817	**—**
						5 years			
						Etanercept plus NSAIDs	£26,389,802	2,646	**£23,649**
						NSAIDs alone	£7,109,054	1,831	**—**
						15 years			
						Etanercept plus NSAIDs	£51,415,277	5,739	**£22,580**
						NSAIDs alone	£18,596,422	4,286	**—**
						25 years			
						Etanercept plus NSAIDs	£62,516,684	7,285	**£22,704**
						NSAIDs alone	£26,538,439	5,700	**—**
Armstrong (2013)[197]	UK; NR	Initial decision tree and then a Markov model	HTA submission	20 years in the base case. Lifetime in the ERG analysis.	Adults with severe, active AS whose response to conventional therapy has been	Base-case results			
						Golimumab	Total=£93,786 Incremental=£5,119	Total=6.8506 Incremental=0.1925	**£26,597 vs conventional**
						Etanercept	Total=£93,782	Total=6.8504	**NA**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
					inadequate. Average age: NR.		Incremental=£5,115	Incremental=0.1923	**(extendedly dominated)**
						Adalimumab	Total=£93,601 Incremental=£4,934	Total=6.8426 Incremental=0.1845	**NA (extendedly dominated)**
						Conventional treatment	£88,667	Total=6.6581	**Reference**
						ERG analysis			
						Golimumab	Total=£99,361 Incremental=£4,134	Total=8.0296 Incremental=0.1534	**NA (extendedly dominated)**
						Etanercept	Total=£108,347 Incremental=£52	Total=8.3712 Incremental=0.0029	**£26,505 vs conventional**
						Adalimumab	Total=£108,295 Incremental=£8,934	Total=8.3683 Incremental=0.3387	**NA (extendedly dominated)**
						Conventional treatment	Total=£95,227	Total=7.8762	**Reference**
Botteman (2007)[198]	UK; 2004	The analysis was based on pooled data from 2 phase 3 studies of adalimumab in patients with active AS. A micro-simulation model was used to simulate	This study evaluated the cost-effectiveness of adalimumab vs conventional therapy in patients with active AS.	1, 5, and 30 years	A total of 397 patients with active AS were enrolled. 354 met the spinal pain VAS and BASDAI criteria at baseline, and 315 met both criteria at baseline and pre-baseline	**1 year (48 weeks)**			
						Adalimumab	Total costs=£9,857 AS-specific costs=£3,668 ADA therapy=£6,189 (drug costs=£5,233, monitoring costs=£905, AE costs=£51)	0.5529	**£47,083**
						Conventional therapy	Total cost=£4,832 AS-specific	0.4461	**—**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		individual histories of patients enrolled in 2 adalimumab clinical trials.			and therefore were included in the simulation. Compared with the trial patient population, those included in the simulation were very comparable in average baseline age (42.0 years old vs 42.2 years old, respectively), sex (76% vs 75% male, respectively) and race (96% vs 95% white, respectively).		costs=£4,832		
						5 years			
						Adalimumab	Total costs=£36,802 AS-specific costs=£18,136 ADA therapy=£18,666 (drug costs=£16,566, monitoring costs=£1,929, AE costs=£171)	2.6653	**£26,332**
						Conventional therapy	Total cost=£23,529 AS-specific costs=£23,529	2.1613	—
						30 years			
						Adalimumab	Total costs=£115,937 AS-specific costs=£81,330 Adalimumab therapy=£34,607 (drug costs=£30,999, monitoring=£3,230, AE costs=£378)	9.2220	**£23,097**
						Conventional therapy	Total costs=£92,080 AS-specific costs=£92,080	8.1891	—
Kobelt (2004)[199]	UK; 2002	Cost-effectiveness of infliximab	The aims of this study were to	Main cost-effectiveness model=2	All patients had confirmed and active AS.	Infliximab	Main model		
						Base case, societal	£6,214	0.175	**£35,400**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		was modelled using an individual simulation based on a 3-month placebo-controlled clinical trial with open, 1-year extension in 70 patients, over a total time frame of 2 years. The effect of long-term treatment was evaluated in a hypothetical Markov model over 30 years based on epidemiological data to illustrate potential long-term treatment and compliance with treatment.	investigate the cost of AS in the UK, focusing on the influence of disease severity on cost and QoL, and to construct a disease model to estimate the cost-effectiveness of infliximab in patients with active, unremitting disease.	years. Hypothetical Markov model=30 years.	The economic analysis included the open extension to 54 weeks for the intervention group; while for the purpose of comparison, patients from the placebo group were assumed to receive standard treatment after 12 weeks.	perspective (incremental vs placebo)			
						Base case, only health care costs included (incremental vs placebo)	£12,844	0.175	**£73,300**
						Infliximab	Hypothetical long-term model		
						Base case, societal perspective (incremental vs placebo)	£25,200	2.62	**£9,600**
						Base case, only health care costs included (incremental vs placebo)	£87,700	2.62	**£33,500**
Kobelt (2007)[200]	UK; 2005	Combined decision tree	To compare the cost-	Lifetime	The first trial by Braun et al.	Infliximab (5 mg/kg every 6	Incremental cost (£)	QALY gain	**ICER**
							BRAUN trial		

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		with a subsequent Markov model.	effectiveness of the treatment of AS with infliximab in the UK over a lifetime, estimated from 2 different clinical trials and adjusted for clinical practice guidelines.		(2002) randomised 70 patients with active AS. The mean age was 39.0 and 40.1 years in the placebo and the infliximab groups, respectively. ASSERT included 279 patents with active AS. The mean age in this trial was 41 and 40 years in the placebo and the infliximab groups, respectively. Resource utilisation and cost data were based on a cross-sectional retrospective survey that included 1,413 patients with a mean age of 57 years.	weeks) compared to standard treatment.	**No progression while on treatment** **Top value=societal perspective, all costs** **Bottom value=NHS and Personal Social Services costs only**		
							£–16,862	1.28	**Dominance**
							£36,378	1.28	**£28,332**
							50% progression while on treatment **Top value=societal perspective, all costs** **Bottom value=NHS and Personal Social Services costs only**		
							£–3,975	1.01	**Dominance**
							£35,756	1.01	**£35,332**
							Same progression in both groups **Top value=societal perspective, all costs** **Bottom value=NHS and Personal Social Services costs only**		
							£12,156	0.81	**£15,045**
							£39,336	0.80	**£49,417**
							ASSERT		
							No progression while on treatment **Top value=societal perspective, all costs** **Bottom value=NHS and Personal Social Services costs only**		
							£–15,927	1.27	**Dominance**
							£33,920	1.27	**£26,751**
							50% progression while on treatment **Top value=societal perspective, all costs**		

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							Bottom value=NHS and Personal Social Services costs only		
							£–5,233	1.01	**Dominance**
							£34,408	1.01	**£34,067**
							Same progression in both groups **Top value=societal perspective, all costs** **Bottom value=NHS and Personal Social Services costs only**		
							£10,540	0.88	**£11,937**
							£39,242	0.86	**£46,167**
McLeod (2007)[201]	UK; NR	Exploratory economic modelling. A simple spread-sheet model was developed and combined life-table–adjusted mortality rates with Markov-like transitions between TNFα inhibitor treatments.	To assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of AS. It was commissioned by the National Coordinating Centre of Health Technology Assessment on behalf of NICE.	12 months (short-term model); 20 years (long-term model extension).	Cohort of males aged 40 years with initial mean BASDAI/ BASFI scores of 6.5 and 5.6, respectively.	**Short-term model baseline costs (£):**			
						Conventional therapy	All costs: £213	Mean utility: 0.531 Total QALYs: 521.7	
						Adalimumab	All costs: £5,860 Drug acquisition=£5,453; Drug administration=£0; Therapy monitoring=£92; TB testing=£89; TB treatment=£8; AEs=£173; Disease-related=£173	Mean utility: 0.631 Total QALYs: 620.3 Incremental all costs: £5,647 Incremental QALYs per patient: +0.099	**Incremental cost per QALY gained: £57,258**
						Etanercept	All costs: £5,680 Drug	Mean utility: 0.631	**Incremental cost per**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							acquisition=£5,454; Drug administration=£0; Therapy monitoring=£92; TB testing=£89; TB treatment=£8; AEs=£173; Disease-related=£173	Total QALYs: 620.3 Incremental all costs: £5,647 Incremental QALYs per patient: +0.099	**QALY gained: £57,261**
						Infliximab	All costs: £12,059 Drug acquisition=£9,856; Drug administration=£1,796; Therapy monitoring=£92; TB testing=£89; TB treatment=£8; AEs=£173; Disease-related=£173; Incremental costs=+£11,845	Mean utility: 0.631 Total QALYs=620.3 Incremental QALYs per patient=+0.099 Incremental all costs: £11,845 Incremental QALYs per patient: +0.099	**Incremental cost per QALY gained: £120,109**
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-2 costs (£)			
						Conventional therapy	All costs: £425	Total QALYs: 1,015.6	
						Adalimumab + etanercept	All costs: £9,425 Drug acquisition=£8,750; Drug administration=£0; Therapy	Total QALYs: 1,186.9 Accumulated increment-al costs: 9,000 Accumulated	**Incremental cost per QALY gained: £52,534**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							monitoring=£162; TB testing=£89; TB treatment=£13; AEs=£58; Disease-related=£354; Accumulated incremental costs=+£9,000	increment-al QALYs: +0.171	
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-3 costs (£)			
						Conventional therapy	All costs: £632	Total QALYs: 1,489.2	
						Adalimumab + etanercept	All costs: £12,411 Drug acquisition=£11,479; Drug administration=£0; Therapy monitoring=£220; TB testing=£89; TB treatment=£16; AEs=£69; Disease-related=£539	Total QALYs: 1711.7 Accumulated increment-al costs: +11,780 Accumulated incremental QALYs: +0.223	**Incremental cost per QALY gained: £52,932**
						Infliximab	All costs: £22,779 Drug acquisition=£18,544; Drug administration=£3,301; Therapy monitoring=£220; TB testing=£89; TB treatment=£16; AEs=£69;	Total QALYs: 1,711.7	**Accumulated incremental costs: +22,147** **Accumulated incremental QALYs: +0.223** **Increment-al cost per QALY gained: £99,516**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							Disease-related=£539		
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-5 costs (£)			
						Conventional therapy	All costs: £1,033	Total QALYs: 2,378.6	
						Adalimumab + etanercept	All costs: £12,411 Drug acquisition=£15,791; Drug administration=£0; Therapy monitoring=£311; TB testing=£89; TB treatment=£23; AEs=£86; Disease-related=£913	Total QALYs: 2,662.5 Accumulated increment-al costs: +11,780 Accumulated incremental QALYs: +0.284	**Incremental cost per QALY gained: £56,976**
						Infliximab	All costs: £30,969 Drug acquisition=£25,113; Drug administration=£4,435; Therapy monitoring=£311; TB testing=£89; TB treatment=£23; AEs=£86; Disease-related=£913	Total QALYs: 2662.5	**Accumulated incremental costs: +29,936** **Accumulated incremental QALYs: +0.284** **Increment-al cost per QALY gained: £105,423**
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-10 costs (£)			
						Conventional therapy	All costs: £1,962	Total QALYs: 4,292.3	
						Adalimumab +	All costs: £25,675	Total QALYs:	**Incremental**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						etanercept	Drug acquisition=£23,146; Drug administration=£0; Therapy monitoring=£468; TB testing=£89; TB treatment=£33; AEs=£115; Disease-related=£1,823	4624.2 Accumulated increment-al costs: +23,713 Accumulated increment-al QALYs: +0.332	**cost per QALY gained: £71,454**
						Infliximab	All costs: £44,573 Drug acquisition=£35,782; Drug administration=£6,262; Therapy monitoring=£468; TB testing=£89; TB treatment=£33; AEs=£115; Disease-related=£1,823; Accumulated incremental costs=+£42,610	Total QALYs: 4624.2	**Accumulated incremental costs: +42,610** **Accumulated incremental QALYs: +0.332** **Incremental cost per QALY gained: 128,399**
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-20 costs (£)			
						Conventional therapy	All costs: £3,546	Total QALYs: 7,009.0	
						Adalimumab + etanercept	All costs: £36,705 Drug acquisition=£32,339; Drug	Total QALYs: 7344.2 Accumulated incremental	**Incremental cost per QALY gained: £98,910**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							administration=£0; Therapy monitoring=£665; TB testing=£89; TB treatment=£46; AEs=£153; Disease-related=£3,413	costs: +33,159 Accumulated incremental QALYs: +0.335	
						Infliximab	All costs: £62,213 Drug acquisition=£49,284; Drug administration=£8,563; Therapy monitoring=£665; TB testing=£89; TB treatment=£46; AEs=£153; Disease-related=£3,413	Total QALYs: 7344.2	**Accumulated incremental costs: +£58,667** **Accumulated incremental QALYs: +0.335** **Incremental cost per QALY gained: £175,000**
SMC (2005)[202]	Scotland; Unclear	Individual patient-based cost-utility model.	HTA submission	15 years	Patients with active AS who had shown an inadequate response to 2 NSAIDs were included.	Etanercept (25 mg twice a week)	£9,296 per year	NR	**The result of the base-case model was an incremental cost per QALY ratio of £11,700 at 15 years.**
						Infliximab (5 mg/kg every 6-8 weeks)	£10,894-£14,525 per year (£14,665-£17,877 in first year for patients weighing 60 kg-80 kg; for those weighing < 60 kg, annual costs would be £8,170-£10,894 [£10,999- £13,408 in first year]).	NR	

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
SMC (2006)[203]	Scotland; 2006	Cost utility, micro-simulation model.	HTA submission	30 years	Data to populate the model was taken from 2 clinical trials which included adults with severe, active AS who had an inadequate response to 2 or more NSAIDs.	Adalimumab (40 mg every 2 weeks)	£9,295 per year	NR	**The cost per QALY in the baseline analysis was £23,000, rising to £26,000 if a 5-year time horizon was used or £47,000 if a 48-week horizon was taken.**
						Infliximab (5 mg/kg every 6 to 8 weeks)	£10,910-£14,547 per year (£14,687-£17,903 in first year for patients weighing 60 kg to 80 kg patient; for those weighing < 60 kg, annual costs would be £8,183-£10,910 [£11,015-£13,428 in first year])	NR	
						Etanercept (25 mg twice weekly or 50 mg weekly)	£9,295 per year	NR	
						Conventional therapy	NR	NR	
SMC (2011)[204]	Scotland; 2011	CUA, a decision tree and Markov model was used to assess treatment effect at 12	HTA submission	20 years	Adults with severe, active AS who had responded inadequately to 2 conventional therapies.	Golimumab (50 mg once monthly as a s.c. injection)	£9,156 per year	NR	**If 5% of patients were assumed to require the 100-mg dose of GOL, the cost per QALY vs**
						Adalimumab (40 mg every 2 weeks as a s.c.	£9,156 per year	NR	

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		week cycles CMA was also presented in response to a request from SMC.				injection			**conventional DMARDs was £32,546, which was less cost-effective than ADA or ETN.**
						Etanercept (25 mg twice weekly or 50 mg weekly as a s.c. injection)	£9,295 per year	NR	
						Conventional therapy	NR	NR	
SMC (2014)[205]	Scotland; 2014	The company submitted a CUA for AS and used a dual structure for the model with a decision tree, followed by a Markov structure for the longer-term impact on the disease. CMA was provided in response to a request from SMC reviewers.	HTA submission	Lifetime	Data from the RAPID-axSpA study were used which involved patients with active AS.	Certolizumab pegol (200 mg s.c. every 2 weeks or 400 mg every 4 weeks)	£9,295 per year	NR	**NR**
						Golimumab (50 mg or 100 mg s.c. once monthly)	£9,156-£18,311 per year	NR	**NR**
						Etanercept (25 mg s.c. twice weekly or 50 mg s.c. once weekly)	£9,295 per year	NR	**NR**
						Adalimumab (40 mg s.c. every other week)	£9,156 per year	NR	**NR**
SMC (2015)[206]	(Scotland, UK, 2014)	Cost-minimisation	HTA submission	1 year	Data from the PLANETRA	Infliximab (Remicade®) (3	First year £10,071 Subsequent years	NR	**NR**

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		analysis			study were used. As infliximab (Remsima®) is a biosimilar medicine, the conclusion of clinical equivalence based on this study was assumed to extrapolate to the other indications for the reference product.	mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter)	£7,553 to £8,812 (6 to 7 doses)		
SMC (2015)[207]	(Scotland, UK, 2014)	Cost-minimisation analysis	HTA submission	1 year	Data from the PLANETRA study were used. As infliximab (Remsima®) is a biosimilar medicine, the conclusion of clinical equivalence based on this study was assumed to extrapolate to the other indications for the reference product.	Infliximab (Inflectra®) (3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter)	First year £9,064 Subsequent years £6,798 to £7,931 (6 to 7 doses)	NR	**NR**
						Infliximab (Remicade®) (3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the	First year £10,071 Subsequent years £7,553 to £8,812 (6 to 7 doses)	NR	NR

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						first infusion, then every 8 weeks thereafter)			

Abbreviations: AE, adverse event; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CUA, cost utility analysis; ERG, Evidence Review Group; HTA, Health Technology Assessment; ICER, incremental cost-effectiveness ratio; LRiG, Liverpool Reviews and Implementation Group; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; QALY, quality-adjusted life year; SMC, Scottish Medicines Consortium; TB, tuberculosis; TNFα, tumour necrosis factor alpha.

5.2. De novo analysis

5.2.1. Patient population

The *de novo* cost-utility model considered the population of patients with active AS, as defined by the Modified New York criteria, and for whom conventional therapy (i.e. NSAIDs alongside physiotherapy), or prior biologic therapy, has been inadequately effective or not tolerated.[77] This population is within the terms of the licensed indication for secukinumab in AS and is aligned to the population defined in the final NICE scope of this appraisal. This also matches the population-based eligibility criteria of the systematic review of clinical evidence (see Table 6 and Table 7), and the population recruited to the MEASURE 1 and MEASURE 2 trials of secukinumab in AS (see Section 4.3).

Within this licensed indication, the model specifically considered two distinct patient populations:

- The population of patients who are naïve to biologic therapy: This represents the population of patients for whom conventional care has been inadequately effective or not tolerated but in whom biologic treatment has not yet been administered. Based on existing NICE recommendations and the BSR guidelines for the use of TNFα inhibitors in these patients, and in line with the NICE final scope for this appraisal, the relevant comparators to secukinumab in this population were the TNFα inhibitors (see further discussion in Section 5.2.3). Evidence for efficacy of secukinumab and the relevant comparators in this population came from the base case NMA in biologic naïve patients (Section 4.10.7).
- The population of patients who have previously received one or more biologic therapies: The systematic literature review presented in Section 4.1 identified no data on efficacy of comparator biologics in this population, and the Assessment Group acknowledged the lack of robust data in this population as part of the recent NICE MTA.[19, 20] Furthermore, there are no official guidelines or recommendations for sequencing of biologic therapies. Therefore, no robust comparison to TNFα inhibitors in this population was possible and conventional care was considered to be the most appropriate comparator in the base case analysis for this population. The evidence for efficacy of secukinumab and conventional care in this population came from the pre-specified biologic experienced subgroup of the MEASURE 1 and MEASURE 2 studies, with the placebo arm considered a proxy for conventional care (see Section 5.2.3).

By considering these patient groups, the evaluation addressed the NICE decision problem as outlined in the final scope.

5.2.2. Model structure

The developed model was a short-term 3-month decision tree, followed by a long-term Markov model. The model was built in Microsoft Excel.

Induction period (decision tree model)

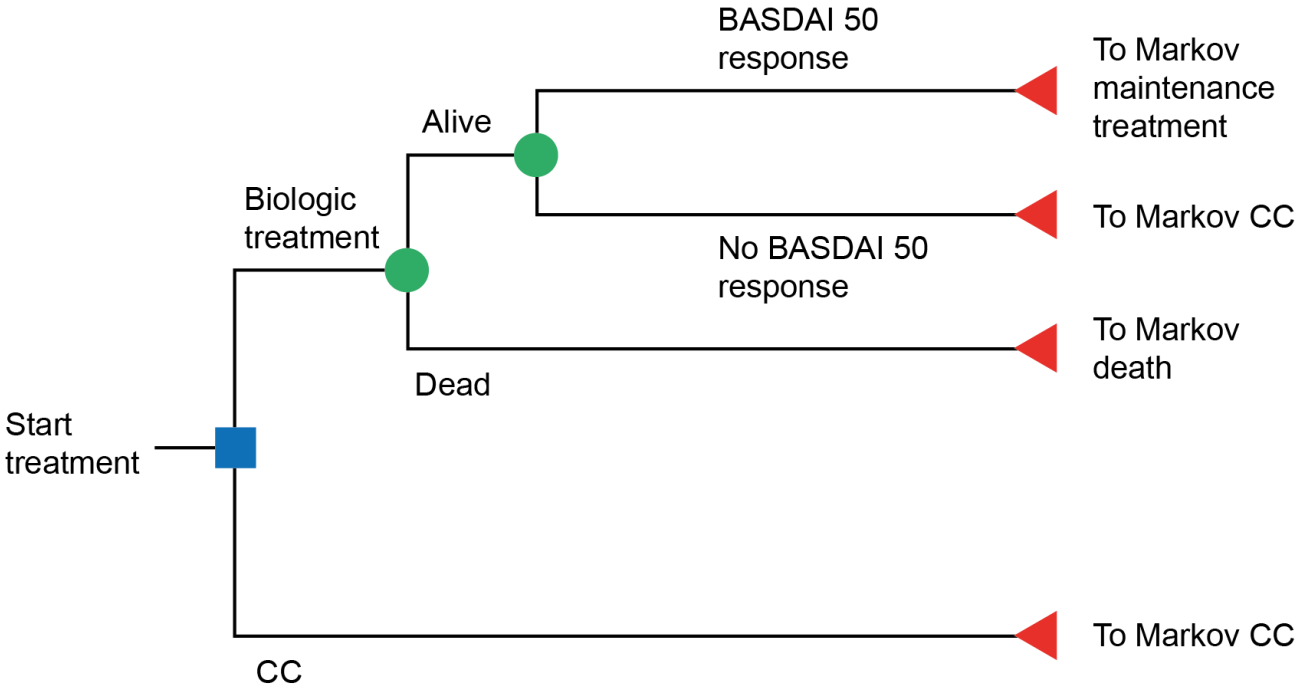
Patients entered the decision tree model and received treatment for a 3 month (12 week) induction period. At the end of this three month period patients entered the Markov model. Figure 22 presents the decision tree structure of the model.

Patients who have received biologics were classed as either responders or non-responders, depending upon whether or not they had achieved a BASDAI 50 response at the 12 week

timepoint. A scenario analysis was conducted in which the definition of response was adjusted to more closely match that in the BSR guidelines (2004); that is a reduction of BASDAI to 50% of the pre-treatment value **or** a fall of ≥2 units in BASDAI score (see Section 5.8.3).[39] An analysis of patient-level data from the MEASURE 2 and MEASURE 1 trial exploring BASDAI 50 response rates according to this definition is presented in Appendix H.

Non-responders at the 12 week assessment point did not continue biologic therapy within the model, but instead moved to receive treatment with conventional care in the Markov model. In contrast, responders were modelled to continue maintenance treatment with the same biologic therapy in the Markov model.

Figure 22. Decision tree model structure (Months 1-3)

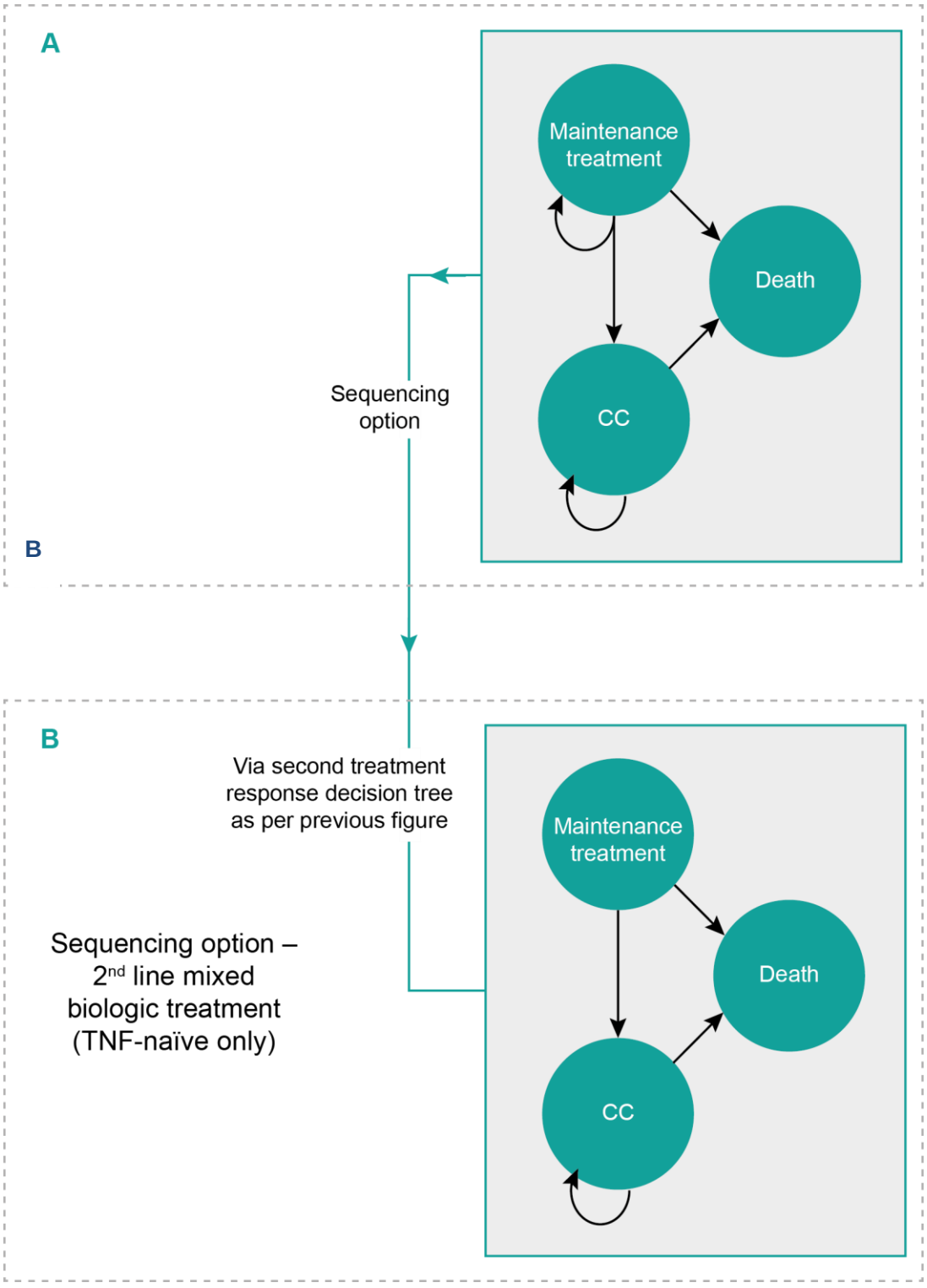


Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care.

Maintenance period (Markov model)

The structure of the Markov model is presented in Figure 23. This consisted of three health states, referring to maintenance biologic treatment, conventional care and death.

Figure 23. Markov model structure: A) initial biologic treatment (all patients) B) sequential biologic treatment (patients entering the model as biologic naïve only)



Abbreviations: CC, conventional care; Mnt Tx., maintenance treatment; TNF, tumour necrosis factor.

Non-responders did not continue biologic therapy beyond 12 weeks and instead moved directly into the conventional care state of the Markov model (Figure 23A). Responders continued maintenance treatment with the same biologic therapy. These patients moved into the "Maintenance treatment" state of the Markov model (Figure 23A). In the base case analysis of the biologic naïve population, transition to conventional care occurred on biologic discontinuation

as it was assumed that patients could not receive a second-line biologic therapy. Patients in the conventional care state were modelled to remain in this state until death. Finally, from any health state, patients also had a risk of dying (moving to the absorbing “Death” state).

The model additionally incorporated potential for adverse events. Patients continuing on biologic therapy were associated with a probability of experiencing a major adverse event (ie. serious infection), which was applied directly to the “Maintenance treatment” health state.

Second-line biologic – exploratory analyses

In addition to the base case analysis, exploratory analyses were conducted in which it was assumed that patients could receive a second-line biologic therapy. Analyses incorporating this assumption were conducted separately for the biologic naïve and biologic experienced populations, with introduction of this assumption resulting in different alterations to the analysis depending on the population, as described below and depicted in Figure 1.

Exploratory analysis of the biologic naïve population

In the biologic naïve population, upon discontinuation of their first biologic, patients who initially entered the model as biologic naïve could transition to receive a second-line biologic therapy. These patients repeated the process of response assessment after 12 weeks for their second-line biologic therapy and subsequently transitioned to maintenance biologic treatment or conventional care, as presented above in Figure 23B.

There are no guidelines or recommendations on specific sequencing of biologic therapies. Therefore, second-line biologic therapy was modelled using a “basket” approach. In this approach, biologic naïve patients moved to a “basket” therapy consisting of a mix of conventional care and all relevant biologic treatments with the exception of that used as the first-line biologic, upon discontinuation of their first biologic treatment,. The contribution of conventional care to this basket therapy was 25%, based on expert clinical feedback that up to 25% of patients would transition to conventional care rather than receive a second-line biologic. The contribution to the basket therapy of the biologics was unweighted. Third-line biologics were not modelled

The model applied an assumption that efficacy of biologic therapy is reduced when used in the second-line setting, and hence applied a relative efficacy reduction to the biologics in the basket therapy (see Section 5.3).

Exploratory analysis of the biologic experienced population

Due to the lack of RCT data on efficacy of biologic comparators when used in a biologic experienced group, the base case analysis for this population compared versus conventional care only. In an exploratory analysis, comparison versus the TNFα inhibitor therapies was incorporated. Given the lack of data to inform this analysis, a reduction in efficacy was applied to the biologic naïve base case NMA, representing a decline in efficacy between first and second line treatments. A constant efficacy reduction was applied across all biologics, according to the reduction observed in the MEASURE 1 and MEASURE 2 studies between the pre-specified TNFα inhibitor-naïve and TNFα inhibitor-IR subgroups.

5.2.2.1. Justification of chosen structure in line with clinical pathway of care

The economic model aimed to reflect the clinical pathway of care with biologic treatment for patients with active AS for whom conventional therapy, or prior biologic therapy, has been

inadequately effective or not tolerated. This pathway of care consists of treatment with biologic therapy for an induction period followed by assessment of response in order to decide whether biologic treatment should be continued. Clinical guidelines specify a timepoint for assessment of response of between 6 – 12 weeks, and note that treatment should not be stopped for ineffectiveness within 12 weeks.[39] The model structure reflected this feature of biologic treatment in clinical practice by assessing response to treatment at the end of a 12 week induction period.

In terms of the outcome measure for assessment of response, the BSR guidelines on prescribing TNFα inhibitors in adults with AS note that response to treatment should be defined as achievement of a BASDAI 50 response or a fall in BASDAI of ≥2 units in addition to a reduction in the spinal pain VAS of ≥2 units.[39] The MTA of biologic treatments in AS noted insufficient data to consider the 2 point BASDAI change as part of the definition of response for the purposes of economic modelling and in this MTA the Assessment Group therefore selected BASDAI 50 response at Week 12 for the definition of response in the model they developed (hereafter referred to as the "York model").[19, 20] For consistency with this appraisal, the same approach was taken for the base case analysis presented in this submission, with BASDAI 50 response at 12 weeks being used for the assessment of response. A scenario analysis was conducted exploring a definition of response more closely aligned to that defined by the BSR guidelines; that is, a reduction in BASDAI to 50% of the pre-treatment value **or** a fall of ≥2 units in BASDAI score (see Section 5.8).[39] The BSR guidelines also note an additional criterion for response of a reduction in the spinal pain VAS (in the last week) by ≥2cm. However, feedback from two clinical experts has provided a mixed picture of the extent to which the spinal pain VAS criterion is used in clinical practice to determine response and, importantly, the VAS score results from the secukinumab studies were subject to considerable missing data that would have resulted in greater uncertainty about the impact of incorporating this response criterion. Therefore, the VAS element of the response definition was not employed in this scenario analysis.

The approach to modelling of sequential treatment in the exploratory analysis aimed to take account of the uncertainty around sequencing of biologic therapies in clinical practice. There are no formal guidelines on the order in which biologics should be used sequentially in the treatment of AS and, as noted in the NICE guidance from the recent MTA of TNFα inhibitor therapies in AS, there is an absence of robust RCT data supporting sequential treatment.[19] Nonetheless, as part of this appraisal the Committee noted that "sequential treatment with TNFα inhibitor is likely to be beneficial".[19] In addition, clinicians have previously expressed a need to be able to switch patients between TNFα inhibitors. However, there are considerable limitations in the data available to model sequencing. Therefore, incorporation of treatment sequencing as was performed here was an exploratory analysis to attempt to reflect the desire to consider sequencing in the recent MTA.

5.2.2.2. How the model structure and its health states capture the condition

The model structure was based on assessment of disease activity by BASDAI 50 response at 12 weeks, thereby reflecting clinical decision-making being driven by response to biologic therapy in terms of disease activity, as outlined above.

The model tracked disease progression via short-term changes in BASDAI and BASFI and long-term changes in BASFI score. Progression of disease in terms of these two measures impacted on utility estimates within the model as described in Section 5.4.5. By adopting this structure, the model captured the nature of the condition as one in which progressive increases in disease activity (BASDAI) and declining physical function (BASFI) impact on patient quality of life.[208]

In the MTA of biologic therapies in AS, the Assessment Group raised concerns over whether BASDAI and BASFI scores provide the most appropriate conceptual basis for modelling the underlying biological and clinical process of the disease and we acknowledge these limitations.[20] However, as was also noted by the Assessment Group, these outcomes currently provide the only way to link disease modelling to costs and QALYs – in view of the lack of any alternative mapping functions to costs and/or utilities our model took the same approach as previous models in AS, including the York model, in using BASDAI and BASFI scores to model the disease.

The model structure allowed for events of tuberculosis reactivation and other serious infections to be captured. A Cochrane Collaboration review of TNFα inhibitors in the treatment of AS previously noted that "regulatory agencies have published warnings about rare adverse events of serious infections, including tuberculosis, malignancies and lymphomas", but concluded that based on moderate quality evidence the effect of TNFα inhibitors on serious adverse events is uncertain, with absolute numbers of such events found to be low.[209] While there is some evidence for an increase in serious infections and tuberculosis associated with the use of TNFα inhibitors, a recent meta-analysis of the association of malignancy with TNFα inhibitors concluded that it was possible to "neither refute nor verify that individual TNFα inhibitor therapies affect the short-term clinical emergence of cancer."[210] The York model in AS did not include malignancies and lymphomas as serious adverse events. As noted in Section 4.12.3, the frequency of malignancy with secukinumab was low and not found to be different to placebo in the secukinumab trials. Therefore, it was considered appropriate for this model to reflect the York model in AS in considering adverse events of tuberculosis and other serious infections only.

Finally, the model structure considered a lifetime time horizon (58 years), with all patients assumed dead by age 101). AS is a chronic, progressive and lifelong condition for which there is no cure and for which therapy is aimed at delaying the progression of disease and alleviating symptoms. As such, it is appropriate to model the disease over a lifetime time horizon, as has been done in previous economic models for AS.

5.2.2.3. Features of the *de novo* analysis

The key features of the *de novo* analysis and their justification are presented in Table 67.

Table 67. Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (58 years)	Lifetime time horizon is consistent with previous models in AS, including the recent MTA of biologic therapies.[19] AS is a chronic, progressive life-long condition for which there is no cure. The mean age of patients entering the model was 43.26; a 58-year time horizon therefore provided a time horizon up to age 101. This is appropriate to represent a lifetime time horizon – only 0.02% of the overall UK population are centenarians.[21]
Were health effects measured in QALYs; if not, what was used?	Health effects were measured in QALYs	NICE reference case
Discount of 3.5% for utilities and costs	Costs and utilities were both discounted at 3.5%	NICE reference case

Perspective (NHS/PSS)	The model adopted the perspective of the NHS/PSS.	NICE reference case
Cycle length	3 months	A 3 month cycle length appropriately captured the frequency of occurrence of events within the model and was aligned with current guidelines from the BSR that response to biologics should be reviewed 3 monthly.[39]
Half-cycle correction	Yes	NA

Abbreviations: PSS, personal social services; QALYs, quality-adjusted life years.
Source: as indicated.

5.2.3. Intervention technology and comparators

The intervention considered in the model was secukinumab 150 mg, representing the licensed dose of secukinumab that is the subject of this appraisal.

As noted in Section 5.2.1, the licensed TNFα inhibitors were considered to be the relevant comparators to secukinumab in the biologic naïve population, in line with the final scope for this appraisal. There are currently five TNFα inhibitors that are licensed for the treatment of AS, all five of which were included in the recent NICE MTA in AS:[19]

- Adalimumab
- Etanercept
- Golimumab
- Infliximab
- Certolizumab pegol

Therefore, all five of these TNFα inhibitors were modelled as comparators in the biologic naïve population and, as discussed in Section 5.2.2, upon initial entry into the model the biologic naive patients received either secukinumab or one of the relevant biologic comparators.

For etanercept, certolizumab pegol and golimumab, multiple licensed doses are available. The NMA presented in Section 4.10 found no statistically significant differences between secukinumab and any of the different licensed doses for golimumab and certolizumab pegol. Given that the administration schedules result in no cost differences between the two certolizumab pegol doses, and the PAS available for golimumab 100 mg renders it the same price as golimumab 50 mg, it was not considered necessary to model all doses of these two interventions; therefore, for simplicity, the efficacy inputs for these therapies were taken as those for certolizumab pegol 200 mg every two weeks and golimumab 50 mg. In terms of etanercept, whilst multiple doses are licensed in AS, the NMA only included the 50 mg weekly licensed dose as no data for the 25 mg twice weekly dose was identified for inclusion. Therefore, for etanercept the licensed 50 mg weekly dose is the only dose considered in the modelling.

For the biologic experienced population, the relevant comparator defined in the NICE scope for this appraisal is established clinical management without secukinumab. There are no formal guidelines on sequencing of biologics (i.e. administering a second biologic following discontinuation of an initial biologic therapy), and there is a lack of robust clinical data to support use of the TNFα inhibitors in this setting, as acknowledged by the Assessment Group as part of

the NICE MTA in AS.[19, 20] This is supported by the systematic literature review presented in Section 4.1, which found no data on the use of comparator biologics in a biologic experienced population. Therefore, no robust comparison to TNFα inhibitors in this population was possible and conventional care was considered to be the base case comparator. Efficacy inputs for this comparison were informed by the pre-specified TNF-IR subgroup from the MEASURE 2 and MEASURE 1 trials. In these studies, concomitant medications such as NSAIDs and corticosteroids, as well as physical therapy, were permitted (see Table 10). The placebo arm of these trials (up to the week 16 and week 24 timepoints, respectively, at which placebo patients were re-randomised to secukinumab), is therefore reflective of conventional care in UK clinical practice .[39]

Key details from the SmPC of each included biologic are summarised in Table 68.

Table 68. Summary of marketing authorisations of included biologics

	Secukinumab[5]	Adalimumab[11]	Etanercept[10]	Golimumab[9]	Infliximab[12]	Certolizumab pegol[13]
Indication of marketing authorisation	Patients with active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.	Patients with severe, active ankylosing spondylitis who have had an inadequate response to conventional therapy.	Patients with severe, active ankylosing spondylitis who have had an inadequate response to conventional therapy.	Patients with severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.	Patients with severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.	Patients with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to NSAIDs.
Posology	150 mg by s.c. injection with initial dosing at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4.	40 mg adalimumab administered every other week as a single dose via s.c. injection.	25 mg twice weekly or 50 mg once weekly via s.c. injection	50 mg given once a month via s.c. injection, on the same date each month. For patients with a body weight >100 kg whose disease does not respond adequately after 4 doses (50 mg each), increasing the dosage to 100 mg once a month may be considered.	5 mg/kg given as an i.v. infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks.	**Loading dose:** 400 mg (as 2 s.c. injections of 200 mg each) at weeks 0, 2 and 4. **Maintenance dose:** 200 mg every 2 weeks or 400 mg every 4 weeks.
Continuation rule	Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks	Continued therapy past 12 weeks should be carefully reconsidered in a patient not responding within this time period	Continued therapy past 12 weeks should be carefully reconsidered in a patient not responding within this time period	Continued therapy past 12 to 14 weeks should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.	No additional treatment with infliximab should be given if the patient does not respond by 6 weeks.	Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Abbreviations: s.c., subcutaneous.

All biologics were considered within the model according to their dosing schedules as described in Table 68. Although the SmPCs of individual biologics propose continuation rules as described in Table 68, there is no clear description of the criteria for response assessment in applying these. The BSR guidelines state that "assessments of response should be carried out between 6 and 12 weeks after initiation of treatment….Treatment should not be stopped because of ineffectiveness within 12 weeks" and therefore support a continuation rule across the TNFα inhibitor therapies of 12 weeks.[39] Consistent with this, the timepoint for assessment ultimately adopted by the Assessment Group in their model for the MTA of biologic treatments in AS was 12 weeks.[19, 20] Therefore, for consistency with the BSR guidelines and this NICE appraisal, a 12 week timepoint for response assessment within the model was considered appropriate.

In addition to the continuation rule around assessment of response, the BSR guidelines for prescribing of TNFα inhibitor therapies suggests that biologic therapy should be withdrawn upon development of severe adverse events or evidence of inefficacy.[39] Within the model, this is captured by discontinuation of biologic therapy, which could be for any reason including adverse events or loss of efficacy. No discontinuation rate is applied to the "Start treatment" state – patients experiencing an adverse event prior to response assessment are categorised as non-responders.

5.3. Clinical parameters and variables

As discussed in Section 5.2.1, two populations were ultimately considered in the model: the biologic naïve population and the biologic experienced population.

Clinical parameters for the biologic naïve population were based on the TNFα inhibitor naïve population of the pooled MEASURE 2 and MEASURE 1 trials (for patient characteristics) alongside the base case biologic naïve NMA (for relatively effectiveness estimates). Where NMA endpoints were unavailable for a given TNFα inhibitor comparator, the average of the available endpoints from the NMA for the other TNFα inhibitors was used. This assumption was considered appropriate given that the Assessment Group for the MTA of TNFα inhibitors in AS adopted a preferred assumption of similarity between the TNFα inhibitors.[20]

Clinical parameters for the biologic experienced population were based on the TNFα inhibitor–IR population of the pooled MEASURE 2 and MEASURE 1 trials in the base case comparison versus conventional care only. In the exploratory analyses versus other biologics in the biologic experienced population, a reduction in efficacy was applied to the biologic naïve base case NMA. This reduction was based on the observed reduction with secukinumab and is constant across all biologics.

5.3.1. Starting patient characteristics

The base case inputs for the model in terms of patient age, gender distribution and weight are detailed in Table 69, alongside a discussion of their appropriateness for reflecting the patient population considered in the decision problem.

Table 69. Patient characteristics in the model

Model parameter	Value	Source and appropriateness for modelling UK active AS population
Mean age, years	42.37	Mean age of population pooled across MEASURE 2 and MEASURE 1 trials, which recruited patients directly matching the decision problem and consistent with the anticipated AS

		population in clinical practice.
Percentage male/female	69.5%	Pooled distribution across population in MEASURE 2 and MEASURE 1 trials.
Mean (SD) weight, kg	78.20 (16.88)	Mean weight of population pooled across MEASURE 2 and MEASURE 1 trials.

5.3.2. Response assessment at 12 weeks (BASDAI 50)

As described in Section 5.2.2, response to biologic treatment and conventional care was assessed by BASDAI 50 response at a 12 week (3 months) timepoint. For the modelled biologic naïve population, BASDAI 50 response rates for each treatment were determined directly from the predicted absolute estimates of BASDAI 50 response for each biologic or for placebo (representing conventional care) from the base case NMA analysis in the TNFα inhibitor naive population (xxxxxxx). As noted in Section 4.10.4 and Section 4.10.5, it should be borne in mind that whilst the secukinumab inputs to the NMA for dichotomous endpoints were based on NRI data, input data for these endpoints for some other comparators were based on less conservative LOCF or observed dataset analyses. This might be expected to bias against secukinumab in in some comparisons on the BASDAI 50 outcome.

For the modelled biologic experienced population the base case comparator was conventional care only and the comparison was based on the pooled results of the MEASURE 1 and MEASURE 2 studies.

The base case BASDAI 50 inputs are presented in Table 70.

Table 70. BASDAI 50 response applied in the model base case

Therapy	BASDAI 50 response for the modelled biologic naïve population	BASDAI 50 response for the modelled biologic experienced population
Secukinumab 150 mg	[redacted]	[redacted]
Adalimumab	[redacted]	
Etanercept	[redacted]	
Golimumab	[redacted]	
Infliximab	[redacted]	
Certolizumab pegol	[redacted]	
CC	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care.

In the exploratory analysis in the biologic naïve population when sequential biologic treatment was modelled using the basket therapy, the percentage of BASDAI 50 responders was based on the average of the biologics in the basket, which excluded the biologic that was used first-line. A relative efficacy reduction of 45.1%, based on the reduction in response observed with secukinumab in naïve vs experienced patients, was applied to this to account for the fact that fewer patients respond to a second-line biologic. In the exploratory analyses in which biologic comparators are included for the biologic experienced population, this same 45.1% constant proportional reduction in response from the base case biologic naïve NMA was assumed, in light of a lack of data to conduct an NMA in the biologic experienced population.

5.3.3. Changes in BASDAI and BASFI over time

The model considered changes in BASDAI and BASFI scores over time and used absolute BASDAI and BASFI scores to determine utilities and costs in order to allow disease progression to be reflected in these outputs. As BASDAI 50 response at Week 12 in the model determined continuation or not on biologic therapy, it was therefore important to ensure that the estimates of absolute BASDAI and BASFI were conditional on BASDAI 50 response or non-response. This therefore required baseline BASDAI and baseline BASFI scores, in addition to the treatment-specific change from baseline estimates, to be conditional on BASDAI 50 response or non-response.

The baseline BASDAI and BASFI represented the average BASDAI and BASFI of the model cohorts at the start of treatment. These data were taken as the average of secukinumab 150 mg and placebo from the pooled MEASURE 2 and MEASURE 1 trials, for the respective populations, and are shown in Table 71.

Table 71. Baseline BASDAI and BASFI for the biologic naïve and biologic experienced populations

Input	Biologic-naïve	Biologic experienced
Overall baseline BASDAI	6.51	6.52
Overall baseline BASFI	5.90	5.89

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

The treatment-specific (biologic or conventional care) baseline BASDAI and BASFI were then modelled as conditional on BASDAI response. The baseline responder and non-responder BASDAI and BASFI values were set to the values for secukinumab 150 mg from the pooled MEASURE 2 and MEASURE 1 trials for secukinumab and all biologic comparators. For conventional care, the values were set to the values for placebo from the pooled MEASURE 2 and MEASURE 1 trials.

Table 72. Treatment-specific baseline BASDAI and BASFI conditional on BASDAI 50 response

	Biologic naive		Biologic experienced	
Input	**Biologics**	**CC**	**Biologics**	**CC**
Baseline BASDAI				
Responders	6.42	6.12	6.59	6.24
Non-responders	6.39	6.73	6.48	6.61
Baseline BASFI				
Responders	5.44	4.75	5.39	5.49
Non-responders	6.07	6.22	6.04	5.85

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care.

In the exploratory analysis incorporating sequential biologic use, the BASDAI responder and non-responder baseline scores applied to second-line treatment were as per the first-line baseline scores shown in Table 72. For the BASFI baseline scores, the BASFI at the median cycle of discontinuation of first-line treatment was calculated. The difference between this and the initial overall baseline score of the population at model entry (the scores in Table 71) was added onto the baseline BASFI scores at initiation of second-line treatment. This is to reflect the fact that

patients will have experienced a long-term progression in BASFI score since they first entered the model, regardless of whether they were on treatment or not (see Section 5.3.3.2).

5.3.3.1. Short-term changes in BASDAI and BASFI

Over the short term (up to 3 months), patients were assumed to experience improvements in BASDAI and BASFI scores dependent upon their treatment. Changes in BASDAI and BASFI were considered to be conditional on BASDAI 50 response. In order to calculate change from baseline at 3 months conditional on response, 12 week data from the MEASURE 2 and MEASURE 1 trials of secukinumab and published conditional data for adalimumab and golimumab from the York model assessment report were used to compute the proportional change from baseline for BASDAI 50 responders compared to non-responders for secukinumab, adalimumab and golimumab, respectively.[20] For the other comparator biologics, the average proportional change from baseline from across these sources (MEASURE 2, MEASURE 1, York model adalimumab data and York model golimumab data) was used, in the absence of any conditional data for these comparators. Two clinical experts [redacted] were consulted regarding the assumption that conditional data for comparators could be estimated in this manner, both of whom agreed that this was a reasonable assumption.[85, 211] Absolute change from baseline in BASDAI and BASFI at 12 weeks for all patients (responders and non-responders) from the biologic naïve NMA presented in Section 4.10 (xxxxxxx and xxxxxxx), in addition to the proportion of BASDAI 50 responders and non-responders from this NMA (xxxxxxx), could then be used to estimate conditional change from baseline for comparators where this data was not available. For the modelled biologic experienced population, secukinumab 150mg and placebo arm data from the MEASURE 1 and MEASURE 2 trials was used. Changes in BASDAI and BASFI at 3 months are presented in Table 73 (BASDAI) and Table 74 (BASFI).

Given the lack of conditional data for comparators other than adalimumab and golimumab, a scenario analysis was explored in which it was assumed that BASDAI 50 responders and non-responders were associated with the same change from baseline in BASDAI and BASFI.

Table 73. Change from baseline in BASDAI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-3.31	-3.78	-2.35	-3.18	-6.06	-3.51	-
BASDAI 50 non-responders	-0.78	-0.87	-0.54	-0.56	-1.39	-0.90	
Biologic experienced population							
BASDAI 50 responders	-4.98	-	-	-	-	-	-3.81
BASDAI 50 non-responders	-0.94	-	-	-	-	-	-0.36

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

Table 74. Change from baseline in BASFI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-2.93	-3.00	-2.27	-2.87	-3.99	-2.99	-1.70
BASDAI 50 non-responders	-0.91	-0.74	-0.56	-0.71	-0.98	-0.52	-0.42
Biologic experienced population							
BASDAI 50 responders	-3.79	-	-	-	-	-	-2.73
BASDAI 50 non-responders	-0.73	-	-	-	-	-	0.06

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

For the second-line biologic changes from baseline, the average of the BASDAI or BASFI changes for all biologics in the basket therapy, which excluded the biologic used at first-line, was calculated. A relative efficacy reduction of 41.9% (BASDAI) and 50.4% (BASFI) was applied to this to account for the fact that patients respond less well to a second-line biologic.

The initial mean change from baseline in BASDAI and BASFI was assumed to remain constant for the entire duration of treatment with the given therapy – in other words, this treatment benefit was maintained whilst on treatment. In addition to the modelled initial improvement in BASDAI and BASFI, the model incorporated long-term changes in BASFI as described in the "Long-term changes in BASFI" section below.

5.3.3.2. Long-term changes in BASFI

In addition to the modelled short-term treatment benefit in BASDAI and BASFI scores over the initial 3 months described above, patients in the model who continued to respond to treatment were assumed to benefit from a slower rate of BASFI progression over the longer term. Long-term changes in BASFI were estimated based on the approach taken in the York model and described below.[20]

For longer term BASFI progression, the York model in AS assumed that the natural history of BASFI progression is a function of separate processes which are independently related to disease severity/activity (BASDAI) and to the extent and subsequent progression of radiographic disease (modified Stoke Ankylosing Spondylitis Spinal Score; mSASSS).[20] The rationale for this was that the association between BASDAI and BASFI was already accounted for in the separate mean change from baseline scores applied to both BASDAI and BASFI for responders vs. non-responders/conventional care patients (i.e. the short-term changes described in Section 5.3.3.1). The differences in BASDAI from baseline were assumed to remain constant over the longer-term horizon, for as long as patients continued on their initial treatment. Therefore, any additional changes which might affect BASFI needed to be modelled as more explicitly related to a separate clinical process. The York model therefore accounted for these additional effects on BASFI by modelling longer-term changes in BASFI as a function of mSASSS scores and this approach is taken within the model presented in this submission.

Using this approach, the annual rate of BASFI change is calculated as:

$$\textit{Annual rate of BASFI change} = \textit{annual rate of mSASSS change x BASFI change with 1 unit change in mSASSS}$$

Consistent with the York model, the independent effect of a 1 unit change in mSASSS on BASFI scores was taken to be modelled by the multivariate relationship reported in Landewe *et al.* 2009 (mean: 0.057; SE: 0.0049).[212] The annual rate of mSASSS change was taken as 1.440, based on the annual rate of change in a subgroup of patients with baseline mSASSS ≥10 in the Ramiro *et al.* 2013 study (this subgroup of the Ramiro *et al.* 2013 study was considered to more accurately reflect the population likely to be eligible to receive biologic therapy than the full study population).[212, 213]

The above calculation estimated the annual rate of BASFI change independent of any impact of biologic treatment in slowing the rate of radiographic progression. The model then assumed that biologic therapies were associated with a relative rate of mSASSS change (i.e. a treatment effect on BASFI change) of 0.42, taken from Haroon *et al.* 2013 and consistent with the York model in AS.[20, 214] This was assumed to be the same across all biologic therapies, as the York model applied this relative rate across all TNFα inhibitors. However, this may be a conservative assumption as secukinumab has demonstrated efficacy upon radiographic outcomes (Section 4.8.3) that may be better than that of TNFα inhibitors. In the MEASURE 1 study, mean ± SD change in mSASSS from baseline to Week 104 was 0.30 ± 1.93 for patients who received the 150 mg maintenance dose of secukinumab; in contrast, in the recent MTA in AS, the Assessment Group collated estimates of 2 year mSASSS change from baseline across TNFα inhibitors that ranged between 0.8 and 1.0.[20] In addition, clinical feedback has suggested that greater treatment effect on radiographic outcomes is a potential differentiating feature of secukinumab and comparator biologics. A scenario analysis is therefore considered in which radiographic progression is lower with secukinumab than with the biologic comparators (0.15 rather than 0.42). This figure was calculated using a the overall background progression rate of 0.98 units/year from the Ramiro *et al.* 2013 study and the MEASURE 1 week 104 mSASSS progression figure of 0.3 [see Section 4.7.2.4].[213]

The effect of biologic treatment on BASFI change was modelled to occur from the outset of treatment in the base case analysis. This is line with the NICE Committee's stated preference for a linear BASFI progression in the recent MTA of biologic therapies in AS; although the Assessment Group's York model had assumed that the effect of biologic treatment on BASFI change did not begin until 4 years after treatment initiation, clinical expert feedback to the Committee did not agree with this assumption.[19, 20] A scenario analysis was conducted to explore the impact of considering treatment effect on BASFI beginning four years after treatment initiation, in line with the York model.[20]

A summary of the parameters used to model long-term changes in BASFI is provided in Table 75.

Table 75. Summary of parameters used to estimate long-term changes in BASFI

Parameter	Value
Annual rate of mSASSS change	1.440[213]
BASFI change associated with a 1 unit change in mSASSS	0.057[212]
Effect of biologic treatment on radiographic progression (relative rate)	0.42[214]
Timepoint from which effect of biologic treatment introduced	Treatment initiation

Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score.

5.3.3.3. Rebound in BASFI

As noted above, the initial mean changes in BASDAI and BASFI were assumed to be maintained whilst patients remained on biologic treatment, and patients who remained on biologic treatment also experienced a slowed rate of BASFI progression. However, upon discontinuation, changes in BASFI and BASDAI resulting from biologic treatment were not assumed to be maintained. BASDAI score was assumed to revert to baseline on discontinuation. For BASFI, two alternative ways of modelling the change in BASFI upon discontinuation of biologics (i.e. two "rebound effects") were considered. These two alternatives were consistent with the scenarios applied in the York model:[19, 20]

1. "Rebound to baseline" scenario: Upon discontinuation of biologic therapy, BASFI deteriorates by the amount equal to the improvement achieved during response to biologic therapy. This represented a more optimistic scenario from the perspective of biologic therapies.
2. "Rebound to natural history" scenario: BASFI deteriorates to the level and subsequent trajectory that would have been had there not initially been a response to therapy for patients who discontinue biologic therapy. This represented a more pessimistic scenario from the perspective of biologic therapies.

In the base case, the "Rebound to baseline" scenario was selected; the "Rebound to natural history" scenario was modelled as a scenario analysis. This choice was made to reflect the judgement of the NICE Committee in the MTA of biologic therapies in AS that the "Rebound to baseline" assumption is more plausible based on clinical expert feedback.[19]

5.3.4. Withdrawal of biologic therapy

The pattern of long-term adherence to biologic therapy was represented in the model by the application of 3-month (i.e. per cycle) probabilities of withdrawal from biologic therapy. Withdrawal probabilities were modelled as treatment-specific and were derived from annual withdrawal risks associated with each biologic for year 1 and years 2+ separately. Where information on treatment rates in subsequent years was unavailable, withdrawal rate was assumed constant to the initial year (year 1). The annual withdrawal risks are detailed in Table 76.

Table 76. Annual withdrawal probabilities applied in base case

	SEC	CZP	ETN	ADA	INF	GOL
Base case						
Year 1	15.2%	12.6%	25.1%	13.0%	2.1%	13.7%
Years 2+	6.0%	11.0%	25.1%	9.3%	15.7%	6.6%
Source	MEASURE 2 Clinical Study Reports[15, 25], MEASURE 1 Clinical Study Reports[16, 24]	Sieper *et al.* 2015[146]	Dougados *et al.* 2012[163], Navarro-Sarabia *et al.* 2011[131]	Sieper *et al.* 2012[98]	van der Heijde *et al.* 2005[92], Braun *et al.* 2008[95]	Deodhar *et al.* 2015[112]

Abbreviations: ADA, adalimumab; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.
Source: as indicated.

In addition, a scenario analysis was conducted in which a constant annual withdrawal rate of 11.0% was assumed across all biologics, based on this rate being applied in the York model.[19]

5.3.5. Mortality

The model considered AS-related mortality by applying a relative risk of death to general population mortality rates. The relative risks applied were gender-specific and are detailed in Table 77.

Table 77. AS-related relative risks of death applied in the economic model

Input	Relative Risk	Source
Male	1.63	Bakland *et al.* (2011)[83]
Female	1.38	Bakland *et al.* (2011)[83]

Source: as indicated.

The general population mortality rates were determined by a Gompertz curve fitted to general population life tables from the Office for National Statistics 2014 dataset, in order to reflect general mortality rates of the UK population. The Gompertz distribution has been shown to fit all-cause mortality well and is linear in ln(h(t)) vs. time (age).[215, 216] Linear regression was used to fit survival curves for the UK general population. The survival functions for the general population life tables (male and female), the fitted Gompertz functions (male and female) and the resultant AS mortality functions (males, females and weighted average) are presented in Appendix R.

5.3.6. Adverse events

The only adverse events considered in the model were serious infections, categorised as TB reactivation and other serious infections. This is based on the results of a Cochrane Collaboration systematic literature review, which found that these were the only specific adverse events that were statistically significantly raised amongst patients treated with biologics compared to control.[217] The distribution of serious infection was assumed to be 5% tuberculosis and 95% other serious infection based on the reported rates in Singh *et al.* 2011.[217] The probability of these events was modelled as treatment-specific. AE risks included in the model were absolute rather than excess risks, although the model conservatively assumed adverse event risk to be zero for conventional care. Per-cycle probabilities of adverse events are presented in Table 78, calculated from the probabilities of adverse events provided in the noted sources.

Table 78. Adverse event risks

Drug	Serious Infection	Source
Secukinumab	0.16%	MEASURE 2 Clinical Study Report[15], MEASURE 1 Clinical Study Report[16]
Certolizumab pegol	0.67%	Sieper *et al.* 2015[146]
Etanercept	0.00%	Dougados *et al.* 2012[163], Navarro-Sarabia *et al.* 2011[131]
Adalimumab	0.35%	Sieper *et al.* 2012[98]
Infliximab	0.52%	Braun *et al.* 2008[95]
Golimumab	0.32%	Deodhar *et al.* 2015[112]
Conventional care	0.00%	-

Source: as indicated.

5.3.7. Validation of clinical parameters

A number of the clinical parameters informing the model are based on those used in the York model developed by the Assessment Group as part of the MTA of biologic treatments in AS.[19, 20] These inputs were considered appropriate by this independent academic group and have been appraised by a NICE committee, and are therefore considered to be highly applicable to this STA of secukinumab compared to other biologic therapies in the treatment of AS.

In addition, NMA results were reviewed by two clinical experts experienced in the treatment of AS, [redacted], who confirmed that the results were reflective of their clinical experiences.[85, 211]

5.4. Measurement and valuation of health effects

5.4.1. Health-related quality-of-life data from clinical trials

The MEASURE 2 and MEASURE 1 trials of secukinumab in AS collected ASQoL and FACIT-FATIGUE quality of life outcomes, as well as the EQ-5D-3L health utilities instrument.

The NICE reference case states that the EQ-5D reported directly by patients/carers is the preferred measure of health-related quality of life in adults and that valuation of health-related quality of life should reflect the preferences of a representative sample of the UK population. Therefore, the EQ-5D-3L outcome, which was reported by patients in the MEASURE 2 and MEASURE 1 trial and can be converted to utilities using the UK value set based on the time trade-off technique, is the most relevant of the outcomes collected in these trials with regards to the NICE reference case.

Results across EQ-5D domain scores from the MEASURE 2 and MEASURE 1 trials are summarised in Appendix F and Appendix G, respectively.

5.4.2. Mapping

Given that the MEASURE 1 and 2 trials collected the EQ-5D health utility instrument, no mapping of other health-related quality of life measures was considered necessary in order to derive utility values from this trial to inform the model.

5.4.3. Health-related quality-of-life studies

As part of the SLR described in Section 5.1, studies reporting utility data associated with AS were identified and reviewed. The original systematic review had included studies reporting quality of life data by measures such as SF-36, but given that there were sufficient utility studies identified, quality of life studies were excluded from the final systematic review.

A total of 45 publications reporting utility data were identified. Of these, 43 used EQ-5D, in line with the NICE reference case. Details of studies identified in the SLR that report utility data and are relevant to this submission are presented in Appendix N. Utility data ultimately informing the submission is presented in Section 5.4.5.4.

5.4.4. Adverse events

As previously described, the modelled adverse events were serious infections (either TB reactivation or other serious infection). In the base case analysis, adverse events were assumed to be associated with no disutility consistent with the approach taken in the York model in AS.[20] This is also supported by a lack of identified disutility data from the literature (see Appendix N). In addition, a further targeted literature search for adverse event disutilities across two indications (AS and PsA) found no studies reporting utilities or disutilities for any specific adverse events (details of search available on request but not presented in this submission).

5.4.5. Health-related quality-of-life data used in cost-effectiveness analysis

5.4.5.1. Patient experience in terms of health-related quality of life

Within the cost-effectiveness analysis, utility was modelled as dependent upon absolute BASDAI and BASFI scores, gender and age via a regression model.

BASDAI is a measure of disease activity that incorporates aspects of AS that are important to patients, including fatigue, pain, swelling, discomfort and stiffness.[218] BASFI is a measure of physical function, which is important to reflect in patient quality of life given that one of the most important complaints of patients with AS is that of disability.[219, 220] As AS progresses, patients find it increasingly difficult to perform physical tasks ranging from physically demanding exercises such as sport to simple tasks such as getting dressed or raising themselves from a chair, and the BASFI outcome measure reflects this patient experience.

These features of the disease captured by the BASDAI and BASFI measures have considerable negative impact on patient quality of life. The negative impact on HRQoL relates to both physical domains in terms of patient mobility and pain/discomfort as well as social domains, such as the ability of patients to carry out their everyday leisure and work activities. The impact of the condition on this ability to carry out normal activities is highlighted by the results of the Work Productivity and Activity Impairment Questionnaire (WPAI-GH) presented in Appendix F and Appendix G. The linking of HRQoL to BASDAI and BASFI scores is consistent with the approach of the York model in AS.[20]

5.4.5.2. Changes in HRQoL over time

Health-related quality of life is not constant over time in patients with AS. AS is a chronic, progressive disease for which the natural history is one of decreasing physical function associated with increasing discomfort and disability. The cost-effectiveness analysis reflects these changes over time through the use of a utility regression model that is dependent upon BASFI score, a parameter that is modelled to change over time as described in Section 5.3. Therefore, baseline utility is dependent upon baseline BASDAI and BASFI scores and the utility experienced by patients within the model then changes over the model horizon according to the extent to which patients experience a decline in physical function.

5.4.5.3. Identified health effects excluded from the analysis

The presented economic analysis captured all health effects that were identified and considered to have a meaningful impact on the assessment of health benefits with biologic therapies and conventional care in the treatment of patients with active AS for whom conventional therapy, or prior biologic therapy, has been inadequately effective or not tolerated.

5.4.5.4. Summary of utility values chosen for cost-effectiveness analysis

The model used a mapping algorithm to link BASDAI and BASFI scores to a generic utility measure, similarly to other previously presented models in AS.[20] A number of algorithms have been used previously, all of which consist of a regression model for utility against covariates of BASDAI score, BASFI score, gender and age.

In the base case of this model, the algorithm developed was derived from MEASURE 2 and MEASURE 1 data. The baseline mean, standard deviation, median, minimum, and maximum were calculated for EQ-5D utility and BASDAI scores. Pearson correlation coefficients and P values were presented for the association between EQ-5D utility and BASDAI scores. Similar analyses were performed and presented for EQ-5D utility and BASFI scores. A linear mixed model was then used to fit EQ-5D utility score as a response variable and BASDAI and BASFI scores, age and sex as predictors. The effect of correlation within the data was explored using subject as a random effect to account for the within-subject correlation between assessments.

The resultant linear algorithm based on the analysis of MEASURE 2 and MEASURE 1 data was as follows:

*Linear: Utility=0.9610 – 0.0442 * BASDAI – 0.0330 * BASFI – 0.0111 * Sex [1=male, 0=female] + 0.0005 * Age*

This linear model derived from MEASURE 2 and MEASURE 1 trial data was used in the base case analysis. Scenario analyses explored the use of two alternative linear models: 1) the linear model reported in Wailoo *et al.* 2015;[221] 2) the linear model reported in McLeod *et al.* 2007, which represents one of the models presented as part of the recent NICE MTA.[20, 201] Both of these alternative utility models were developed based on populations of UK AS patients and are therefore relevant to the decision problem.

The parameter values for the linear algorithms in the base case and scenario analyses are summarised in Table 79.

Table 79. Summary of utility values for cost-effectiveness analysis

	Parameter: Mean (SE)				
	Intercept	**BASDAI coefficient**	**BASFI coefficient**	**Male coefficient**	**Age coefficient**
MEASURE 2 and MEASURE 1 model (base case)	0.9610 (0.02503)	-0.0442 (0.00312)	-0.0330 (0.00316)	-0.0111 (0.01335)	-0.0005 (0.00049)
Wailoo *et al.* 2015[221]* (scenario analysis)	0.7220	$(BASDAI/100)^2$: -0.4700	BASFI/100: -0.2140 $(BASFI/100)^2$: -0.2330	-	0.0030
McLeod *et al.* 2007[201] (scenario analysis)	0.8772	-0.0384	-0.0323	-0.0279	0.0017

*Note: the Wailoo et al. 2015[221] model included age, $(BASDAI/100)^2$, BASFI/100 and $(BASFI/100)^2$ as explanatory variables.
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SE, standard error.

5.5. Cost and healthcare resource use identification, measurement and valuation

5.5.1. Resource identification, measurement and valuation studies

As part of the SLR described in Section 5.1, studies reporting cost or resource utilisation estimates associated with AS were identified and reviewed. A total of 89 studies containing relevant cost or resource utilisation data were identified from the SLR. Ten studies reported cost or resource use estimates from the UK. Details of these studies, and a list of non-UK studies meeting the eligibility criteria of the systematic review, are provided in Appendix M.

5.5.2. Choice of NHS Reference Costs versus PbR tariffs

A number of unit costs included in the model were based on UK NHS Reference Costs 2014-15, which were used in preference to payment-by-results tariffs.[222, 223] The NHS HRG codes used in the model are summarised in Table 80.

Table 80. HRG codes used in the economic analysis

Currency code	Currency description	Unit cost	Use in model
NHS Reference Costs 2014-15			
WF01A	Consultant-led, Non-Admitted Face to Face Attendance, Follow-up	£137.23	Specialist visit cost
SB15Z	Deliver subsequent elements of a chemotherapy cycle	£326.46	Unit cost of an i.v. administration (i.e. administration of infliximab)
DZ14F	Pulmonary, Pleural or Other Tuberculosis, with Interventions	£4,747.77	Contributes to weighted average cost of tuberculosis adverse events
DZ14G	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 7+	£3,266.09	
DZ4H	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 3-6	£2,252.13	
DZ14J	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 0-2	£1,581.18	
WJ06J	Sepsis without Interventions, with CC Score 0-4	£1,533.32	Contributes to weighted average cost of infection adverse events other than tuberculosis
DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	£1,254.23	
LA04M	Kidney or Urinary Tract Infections with Interventions, with CC Score 0-2	£2,669.02	
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0-4	£870.88	
DZ65J	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 0-4	£1,537.60	

Abbreviations: CC, complications and comorbidity; i.v., intravenous.
Source: NHS Reference Costs 2014-15.[222]

5.5.3. Validation of cost and resource use inputs

The unit cost inputs into the model were based on those used in the York model of AS, updated where appropriate to the latest NHS reference costs and cost year.[20, 222] These have been previously considered appropriate for costing resource use in AS by the independent academic group and NICE Committee who reviewed this appraisal.

5.5.4. Intervention and comparators' costs and resource use

The unit costs and resource use associated with the acquisition and administration of the intervention and comparator biologic therapies are provided in Table 81. The monitoring costs associated with these therapies, in the form of laboratory tests and requirements for medical visits, are provided in Table 82. Conventional care was not considered to be associated with any drug acquisition or administration costs, based on the assumption that biologic treatments would be used as add-on to conventional care. *Please note that all cost-effectiveness results quoted in this submission use the PAS price for secukinumab.*

Table 81. Unit costs and resource use associated with drug acquisition and administration

Items	Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
Unit cost							
Acquisition cost	**List price:** £1,218.78 per pack of two 150 mg pre-filled syringes/ SensoReady® pens **PAS price:** [redacted] per pack of two 150 mg pre-filled syringes/ SensoReady® pens	£357.50 per 200 mg pre-filled syringe The NICE MTA in AS also indicates that there is an agreed PAS with the department of health for certolizumab pegol, such that the first 12 weeks of treatment are provided free. This PAS is taken into account in the cost-effectiveness analysis.[19]	£178.75 per 50 mg pre-filled syringe[1]	£352.14 per 40 mg pre-filled syringe	**Originator infliximab:** Remicade®: £419.62 per 100 mg vial Average cost per dose calculated as £1,850.59 – see "Infliximab cost calculations" **Biosimilar infliximab:** Remsima: £377.66 per 100 mg vial Inflectra: £377.66 per 100 mg vial Average cost per dose calculated as £1,665.54 – see "Infliximab cost calculations"	£762.97 per pre-filled syringe[2] Although the 100 mg pre-filled syringe of golimumab has a higher list price than that of golimumab 50 mg, a PAS has been agreed with the department of health that provides the 100 mg dose of golimumab at the same price as the 50 mg dose.[19]	BNF 2015
Administration cost (s.c. therapies – first administration only)	£43.00	£43.00	£43.00	£43.00	NA	£43.00	Assumed self-administered following 1 hour of nurse training on first administration, PSSRU 2015[224]
Administration (i.v.	NA	NA	NA	NA	£326.46[3]	NA	NHS Reference

therapy [infliximab] – per administration)							Costs 2014-15 (health resource group [HRG] code SB15Z)[222]
Frequency of resource use							
No. of doses (month 1-3) – induction period	7.00	9.78	13.00	6.52	3.00	3.00	BNF 2015
No. of doses (month 4 - 6) – maintenance period	3.00	6.52	13.00	6.52	2.00	3.00	BNF 2015
No. of doses (three-monthly period from month 7+) – maintenance period	3.00	6.00	13.04	6.52	1.63	3.00	BNF 2015

[1]Although a biosimilar for etanercept (Benepali®) has been approved at the time of submission, a price for this biosimilar with the NHS has not been agreed and this biosimilar is therefore not available on the NHS in the UK. This biosimilar is therefore not modelled as part of this submission.
[2]The list price for golimumab 100 mg is £1,525.94. However, as described in TA 233 of golimumab in AS, golimumab is made available on the NHS with a PAS that provides the 100 mg dose of golimumab at the same cost as the 50 mg dose of golimumab.[38] Therefore, the cost of the 50 mg dose of golimumab is used to model golimumab 100 mg acquisition costs in the analysis.
[3]An alternative cost of intravenous infliximab administration is available in the costing template for the adalimumab NICE submission in psoriasis and use of this alternative cost was explored as a scenario analysis.[225]
Abbreviations: AS, ankylosing spondylitis; BNF, British National Formulary; HRG, Healthcare Resource Group; i.v., intravenous; MTA, multiple technology appraisal; NA, not applicable; NICE, National Institute of Health and Care Excellence; PSSRU, Personal Social Services Research Unit; QW, once weekly; s.c., subcutaneous.

Table 82. Unit costs and resource use associated with monitoring

Cost parameter	Unit costs		Frequency of resource use (all interventions)		
	Unit cost	Reference	First 3 months	Subsequent 3 month periods	Reference
Medical visits					
GP visits	£44.00	Cost of an 11-minute GP appointment, with qualifications, PSSRU 2015[224]	0	0	York model for MTA in AS[20]
Specialist visits	£137.23	NHS Reference Costs 2014-15 HRG code WF01A[222]	2	0.5	York model for MTA in AS[20]
Laboratory tests					
Full blood counts	£2.99	Costs sourced from the York model for psoriatic arthritis (TA199)[226] and updated to 2015 prices using the HCHS inflation index from PSSRU 2015[224]	2	1	York model for MTA in AS[20]
Erythrocyte sedimentation rate	£2.96		2	1	York model for MTA in AS[20]
Liver function test	£0.75		2	1	York model for MTA in AS[20]
Urea and electrolytes test	£1.39		2	1	York model for MTA in AS[20]
Chest radiograph	£26.23		1	0	York model for MTA in AS[20]
Tuberculosis Heaf test	£8.74		1	0	York model for MTA in AS[20]
Antinuclear antibodies	£4.66		1	0	York model for MTA in AS[20]
DNA double-strand test	£4.66		1	0	York model for MTA in AS[20]

Abbreviations: BSR, British Society for Rheumatology; DNA, deoxyribonucleic acid; GP, general practitioner; HCHS, Hospital and community health services; HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit.

Infliximab cost calculations

Infliximab is purchased in 100 mg vials at a cost of £419.62 per 100 mg vial for the originator product, Remicade®, and £377.66 for the biosimilar products, Remsima® and Inflectra®. All infliximab products are administered at a dose of 5 mg/kg, as per the SmPCs for these products.[12, 17, 18] Therefore, patient weight needed to be considered in order to accurately incorporate the cost of infliximab within the model.

An average infliximab cost per infusion was calculated based on a mean weight of 78.20 (SD 16.88) – the pooled average weight of patients across the MEASURE 2 and MEASURE 1 studies – and the assumption that weight was normally distributed (see Table 83 for calculations). This gave rise to an estimated acquisition cost per dose of infliximab of £1,850.59 for Remicade® and £1,665.54 for biosimilar infliximab.

Table 83. Calculation of infliximab acquisition cost based on patient weight

Patient weight	Total dose at 5 mg/kg	Number of vials required	Distribution	Cost per dose (Remicade®)	Cost per dose (biosimilar)
20	100 mg	1	--	--	--
40	200 mg	2	1.18%	£9.93	£8.93
60	300 mg	3	12.87%	£162.01	£145.81
80	400 mg	4	40.20%	£674.73	£607.26
100	500 mg	5	35.92%	£753.68	£678.32
120	600 mg	6	9.16%	£230.69	£207.62
140	700 mg	7	0.65%	£19.13	£17.22
160	800 mg	8	0.01%	£0.42	£0.38
Total weighted average cost				**£1,850.59**	**£1,665.54**

5.5.5. Health-state unit costs and resource use

Health state costs were modelled as disease management costs estimated based on an exponential BASFI regression model. The approach taken was the same as that used in the York model.[20] This used the following equation to model costs for management of disease dependent upon the extent of disease progression, as determined by BASFI score:

$$Cost = £1{,}284.19 * \exp(0.213 * BASFI\ score)$$

The clinical inputs determining annual change in BASFI score for each comparator are described in Section 5.3.

5.5.6. Adverse reaction unit costs and resource use

Costs for the adverse events considered in the model – TB reactivation and other serious infections – are presented in Table 84. These represented the cost of a single event and hence were incurred each time the adverse event occurred within the model.

Table 84. Unit costs of adverse events included in the analysis

Adverse event	Cost	Cross-reference
Tuberculosis infection	£2,570.71	See Table 85
Other serious infection	£1,299.38	See Table 86

The unit cost for tuberculosis infection represented a weighted average cost of relevant HRG codes for pulmonary, pleural or other tuberculosis events of varying severity from the NHS Reference Costs 2014-15.[222] The derivation of this weighted cost is presented in Table 85. The approach taken was consistent with the costing of tuberculosis in the York model where possible, but with updated costs from the more recent 2014-15 NHS Reference Costs.[20, 222]

Table 85. Calculated of weighted average cost of tuberculosis

Currency Code	Currency Description	Activity	National Average Unit Cost
DZ14F	Pulmonary, Pleural or Other Tuberculosis, with Interventions	825	£4,747.77
DZ14G	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 7+	561	£3,266.09
DZ14H	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 3-6	1,116	£2,252.13
DZ14J	Pulmonary, Pleural or Other Tuberculosis, without Interventions, with CC Score 0-2	1,850	£1,581.18
Weighted average cost			**£2,570.71**

Abbreviations: CC, complication and comorbidities.
Source: NHS Reference Costs 2014-15.[222]

The unit cost for "other serious infection" (ie. serious infection other than tuberculosis) represented a weighted average cost of relevant infection-related HRG codes, weighted by activity, from NHS reference costs 2014-15.[222] The York model for the MTA in AS used the codes PA16B, Major Infections with CC Score 0; WA03C, Septicaemia, with CC Score 0-1; DZ23G, Bronchopneumonia with CC Score 0-4; LA04M, Kidney or Urinary Tract Infections, with Interventions, With CC Score 0-2; DZ22J Unspecified Acute Lower Respiratory Infection with CC Score 0-1; and DZ21U Chronic Obstructive Pulmonary Disease or Bronchitis without NIV, without Intubation, with CC Score 0-3; all from NHS Reference Costs 2012-13. With the exception of LA04M, these codes are not present in the NHS Reference Costs 2014-2015 and have been replaced with the following: WJ06J, Sepsis without Interventions, with CC Score 0-4; DZ23N, Bronchopneumonia without Interventions, with CC Score 0-5; DZ22Q, Unspecified Acute Lower Respiratory Infection with CC Score 0-4; and DZ65J, Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 0-4. No relevant replacement for PA16B was identified in the NHS Reference Costs 2014-15 and this is therefore not included.

Table 86. Calculated of weighted average cost of other infection

Currency Code	Currency Description	Activity	National Average Unit Cost
WJ06J	Sepsis without Interventions, with CC Score 0-4	42,249	£1,533.32
DZ23N	Bronchopneumonia without Interventions, with CC Score 0-5	5,634	£1,254.23
LA04M	Kidney or Urinary Tract Infections with Interventions, with CC Score 0-2	3,432	£2,669.02
DZ22Q	Unspecified Acute Lower Respiratory Infection without Interventions, with CC Score 0-4	64,635	£870.88
DZ65J	Chronic Obstructive Pulmonary Disease or Bronchitis, without Interventions, with CC Score 0-4	56,109	£1,537.60
Weighted average cost			**£1,299.38**

Abbreviations: CC, complication and comorbidities; NIV, non-invasive ventilation.
Source: NHS Reference Costs 2014-15.[222]

5.6. Summary of base-case de novo analysis inputs and assumptions

5.6.1. Summary of base-case de novo analysis inputs

Table 87. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings			
Time horizon	Lifetime (58 years)	NA – not varied in PSA	Section 5.2.2.3
Discount rate (costs and outcomes)	3.5%	NA – not varied in PSA	
Mean age at baseline (years)	42.37	NA – not varied in PSA	Section 5.3.1
Percentage male	69.5%	NA – not varied in PSA	
Mean weight at baseline (kg)	78.20	NA – not varied in PSA	
Clinical inputs			
BASDAI 50 response at 3 months (normally distributed)			Section 5.3.2
Secukinumab 150 mg	Biologic naïve population: [redacted] Biologic experienced population: 19.7%	Log odds SE: [redacted] Log odds SE: 0.322	
Certolizumab pegol	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Etanercept	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Adalimumab	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Infliximab	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Golimumab	Biologic naïve population: [redacted] Biologic experienced population: NA;	Log odds SE: [redacted]	

Conventional care	Biologic experienced population: 3.2%;	Log odds SE: 0.719	
Short-term changes in BASDAI and BASFI			
Baseline BASDAI			
Responders	Biologic naïve: 6.42 (biologics) Biologic experienced: 6.59 (SEC); 6.24 (CC)	SE: 0.060 0.060; 0.060	Section 5.3.3
Non-responders	Biologic naïve: 6.39 (biologics) Biologic experienced: 6.48 (SEC); 6.61 (CC)	SE: 0.060 0.060; 0.060	
Baseline BASFI			
Responders	Biologic naïve: 5.44 (biologics) Biologic experienced: 5.39 (SEC); 5.49 (CC)	SE: 0.087 0.087; 0.087	Section 5.3.3
Non-responders	Biologic naïve: 6.07 (biologics) Biologic experienced: 6.04 (SEC); 5.85 (CC)	SE: 0.087 0.087; 0.087	
Change in BASDAI at 3 months (normally distributed)			
BASDAI 50 responders	Data presented for biologic naive population/biologic experienced population • SEC: -3.02/ -4.98 • CZP: -3.97/NA • ETN: -2.47/NA • ADA: -3.35/NA • INF: -6.36/NA • GOL: -3.67/NA • CC: NA/-3.81	• SEC: 0.390/ 0.498 • CZP: 0.817/NA • ETN: 0.930/NA • ADA: 0.542/NA • INF: 1.129/NA • GOL: 0.704/NA • CC: NA/0.613	Section 5.3.3.1
BASDAI 50 non-responders	Data presented for biologic naive population/biologic experienced population • SEC: -0.71/-0.94 • CZP: -0.91/NA • ETN: -0.57/NA • ADA: -0.59/NA • INF: -1.46/NA • GOL: -0.94/NA	• SEC: 0.091/0.227 • CZP: 0.187/NA • ETN: 0.213/NA • ADA: 0.096/NA • INF: 0.258/NA • GOL: 0.181/NA	Section 5.3.3.1

	• CC: NA/-0.36	• CC: NA/ 0.177	
Change in BASFI at 3 months (normally distributed)			
BASDAI 50 responders	Data presented for biologic naive population/biologic experienced population • SEC: -2.71/ -3.79 • CZP: -3.14/NA • ETN: -2.38/NA • ADA: -3.00/NA • INF: -4.18/NA • GOL: -3.15/NA • CC: NA/-2.73	• SEC: 0.339/ 0.756 • CZP: 0.795/NA • ETN: 0.812/NA • ADA: 0.760/NA • INF: 0.921/NA • GOL: 0.673/NA • CC: NA/0.741	Section 5.3.3.1
BASDAI 50 non-responders	Data presented for biologic naive population/biologic experienced population • SEC: -0.85/ -0.73 • CZP: -0.77/NA • ETN: -0.59/NA • ADA: -0.74/NA • INF: -1.03/NA • GOL: -0.55/NA • CC: NA/0.06	• SEC: 0.106/0.231 • CZP: 0.196/NA • ETN: -0.200/NA • ADA: 0.187/NA • INF: 0.244/NA • GOL: 0.118/NA • CC: NA/0.145	Section 5.3.3.1
Long-term changes in BASFI			
Annual rate of MSASSS change	1.440	SE: 0.133 (Normal)	Section 5.3.3.2
BASFI change with 1 unit change in MSASSS	0.057	SE: 0.005 (Normal)	
Biologic treatment effect on progression	0.420	SE: 0.122 (Normal)	
Time to treatment effect (years)	0 (at treatment initiation)	NA	
Annual withdrawal rates			
Year 1/ Year 2+	• SEC: 15.2%/ 6.0%	0.030/0.012	Section 5.3.4

	• CZP: 12.6%/ 11.0% • ETN: 25.1%/ 25.1% • ADA: 13.0%/ 9.3% • INF: 2.1%/ 15.7% • GOL: 13.7%/ 6.6%	0.025/0.022 0.050/0.050 0.026/0.019 0.004/0.031 0.027/0.013	
Adverse event rates			
Infection	• SEC: 0.16% • CZP: 0.67% • ETN: 0.00% • ADA: 0.35% • INF: 0.52% • GOL: 0.32% • CC: 0.0%	• SE: 0.000 • SE: 0.001 • SE: 0.000 • SE: 0.001 • SE: 0.001 • SE: 0.001 • SE: 0.000 (Beta for all therapies)	Section 5.3.6
Distribution of infection (tuberculosis vs other serious infection)	5% tuberculosis 95% other serious infection	0.008 (Beta distribution)	
Mortality inputs			
Relative risk of mortality for AS patient			
Male	1.63	SE: 0.326 (Log-normal)	Section 5.3.5
Female	1.38	SE: 0.276 (Log-normal)	
Utility inputs			
Parameters for utility weight regression model in the base case			
Intercept	0.9610	SE: 0.02503 (Beta)	Section 5.4.5.4
BASFI coefficient	-0.0330	SE: 0.00316 (Beta)	
BASDAI coefficient	-0.0442	SE: 0.00312 (Beta)	
Male coefficient	-0.0111	SE: 0.01335 (Beta)	
Age coefficient	-0.0005	SE: 0.00049 (Beta)	
Cost and resource use inputs			

Drug acquisition and administration						
Biologic acquisition costs (per dose)	• SEC: [redacted] (PAS price) • CZP: £357.50 • ETN: £178.75 • ADA: £352.14 • INF: £1,850.59 (Remicade®); £1,665.54 (biosimilar) • GOL: £762.97				N/A	Section 5.5.4
s.c. drug administration (first dose only)	£43.00				SE: 8.60 (Normal)	
i.v. drug administration (per administration)	£326.46				SE: 65.292 (Normal)	
Number of doses	**Treatment**	**Months 1 - 3**	**Months 4 - 6**	**Subsequent 3 month periods**		
	SEC	7.00	3.00	3.00	NA – not varied in PSA	
	CZP	9.78	6.52	6.00	NA – not varied in PSA	
	ETN	13.00	13.00	13.04	NA – not varied in PSA	
	ADA	6.52	6.52	6.52	NA – not varied in PSA	
	INF	3.00	2.00	1.63	NA – not varied in PSA	
	GOL	3.00	3.00	3.00	NA – not varied in PSA	
Monitoring costs						
	Cost (per test)	**Frequency (first 3 months)**	**Frequency (subsequent 3 month periods)**			Section 5.5.4
GP visit	£44.00	0.00	0.00		SE: 8.800 (Gamma)	
Specialist visit	£137.23	2.00	0.50		SE: 27.446 (Gamma)	
Full blood count	£2.99	2.00	1.00		SE: 0.598 (Gamma)	
Erythrocyte sedimentation rate	£2.96	2.00	1.00		SE: 0.591 (Gamma)	
Liver function test	£0.75	2.00	1.00		SE: 0.151 (Gamma)	
Urea and electrolytes test	£1.39	2.00	1.00		SE: 0.277 (Gamma)	

Chest radiograph	£26.23	1.00	0.00	SE: 5.247 (Gamma)	
Tuberculosis Heaf test	£8.74	1.00	0.00	SE: 1.748 (Gamma)	
Antinuclear antibodies	£4.66	1.00	0.00	SE: 0.932 (Gamma)	
DNA double-strand test	£4.66	1.00	0.00	SE: 0.932 (Gamma)	
Health state cost					
Intercept	£1,284.19			SE: 0.165 (Log-normal)	Section 5.5.5
BASFI coefficient	0.213			SE: 0.038 (Normal)	
Adverse event costs					
Tuberculosis	£2,570.71			SE: 514.142 (Gamma)	Section 5.5.6
Other serious infection	£1,299.38			SE: 259.876 (Gamma)	

Abbreviations: ADA, adalimumab; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care; CZP, certolizumab pegol; DNA, deoxyribonucleic acid; ETN, etanercept; GOL, golimumab; GP, general practitioner; i.v., intravenous; INF, infliximab; NA, not applicable; s.c., subcutaneous; SE, standard error; SEC, secukinumab.

5.6.2. Assumptions

There are a number of assumptions required in the model; these assumptions and their justifications are listed in Table 88.

Table 88. List of model assumptions and their justifications

Model assumption	Justification
It is assumed that patients who respond to biologic therapy experience a treatment-dependent improvement in BASDAI and BASFI which is maintained for the duration of biologic therapy.	Consistent with the York model in AS.[20]
The ratio of BASDAI and BASFI change from baseline amongst responders vs. non-responders, for comparators for which no conditional response data is available (infliximab, etanercept and certolizumab pegol), is assumed to be the average of the ratios for the comparators where conditional data is available (adalimumab, golimumab and secukinumab)	This assumption was verified with two clinical experts.[85, 211] Please see Section 0.
It is assumed that changes in BASFI (physical function) are a function of both BASDAI (disease activity) and mSASSS (radiographic progression).	Consistent with the York model in AS.[20]
For comparators with no available endpoint data for particular NMA scenarios, the average of the available endpoint data for TNFα inhibitors was assumed to apply.	The York Assessment Group assumed a similar clinical effect between the alternative TNFα inhibitors.[20]
It is assumed that the biologic treatment effect on mSASSS is the same across all biologic therapies.	The York model in AS applied a consistent treatment effect on mSASSS across all TNFα inhibitor therapies.[20] Secukinumab has demonstrated efficacy on radiographic outcomes including mSASSS as reported in Section 4.7.2.4.
It is assumed that the biologic treatment effect on BASFI progression occurs from treatment initiation for all biologics (ie. linear BASFI progression).	In the recent MTA of TNFα inhibitors in AS the Committee's preferred assumption was for linear BASFI progression, rather than treatment effect on BASFI progression from 4 years following treatment initiation.[19] This was based on clinical expert feedback.
In the base case, it is assumed that upon discontinuation of biologic therapy, BASFI score deteriorates by the amount equal to the improvement during response to biologic therapy ("Rebound to baseline"). A scenario analysis explores an alternative rebound assumption that upon discontinuation of biologic therapy BASFI deteriorates to the level and subsequent trajectory that would have been had there not been an initial response to biologic therapy ("Rebound to natural history").	This reflects the judgement of the NICE Committee in the MTA of biologic therapies in AS that the "Rebound to baseline" assumption is more plausible based on clinical expert feedback.[19]
In the exploratory analysis of the biologic experienced population, it is assumed that the decline in efficacy for the anti-TNFs is the same as that observed with secukinumab.	The York Assessment Group assumed a similar clinical effect between the alternative anti-TNFs. This assumption is made in the absence of any data on the efficacy of the biologic comparators

	in a biologic experienced population. Based on secukinumab's innovative mechanism of action, this could be interpreted as a conservative assumption.[20]
It is assumed that there is no disutility associated with adverse events of tuberculosis infection or other serious infection.	Consistent with the York model in AS.[20]
It is assumed that biologic therapies administered subcutaneously can be self-administered, with no associated NHS resource use, following a single 1 hour training session with a nurse.	Consistent with the York model in AS.[20]
For the calculation of infliximab dose requirements, which are weight-dependent, it is assumed that population weight is normally distributed with mean (SD) 78.20 kg (16.88 kg).	Simplifying assumption to allow weight-dependent cost of infliximab to be taken into account.

5.7. Base-case results

5.7.1. Base-case incremental cost effectiveness analysis results

The summary results of the base case analysis are presented in Table 89 for the biologic naïve population and Table 90 for the biologic experienced population.

Table 89. Summary base case results – biologic naïve population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£114,847	9.328	-	-	-	-
Etanercept	£115,779	8.566	£932	-0.762	Dominated	Dominated
Certolizumab pegol	£124,557	9.111	£9,710	-0.216	Dominated	Extendedly dominated
Adalimumab	£127,919	9.153	£13,072	-0.175	Dominated	Extendedly dominated
Golimumab	£131,157	9.369	£16,310	0.041	£397,064	Extendedly dominated
Infliximab biosimilar	£136,095	9.420	£21,248	0.092	£230,769	£96,824
Infliximab	£139,598	9.420	£24,751	0.092	£268,811	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 90. Summary base case results – biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£107,417	8.105	-	-	-
Secukinumab	£109,164	8.883	£1,747	0.778	£2,245

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.7.2. Clinical outcomes from the model

Outcomes specified in the scope include disease activity, functional capacity and disease progression. BASDAI is used as the measure of disease activity within the model, whilst BASFI is the measure of functional capacity and disease progression.

MEASURE 1 and MEASURE 2 data amongst BASDAI 50 responders to secukinumab on BASDAI and BASFI scores over time in both biologic naïve and biologic experienced populations are shown in Table 91 to Table 94 below, and compared with modelled estimates. Trial data from responders is selected for comparison purposes since the model assumes discontinuation of non-responders at 12 weeks.

It is noticeable that the trial data is more variable over time than the modelled values, in both populations. In the naïve populations the modelled values are somewhat higher than the trial data, which is likely to be because the model change from baseline estimates are derived from the NMA, which employs overall change from baseline estimates, not just responder changes from baseline. Underestimating the changes from baseline amongst responders would result in conservative estimates of secukinumab cost effectiveness. In the biologic experienced population, sample sizes are small for BASDAI 50 responders, although the modelled estimates seem a reasonable approximation to the trial data.

Table 91. BASFI scores over time: MEASURE 1 / 2 TNFα inhibitor naïve population and modelled biologic naïve population

	Week 0	Week 12	Week 24	Week 52	Week 104
MEASURE 1 - BASDAI 50 responders: n	35	35	34	32	30
MEASURE 1 - BASDAI 50 responders: BASFI score	5.32	1.57	1.74	1.44	1.50
MEASURE 2 - BASDAI 50 responders: n	16	16	16	16	16
MEASURE 2 - BASDAI 50 responders: BASFI score	5.69	1.41	1.52	1.54	1.56
Model – patients in maintenance treatment state	5.44	2.51	2.52	2.54	2.57

Abbreviations: BASDAI; Bath Ankylosing Spondylitis Disease Activity Score, BASFI; Bath Ankylosing Spondylitis Functional Index.

Table 92. BASDAI scores over time: MEASURE 1 / 2 TNFα inhibitor naïve population and modelled biologic naïve population

	Week 0	Week 12	Week 24	Week 52	Week 104
MEASURE 1 - BASDAI 50 responders: n	35	35	34	32	30
MEASURE 1 - BASDAI 50 responders: BASDAI score	6.52	1.75	1.89	1.55	1.72
MEASURE 2 - BASDAI 50 responders: n	16	16	16	16	16
MEASURE 2 - BASDAI 50 responders: BASDAI score	6.23	1.71	2.09	2.15	2.30
Model – patients in Mnt tx state	6.42	3.11	3.11	3.11	3.11

Abbreviations: BASDAI; Bath Ankylosing Spondylitis Disease Activity Score.

Table 93. BASFI scores over time: MEASURE 1 / 2 TNFα inhibitor naïve and modelled biologic experienced population

	Week 0	Week 12	Week 24	Week 52	Week 104
MEASURE 1 - BASDAI 50 responders: n	7	7	7	7	6
MEASURE 1 - BASDAI 50 responders: BASFI score	4.57	1.43	1.73	1.13	1.25
MEASURE 2 - BASDAI 50 responders: n	7	7	7	7	6
MEASURE 2 - BASDAI 50 responders: BASFI score	6.2	1.77	3.16	2.78	1.82
Model – patients in Mnt tx state	5.39	1.61	1.62	1.63	1.67

Abbreviations: BASDAI; Bath Ankylosing Spondylitis Disease Activity Score, BASFI; Bath Ankylosing Spondylitis Functional Index.

Table 94. BASDAI scores over time: MEASURE 1 / 2 TNFα inhibitor naïve and modelled biologic experienced population

	Week 0	Week 12	Week 24	Week 52	Week 104
MEASURE 1 - BASDAI 50 responders: n	7	7	7	7	6
MEASURE 1 - BASDAI 50 responders: BASDAI score	6.11	1.63	2.1	1.35	1.49
MEASURE 2 - BASDAI 50 responders: n	7	7	7	7	6
MEASURE 2 - BASDAI 50 responders: BASDAI score	7.07	1.59	3.13	3.00	1.54
Model – patients in Mnt tx state	6.59	1.61	1.61	1.61	1.61

Abbreviations: BASDAI; Bath Ankylosing Spondylitis Disease Activity Score.

Other clinical outcomes from the model in the biologic naïve and biologic experienced populations are reported in Table 95 and Table 96, respectively. The proportion of BASDAI 50 responders at 12 weeks aligns with the NMA result and no comparison is possible for time spent in a BASDAI 50 responder state.

Table 95. Clinical outcomes from the model – biologic naïve population

	SEC	CZP	GOL	ETN	ADA	INF
BASDAI 50 responders at 12 weeks	0.488	0.404	0.439	0.338	0.438	0.404
Time spent in BASDAI 50 responder state (years)	5.71	3.25	4.98	1.20	3.95	2.95

Abbreviations: ADA, adalimumab, BASDAI; Bath Ankylosing Spondylitis Disease Activity Score; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

Table 96. Clinical outcomes from the model – biologic experienced population

	SEC	CC
BASDAI 50 responders at 12 weeks	0.197	0.032
Time spent in BASDAI 50 responder state (years)	2.300	0.008

Abbreviations: BASDAI; Bath Ankylosing Spondylitis Disease Activity Score; CC, conventional care; SEC, secukinumab

Other outcomes listed in the scope included pain, peripheral symptoms, symptoms of extra-articular manifestations and adverse effects of treatment which are not modelled outcomes and

hence no comparison can be made between model results and the clinical trial data on these outcomes.

Health-related quality of life measures from the MEASURE 1 and MEASURE 2 trials inform the utility values used in the cost-effectiveness model but these are not modelled as an outcome for which a comparison of model vs. trial would be possible.

5.7.3. Disaggregated results of the base case incremental cost effectiveness analysis

Disaggregated discounted QALYs and costs by health state are reported in Table 97 to Table 100 for the biologic naïve and biologic experienced population. Summaries of resource use by cost category in these two populations are provided in Table 101 and Table 102.

Table 97. Summary of QALY gain by health state – biologic naïve population

	Induction treatment	Maintenance treatment	Conventional care	Total
Secukinumab	0.112	2.713	6.503	9.328
Certolizumab pegol	0.112	1.872	7.127	9.111
Absolute increment (% increment) vs. secukinumab	100%	69%	110%	98%
Golimumab	0.112	2.558	6.698	9.369
Absolute increment (% increment) vs. secukinumab	100%	94%	103%	100%
Etanercept	0.112	0.692	7.762	8.566
Absolute increment (% increment) vs. secukinumab	100%	25%	119%	92%
Adalimumab	0.112	2.109	6.932	9.153
Absolute increment (% increment) vs. secukinumab	100%	78%	107%	98%
Infliximab (originator or biosimilar product*)	0.112	2.137	7.170	9.420
Absolute increment (% increment) vs. secukinumab	100%	79%	110%	101%

*The use of the infliximab originator (Remicade®) or infliximab biosimilar does not affect the QALY gain as equal efficacy is assumed

Table 98. Summary of QALY gain by health state – biologic experienced population

	Induction treatment	Maintenance treatment	Conventional care	Total
Secukinumab	0.112	1.281	7.489	8.883
Conventional care	0.112	0.006	7.987	8.105
Absolute increment (% increment) vs. secukinumab	100%	0%	107%	91%

Table 99. Summary of costs by health state – biologic naïve population

	Induction treatment	Maintenance treatment	Conventional care	Total
Secukinumab	[redacted]	[redacted]	[redacted]	£114,847
Certolizumab pegol	[redacted]	[redacted]	[redacted]	£124,557
Absolute increment (% increment) vs. secukinumab	128%	103%	109%	108%
Golimumab	[redacted]	[redacted]	[redacted]	£131,157
Absolute increment (% increment) vs. secukinumab	97%	151%	103%	114%
Etanercept	[redacted]	[redacted]	[redacted]	£115,779
Absolute increment (% increment) vs. secukinumab	98%	47%	119%	101%
Adalimumab	[redacted]	[redacted]	[redacted]	£127,919
Absolute increment (% increment) vs. secukinumab	97%	128%	107%	111%
Infliximab	[redacted]	[redacted]	[redacted]	£139,598
Absolute increment (% increment) vs. secukinumab	205%	144%	110%	122%
Infliximab biosimilar	[redacted]	[redacted]	[redacted]	£136,095
Absolute increment (% increment) vs. secukinumab	190%	133%	110%	119%

Table 100. Summary of costs by health state – biologic experienced population

	Induction treatment	Maintenance treatment	Conventional care	Total
Secukinumab	[redacted]	[redacted]	[redacted]	£109,164
Conventional care	[redacted]	[redacted]	[redacted]	£107,417
Absolute increment (% increment) vs. secukinumab	29%	0%	112%	98%

Table 101. Summary of predicted resource use by category of cost – biologic naïve population

	Biologic drug costs	Background disease costs	Administration costs	Monitoring costs	Costs due to infection	Total
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	134%	104%	100%	71%	269%	108%
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	184%	101%	100%	91%	173%	114%
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	65%	109%	100%	42%	0%	101%
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	158%	103%	100%	80%	163%	111%
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	185%	103%	14,371%	69%	199%	122%
Infliximab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	167%	103%	14,371%	69%	199%	119%

Table 102. Summary of predicted resource use by category of cost – biologic experienced population

	Biologic drug costs	Background disease costs	Administration costs	Monitoring costs	Costs due to infection	Total
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute increment (% increment) vs. secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.7.4. Exploratory cost-effectiveness analyses in biologic naïve and biologic experienced populations

The summary results for the exploratory analysis of the biologic naïve population, including sequencing, are provided in Table 103 below.

Table 103. Summary results – exploratory sequencing analyses on biologic naïve population

Treatment pathway	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Secukinumab -> Mixed Tx	£122,981	9.463	-	-	-
Etanercept -> Mixed Tx	£126,467	8.783	£3,486	-0.680	Dominated
Certolizumab pegol -> Mixed Tx	£133,043	9.266	£10,062	-0.197	Dominated
Adalimumab -> Mixed Tx	£136,073	9.302	£13,092	-0.161	Dominated
Golimumab -> Mixed Tx	£138,911	9.508	£15,930	0.045	Extendedly dominated
Infliximab biosimilar -> Mixed Tx	£143,760	9.566	£20,779	0.103	£83,440
Infliximab -> Mixed Tx	£147,263	9.566	£24,032	0.103	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The summary results for the exploratory analysis of the biologic experienced population, comparing secukinumab to the other biologic therapies, are provided in Table 104.

Table 104. Summary results – exploratory comparison with TNFα inhibitors in biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,376	8.110	-	-	--
Etanercept	£111,754	8.366	£4,378	0.256	Extendedly dominated
Secukinumab	£112,707	8.606	£5,331	0.496	£3,962
Certolizumab pegol	£117,925	8.537	£10,549	0.427	Dominated
Adalimumab	£119,423	8.550	£12,047	0.440	Dominated
Golimumab	£121,529	8.617	£14,153	0.507	Extendedly dominated
Infliximab biosimilar	£125,446	8.632	£18,070	0.522	£498,327
Infliximab	£127,619	8.632	£20,243	0.522	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

5.8. Sensitivity analyses

5.8.1. Probabilistic sensitivity analysis

Probabilistic mean costs, QALYs and resultant ICERs for the analysis of the biologic naïve population are presented in Table 105, followed by the scatterplots for the comparison of secukinumab to each comparator (Figure 24 to Figure 28) and the CEAC (Figure 30) in this population. The ICERs for the probabilistic analysis in the biologic experienced population are presented in Table 106, followed by the scatterplot (Figure 31) and CEAC (Figure 32).

Table 105. Summary probabilistic base case results – biologic naïve population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Secukinumab	£118,435	£30,783	10.372	1.026	-	-	-
Etanercept	£120,251	£34,797	9.414	1.020	£1,815	-0.958	Dominated
Certolizumab pegol	£130,246	£35,106	10.045	1.081	£11,811	-0.328	Dominated
Adalimumab	£132,061	£32,631	10.229	1.035	£13,626	-0.143	Dominated
Golimumab	£134,964	£32,749	10.457	1.071	£16,528	0.085	£194,686
Infliximab biosimilar*	£157,583	£48,320	9.775	1.101	£39,148	-0.598	Dominated
Infliximab	£162,466	£48,970	9.802	1.090	£44,031	-0.571	Dominated

Abbreviations: SD, standard deviation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SEC, secukinumab.

*Please note results for infliximab biosimilar require a separate PSA run in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 24. Scatterplot for secukinumab vs etanercept – biologic naïve population

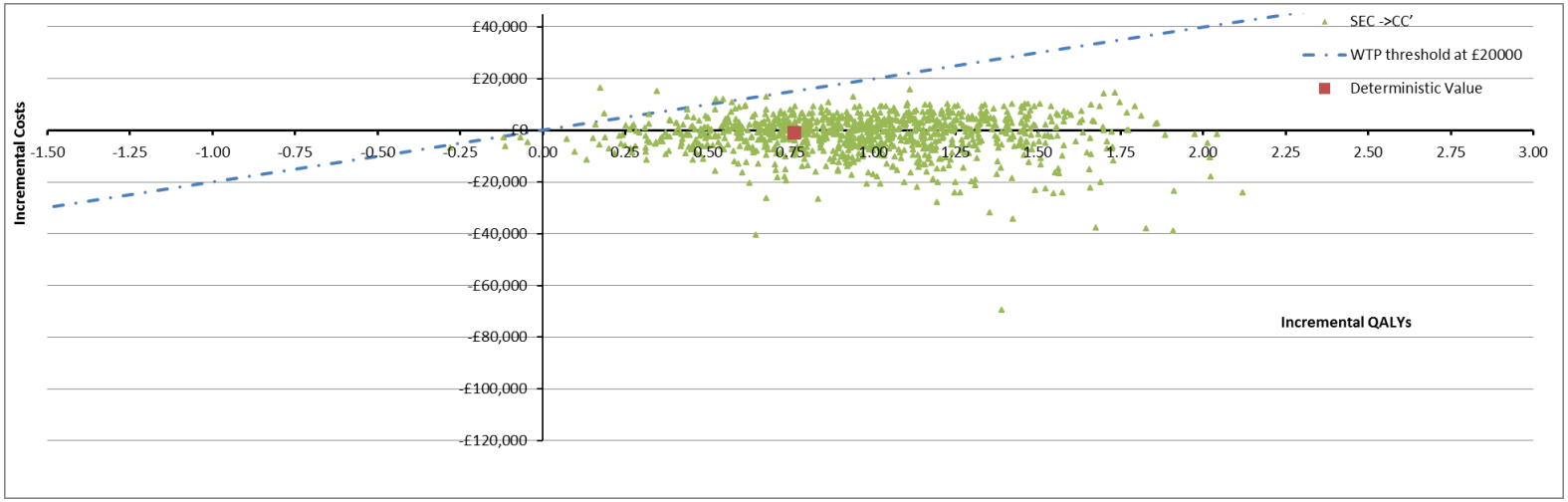


Figure 25. Scatterplot for secukinumab vs certolizumab pegol – biologic naïve population

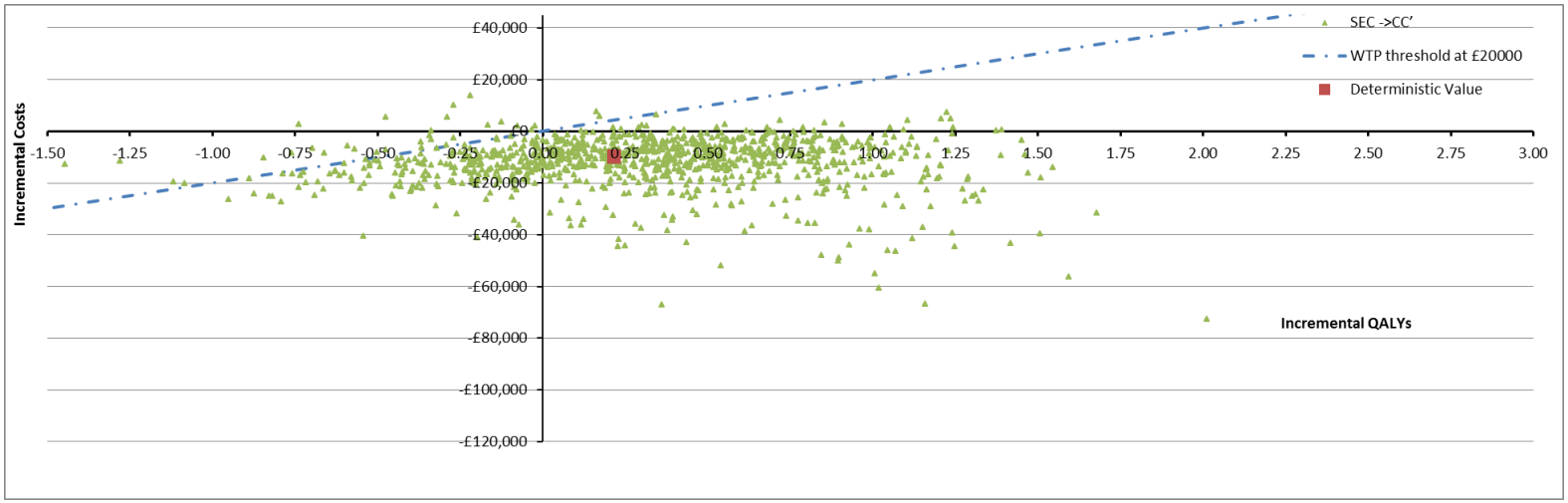


Figure 26. Scatterplot for secukinumab vs adalimumab – biologic naïve population

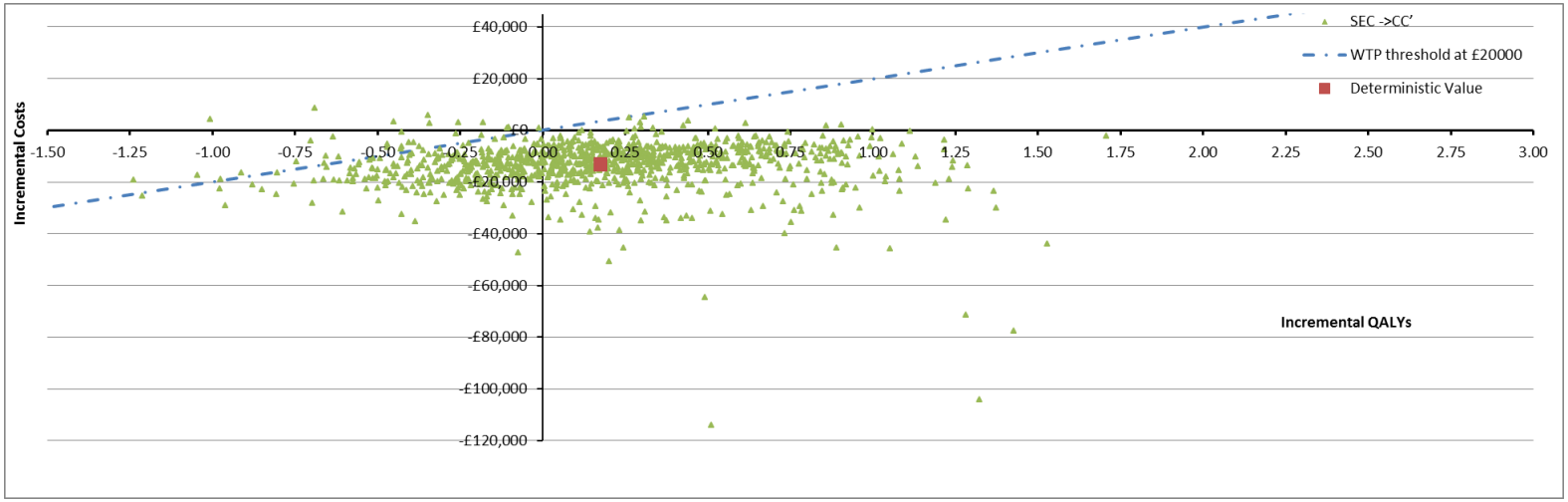


Figure 27. Scatterplot for secukinumab vs golimumab – biologic naïve population

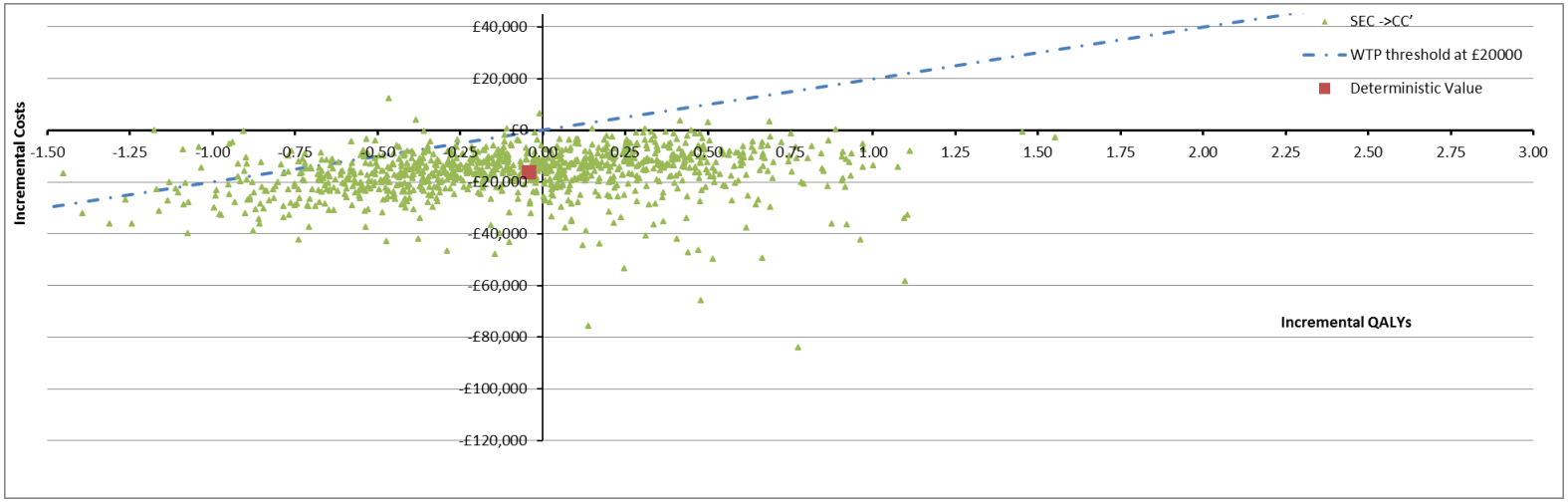


Figure 28. Scatterplot for secukinumab vs infliximab – biologic naïve population

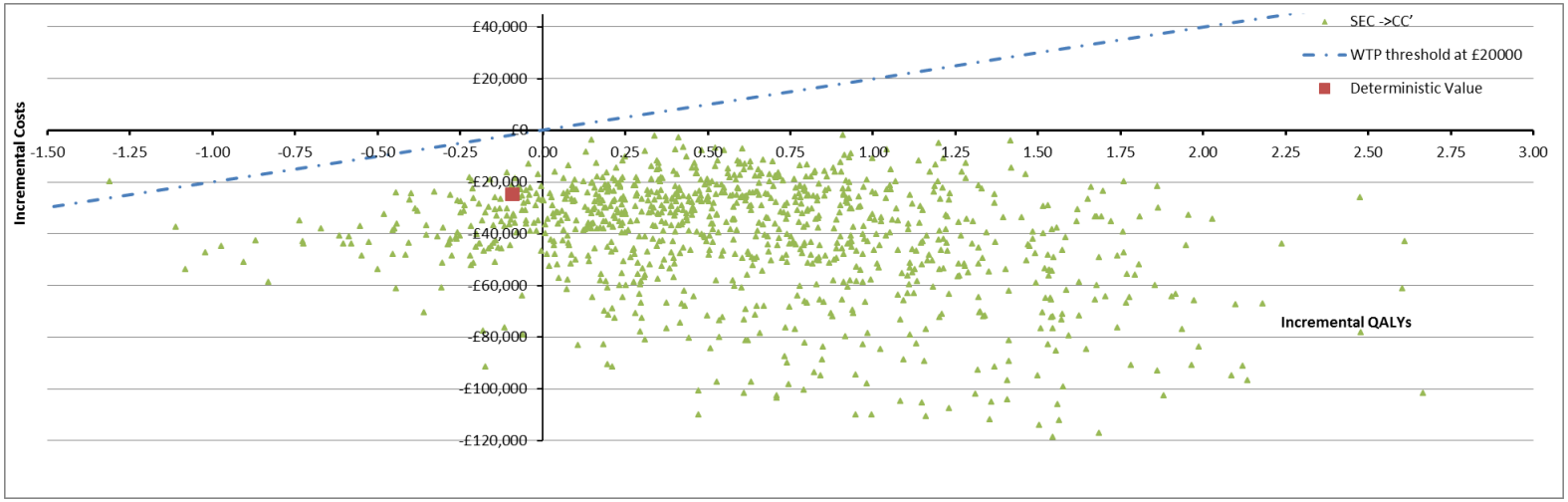
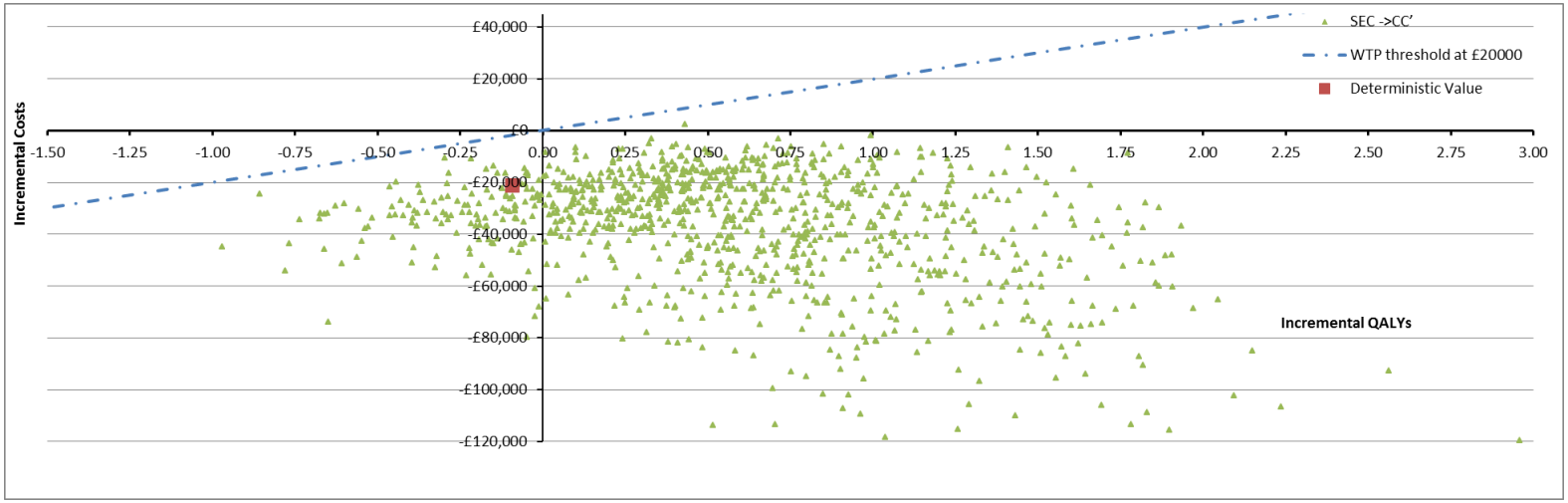
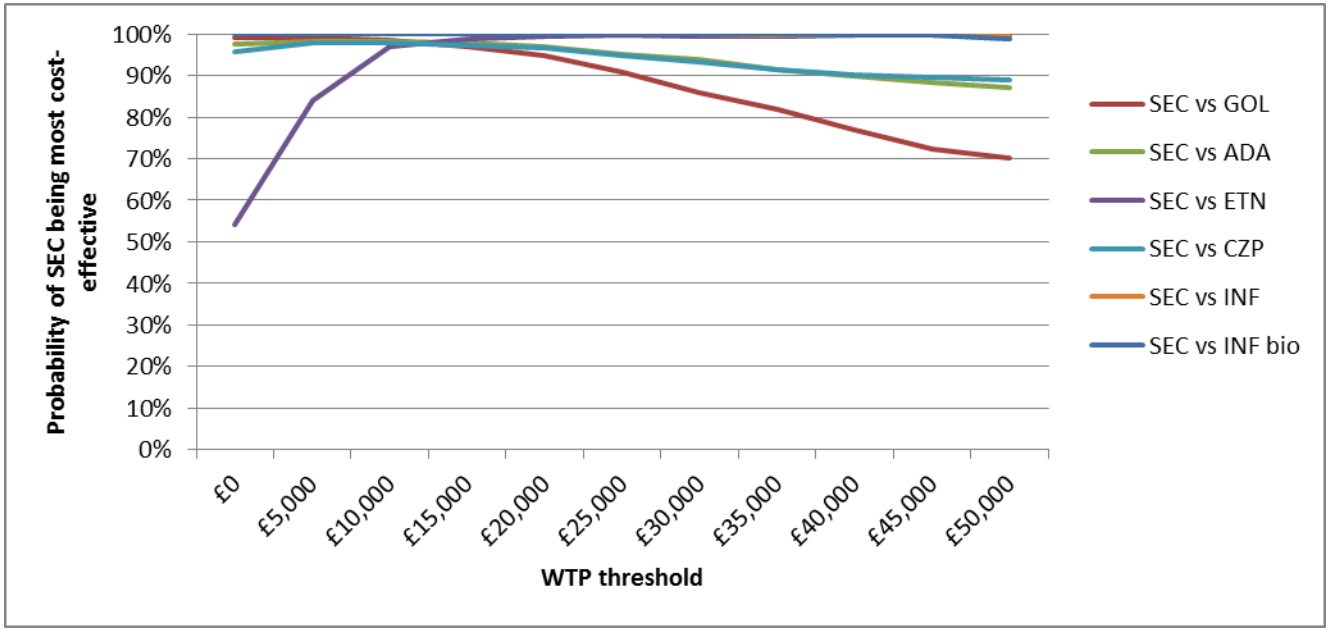


Figure 29. Scatterplot for secukinumab vs infliximab biosimilar – biologic naïve population*



*Please note results for infliximab biosimilar require a separate PSA run in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 30. CEAC for secukinumab versus comparators in the biologic naïve population*



*The above chart combines results of two comparator CEAC results for secukinumab versus each comparator.

Table 106. Summary probabilistic base case results – biologic experienced population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Conventional care	£110,509	£36,487	8.837	0.998	-	-	-
Secukinumab	£112,049	£32,021	9.635	1.055	£1,540	0.798	£1,929

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SEC, secukinumab.

Figure 31. Scatterplot for secukinumab vs conventional care – biologic experienced population

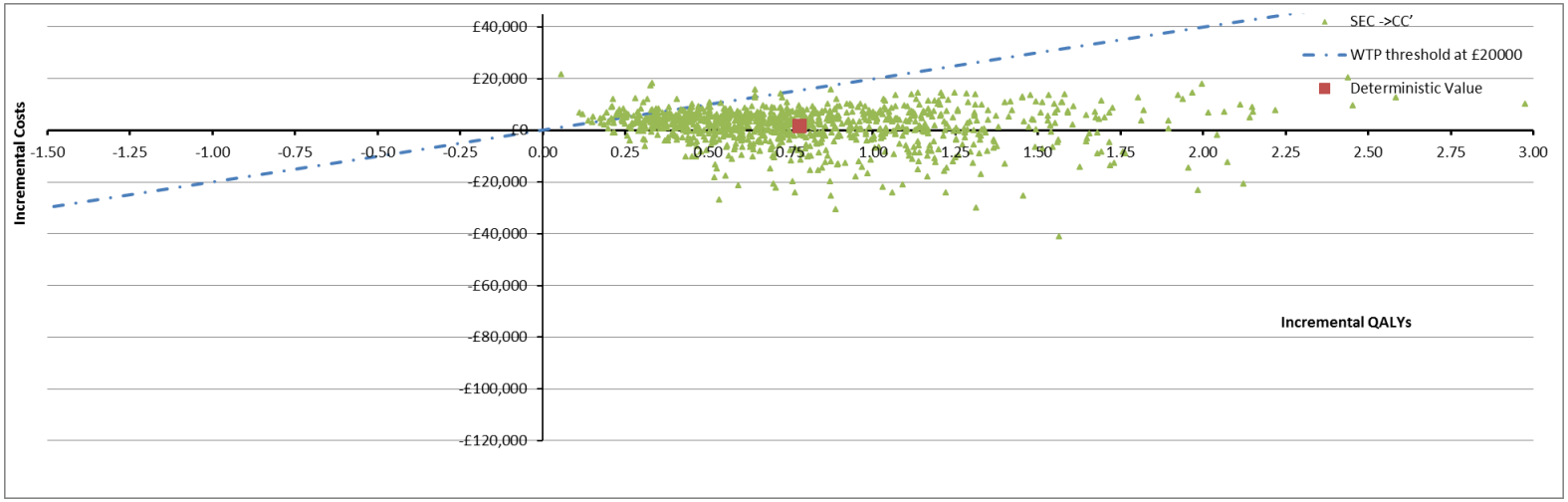
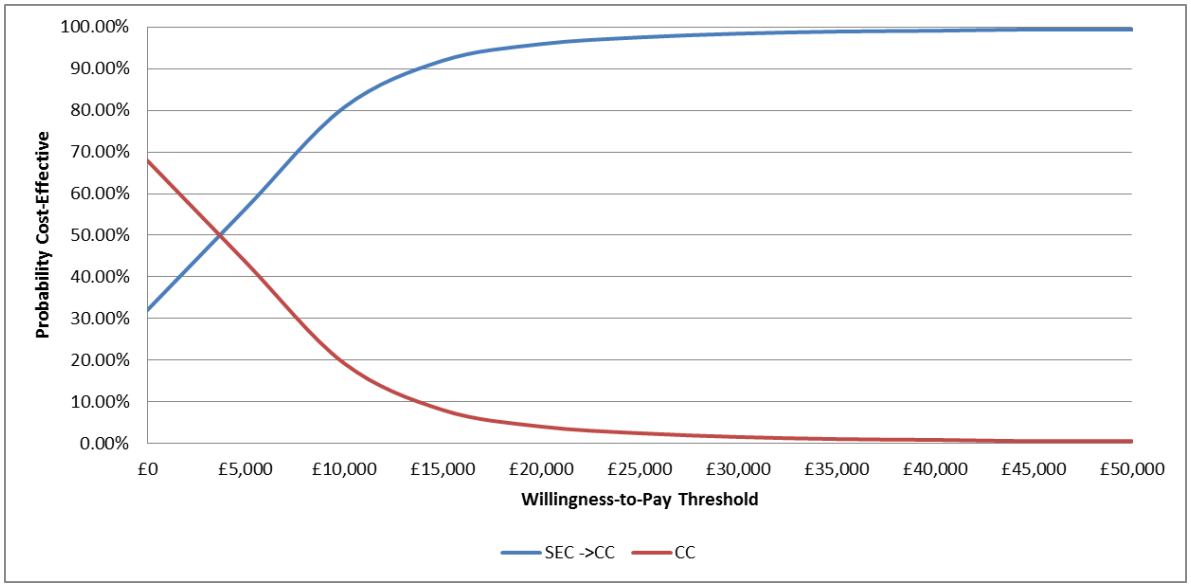


Figure 32. CEAC for secukinumab vs. conventional care – biologic experienced population



5.8.2. Deterministic sensitivity analysis

The tornado diagrams below present the variation in base case model results from OWSA in terms of net monetary benefits (valuing one QALY at £20,000). Net monentary benefits are presented instead of ICERs due to incremental costs of secukinumab being negative versus all comparators i.e. in the southern quadrants of the cost-effectiveness plane, where ICERs are not informative. Tornado diagrams for the biologic naïve population are provided in Figure **33** to Figure 38. The tornado diagram for the analysis in the biologic experienced population is provided in Figure 39.

Figure 33. OWSA results for secukinumab vs etanercept – biologic naïve population

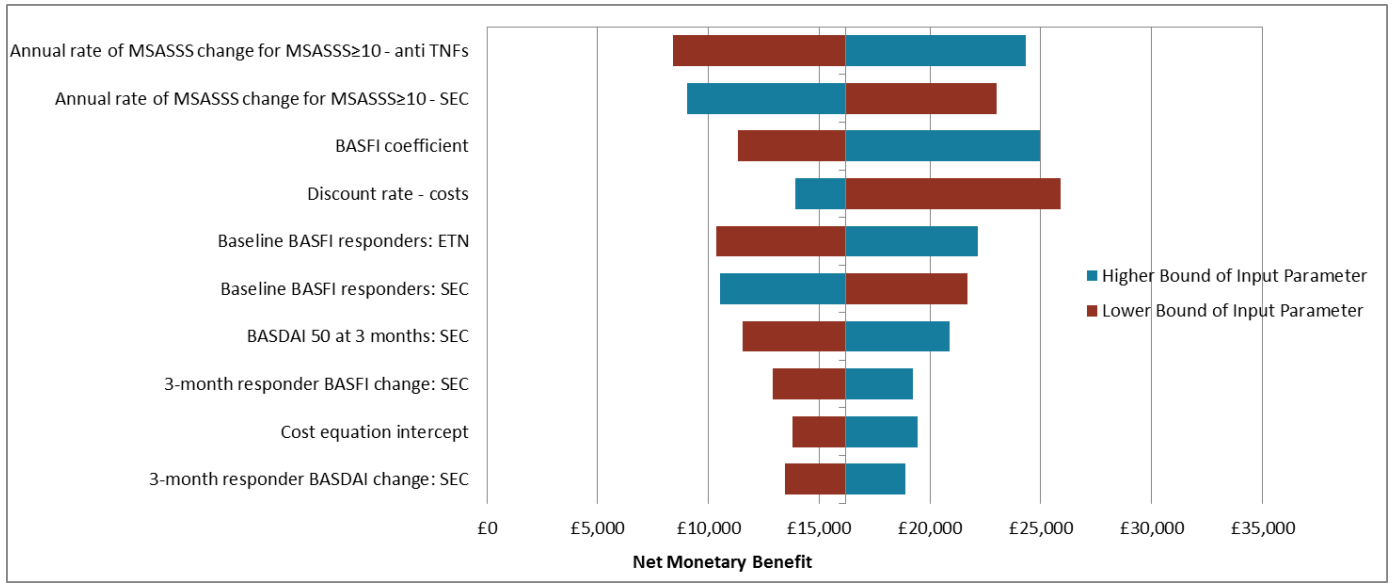


Figure 34. OWSA results for secukinumab vs certolizumab – biologic naïve population

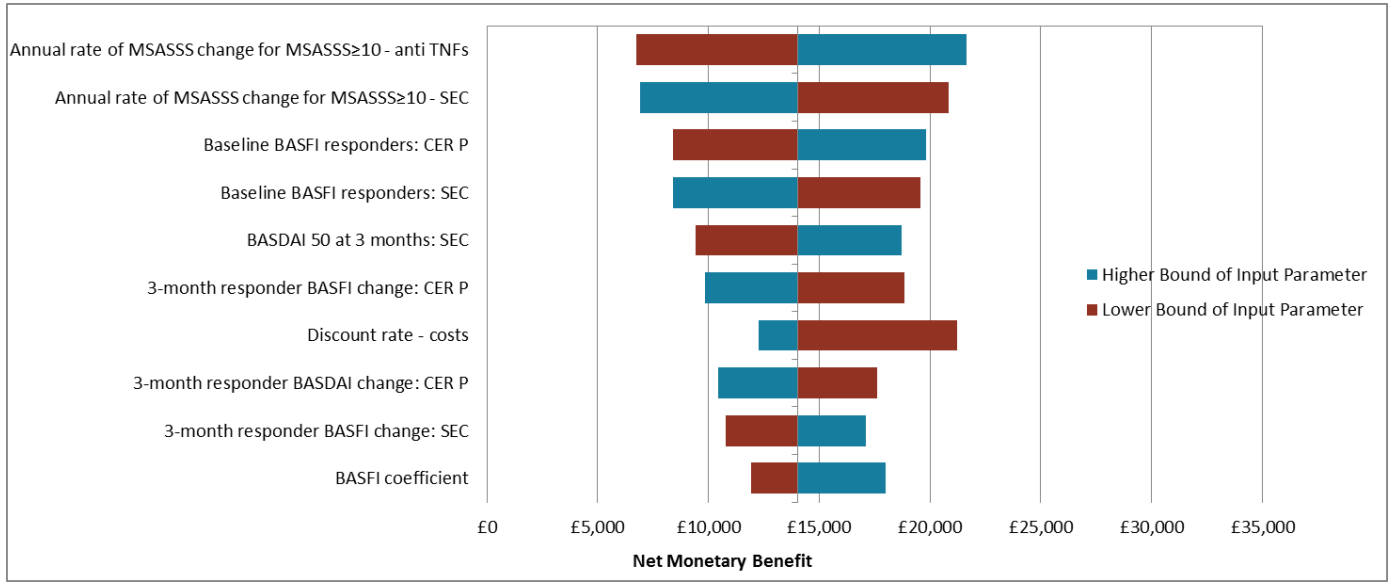


Figure 35. OWSA results for secukinumab vs adalimumab – biologic naïve population

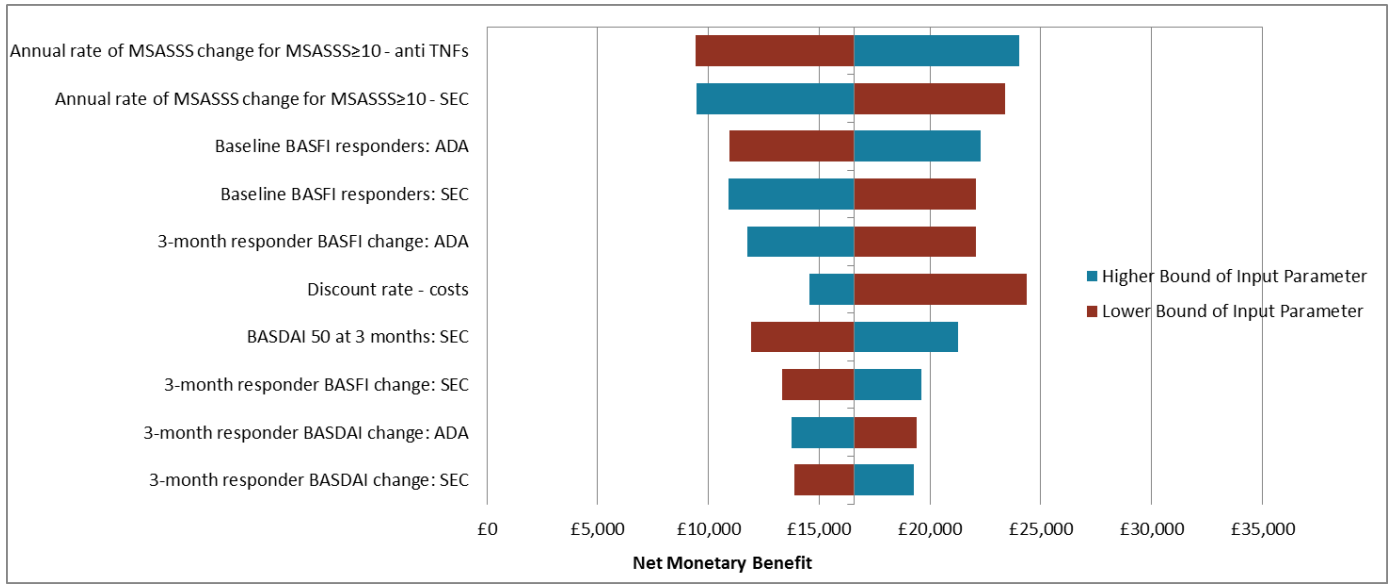


Figure 36. OWSA results for secukinumab vs golimumab – biologic naïve population

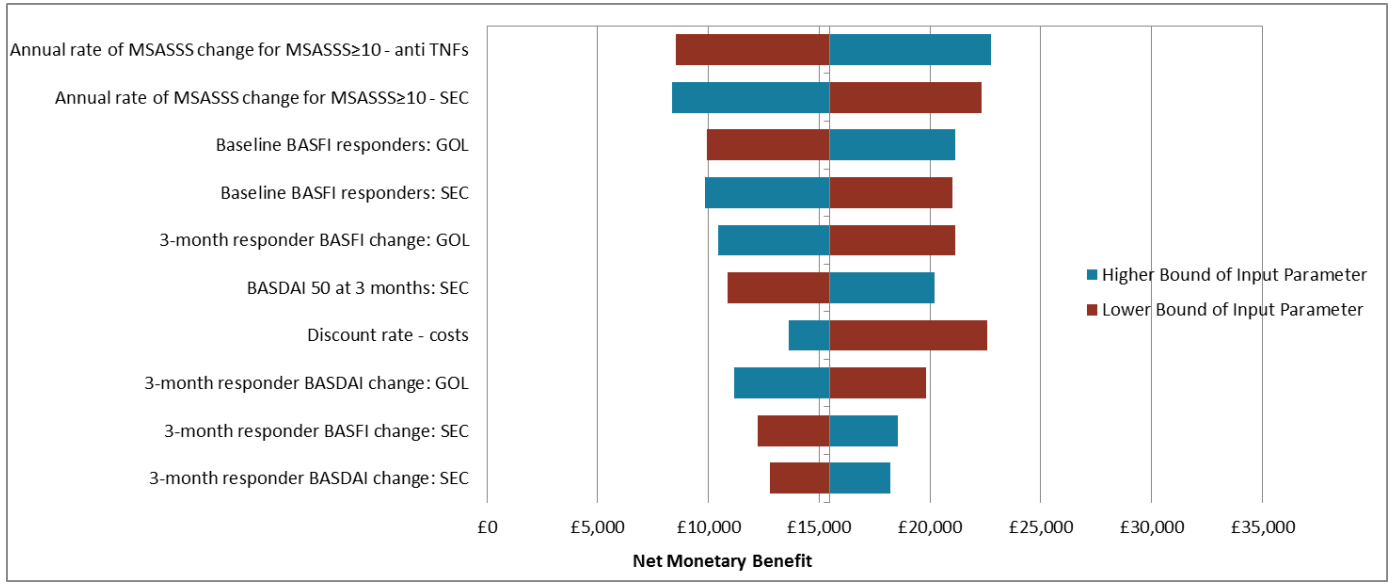


Figure 37. OWSA results for secukinumab vs infliximab – biologic naïve population

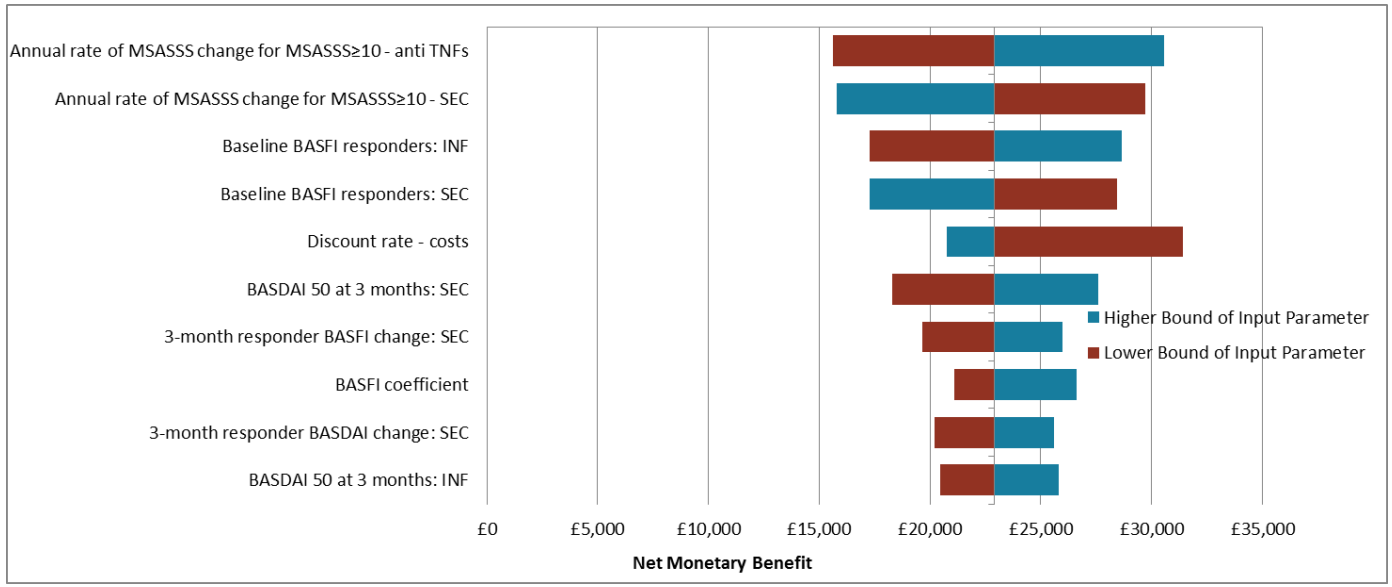


Figure 38. OWSA results for secukinumab vs infliximab biosimilar – biologic naïve population

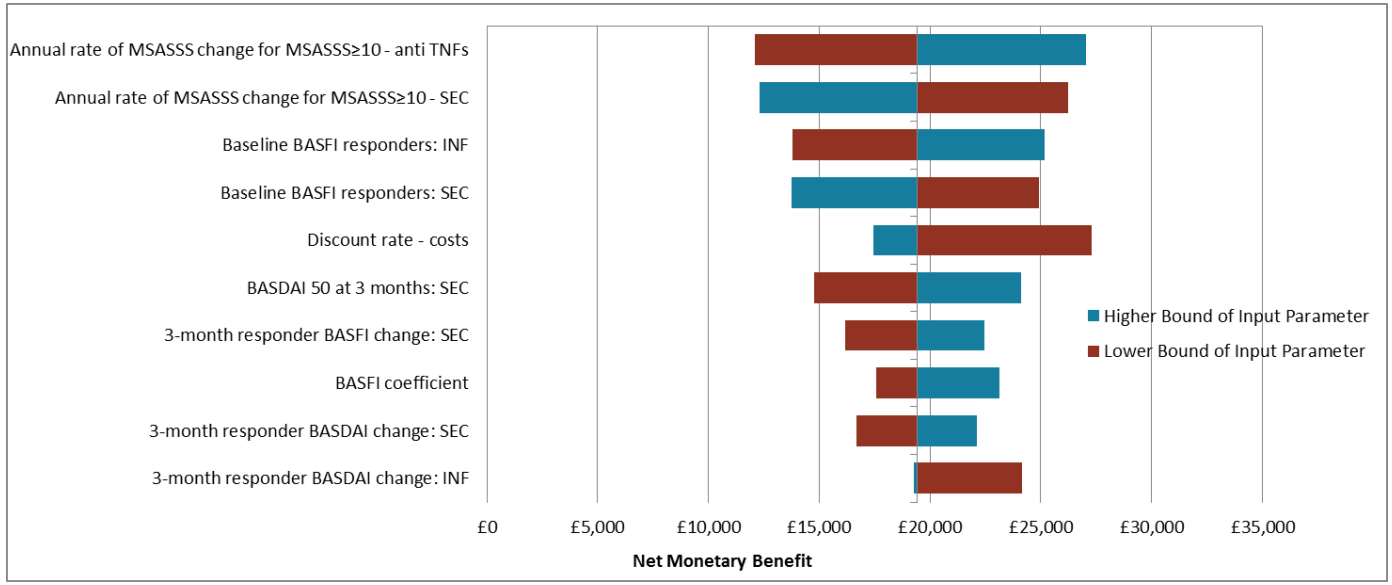
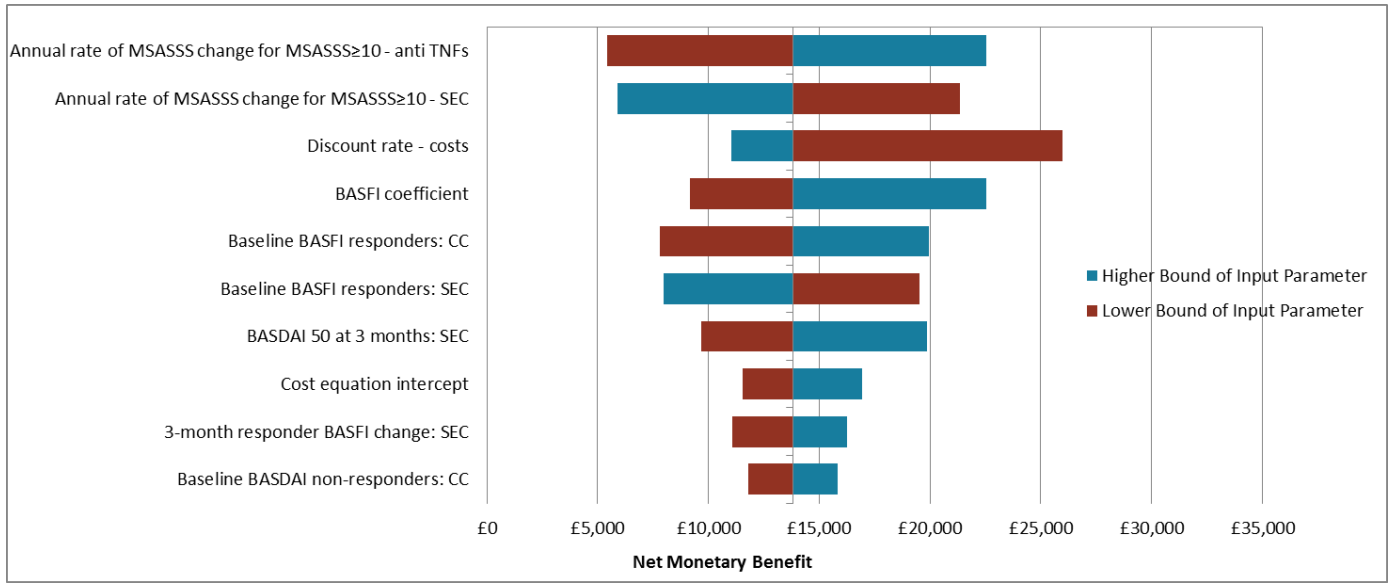


Figure 39. OWSA results for secukinumab vs conventional care – biologic experienced population



5.8.3. Scenario analysis

The economic evaluation explored a number of scenario analyses in which key model assumptions or parameters were altered. The scenario analyses considered in the economic modelling are presented in Table 107.

Table 107. Summary of scenario analyses

#	Scenario analysis	Description of scenario analysis
1	Alternative time horizons	Alternative time horizons are explored.
a	*Time horizon of 40 years*	
b	*Time horizon of 20 years*	
2	Alternative rebound assumption	In the base case it is assumed that BASFI deteriorates to the baseline level on discontinuation of biologic – "rebound to baseline". This scenario analysis explores a more pessimistic assumption that BASFI deteriorates to the level and subsequent trajectory that would have been had there not initially been a response to therapy for patients who discontinue biologic therapy – "rebound to natural history".
3	BASDAI and BASFI change from baseline not conditional on BASDAI 50 response	In the base case, short-term changes in BASDAI and BASFI are modelled as conditional on BASDAI 50 response. However, the lack of conditional data for comparators other than adalimumab and golimumab limits this analysis and therefore this scenario analysis explores the impact of removing the conditionality of changes in BASDAI and BASFI on BASDAI 50 response.
4	Alternative source of biologic drop-out rates	Assumed that all biologics are associated with an annual withdrawal rate of 11%, as per the York model in AS.[20]
5	Alternative definition of response	The base case analysis uses a definition of response of reduction to BASDAI to 50% of the pre-treatment value, aligned with the BASDAI 50 response outcome assessed in the trials of secukinumab and a number of comparators. The 2004 BSR guidelines for use of TNFα inhibitors in AS define a response as a reduction to BASDAI to 50% of the pre-treatment value **or** a fall of ≥2 units in BASDAI score and a reduction in the spinal pain VAS (in the last one week) by ≥2cm.[39] This scenario analysis used a definition of response of a reduction to BASDAI to 50% of the pre-treatment value **or** a fall of ≥2 units in BASDAI score to more closely align with BSR guidelines. For assigning this response definition to comparator therapies, the same proportional difference between the response rate by the BASDAI 50 definition and the BASDAI 50 or fall of ≥2 units in BASDAI score definition from the secukinumab data at 12 weeks was applied to the comparators BASDAI 50 response rates. The secukinumab data for response by this alternative definition can be found in Appendix H. Proportional changes in conditional BASDAI and BASFI changes from baseline between naïve and experienced populations, based on pooled MEASURE 1 and MEASURE 2 data, were also applied in this scenario.

6	Alternative NMA scenario inputs	To explore the impact of differing treatment effect estimates depending on the NMA scenario considered most appropriate.
a	NMA inputs from the Week 12-16 analysis including MEASURE 2 only (i.e. excluding MEASURE 1)	
b	NMA inputs from the Week 12 analysis, including MEASURE 2 and MEASURE 1	
c	NMA inputs from the Week 12 analysis including MEASURE 2 only (i.e. excluding MEASURE 1)	
7	Alternative utility models	To explore the impact of differing models of utility estimation.
a	Wailoo *et al.* 2015[221]	
b	McLeod *et al.* 2007 model[201]	
8	Alternative assumption around cost of intravenous infliximab administration	Cost of intravenous infliximab administration available in the costing template for the adalimumab NICE submission in psoriasis (£1,453.48) explored as an alternative source to the base case cost based on NHS Reference Costs 2014-15 (£326.46).[225]
9	Rate of radiographic progression (change in mSASSS) is lower with secukinumab than with biologic comparators – treatment effect on mSASSS progression rate is decreased from base case of 0.42 to 0.15	In the MEASURE 1 study, mean ± SD change in mSASSS from baseline to Week 104 was 0.30 ± 1.93 which compares with an estimate of 0.8 – 1.0 for TNFα inhibitors.
10	Considering treatment effect on long-term BASFI to begin four years after treatment initiation, rather than at treatment initiation	The York model in the recent MTA assumed treatment effect to begin four years after treatment initiation rather than at treatment initiation. Although the NICE Committee in this MTA ultimately adopted a preference for no delay in initiation of treatment effect, this scenario analysis explores the impact of using the Assessment Group's alternative assumption.

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; NICE, National Institute of Health and Care Excellence; NMA, network meta-analysis; TNFα, tumour necrosis factor alpha; VAS, visual analogue scale.

Table 108 below shows the results of the scenario analyses for each biologic comparator versus secukinumab in the biologic naïve population. Results are presented in this way since secukinumab is the lowest cost option in all but two scenarios (scenarios 3 and 6c, where etanercept is in the least expensive option).

Table 109 presents the results of the scenario analyses in the biologic experienced population. In this case, results are expressed as ICERs for secukinumab versus conventional care.

Table 108. Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population

	Etanercept			Adalimumab			Certolizomab Pegol			Golimumab			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£932	-0.762	SEC dominates	£13,072	-0.175	SEC dominates	£9,710	-0.216	SEC dominates	£16,310	0.041	£397,064	£24,751	0.092	£268,811	£21,248	0.092	£230,769
Scenario 1a	£737	-0.755	SEC dominates	£12,992	-0.170	SEC dominates	£9,608	-0.211	SEC dominates	£16,232	0.042	£384,150	£24,639	0.098	£251,356	£21,136	0.098	£215,625
Scenario 1b	£286	-0.628	SEC dominates	-£12,254	-0.107	SEC dominates	£9,193	-0.129	SEC dominates	£14,612	0.052	£283,050	£24,374	0.195	£125,037	£20,916	0.195	£107,298
Scenario 2	£2,072	-0.801	SEC dominates	£13,795	-0.196	SEC dominates	£10,610	-0.243	SEC dominates	£16,530	0.034	£482,391	£25,913	0.058	£446,706	£22,410	0.058	£386,321
Scenario 3	-£519	-0.527	£983*	£12,971	-0.170	SEC dominates	£9,445	-0.204	SEC dominates	£16,973	-0.034	SEC dominates	£24.614	-0.037	SEC dominates	£21,112	-0.037	SEC dominates
Scenario 4	£10,088	-0.318	SEC dominates	£13,378	-0.012	SEC dominates	£11,512	0.012	£986,619	£13,112	0.044	£299,833	£28,113	0.377	£74,598	£24,392	0.377	£64,724
Scenario 5	£14	-0.274	SEC dominates	£5,345	-0.063	SEC dominates	£4,583	-0.078	SEC dominates	£6,779	0.014	£487,938	£12,654	0.031	£408,746	-£10,858	0.031	£350,723
Scenario 6a	£3,050	-0.617	SEC dominates	£15,819	0.051	£307,693	£12,228	-0.002	SEC dominates	£19,328	0.293	£66,018	£28,258	0.314	£89,998	£24,503	0.293	£66,018
Scenario 6b	£2,183	-0.382	SEC dominates	£15,271	0.219	£69,846	£10,886	0.155	£70,293	£15,718	0.330	£47,653	£26,399	0.481	£54,924	£22,778	0.481	£47,390
Scenario 6c	-£2,583	-0.726	£3,558*	£8,183	-0.100	SEC dominates	£4,543	-0.191	SEC dominates	£8,050	-0.008	SEC dominates	£17,921	0.045	£396,772	£14,813	0.045	£327,957
Scenario 7a	£932	-0.893	SEC dominates	£13,072	-0.234	SEC dominates	£9,170	-0.323	SEC dominates	£16,310	-0.013	SEC dominates	£24,751	-0.213	SEC dominates	£21,248	-0.213	SEC dominates
Scenario 7b	£932	-0.700	SEC dominates	£13,072	-0.161	SEC dominates	£9,710	-0.202	SEC dominates	£16,310	0.036	£458,267	£24,751	0.074	£336,166	£21,248	0.074	£288,592
Scenario 8	£932	-0.762	SEC dominates	£13,072	-0.175	SEC dominates	£9,710	-0.216	SEC dominates	£16,310	0.041	£397,064	£46,084	0.092	£500,499	£42,582	0.092	£462,457
Scenario 9	£2,271	-0.812	SEC dominates	£14,412	-0.224	SEC dominates	£11,050	-0.266	SEC dominates	£17,650	-0.009	SEC dominates	£26,091	0.042	£615,250	£22,588	0.042	£532,651
Scenario 10	£565	-0.744	SEC dominates	£13,033	-0.171	SEC dominates	£9,606	-0.210	SEC dominates	£16,207	0.045	£364,083	£24,784	0.094	£262,384	£21,281	0.094	£225,300

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

The results of the scenario analyses presented in Table 108 show three classes of results across all of the scenario analyses:

1. Comparators associated with lower QALYs and higher cost versus secukinumab: therefore **secukinumab dominates the comparator**

2. Comparators associated with higher QALYs and higher cost versus secukinumab: in all such cases the ICER for the comparator therapy versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY applied by NICE, **showing cost-effectiveness of secukinumab**

3. In two cases, a comparator (etanercept) is associated with lower QALYs and lower costs versus secukinumab, so ICERs represent costs saved per QALY lost. In this situation, high ICERs represent more cost-effective options so these low ICERs (£983 and £3,558) indicate that etanercept is not cost-effective versus secukinumab. Hence we can again conclude that **secukinumab is cost-effective**.

Table 109. Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population

	Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
Base case	£1,747	0.778	£2,245
Scenario 1a	£1,979	0.769	£2,574
Scenario 1b	£3,358	0.643	£5,223
Scenario 2	£8,556	0.601	£14,248
Scenario 3*	N/A	N/A	N/A
Scenario 4	£1,363	0.654	£2,083
Scenario 5	£2,322	0.723	£3,213
Scenario 6a	N/A	N/A	N/A
Scenario 6b	N/A	N/A	N/A
Scenario 6c	N/A	N/A	N/A
Scenario 7a	£1,747	0.882	£1,979
Scenario 7b	£1,747	0.711	£2,455
Scenario 8	N/A	N/A	N/A
Scenario 9	£1,238	0.798	£1,551
Scenario 10	£2,173	0.762	£2,853

Note: Scenarios 3, 6a, 6b & 6c are not relevant to comparison versus conventional care since the ratio of BASDAI / BASFI change from baseline amongst responders versus non-responders and the network meta-analysis results only affect comparisons versus the TNFα inhibitors. Scenario 8 is not relevant to comparison versus conventional care since it only affects comparison with infliximab and infliximab biosimilar.

The results of the scenario analyses in Table 109 demonstrate that secukinumab remains a cost-effective treatment option compared to conventional care across all changes in key model assumptions.

5.8.4. Summary of sensitivity analyses results

The results of the probabilistic sensitivity analyses to account for uncertainty across model parameters found secukinumab 150 mg to be associated with a high probability (95% or greater) of cost-effectiveness in both the biologic naïve population (versus all TNFα inhibitor comparators) and the biologic experienced population (versus conventional care). The OWSA found estimates to be most sensitive to annual rates of mSASSS change and baseline BASFI, as well as the discount rate applied. In all cases, however, secukinumab was associated with net monetary benefits in excess of £5,000, with each QALY valued at £20,000. Finally, a range of scenario analyses to explore the impact of changes in key model assumptions found the overall model conclusions to be highly robust to these changes. Secukinumab remained a cost-effective treatment option at the conventional NICE threshold across all scenarios and all comparisons; to TNFα inhibitors in the biologic naïve population and to conventional care in the biologic experienced population.

5.9. Subgroup analysis

No further subgroup analysis beyond the exploration of individual subgroup populations of biologic naïve and biologic experienced patients were explored.

5.10. Validation

As previously mentioned, the NMA informing the model has been reviewed by two clinical experts in the field of rheumatology: [redacted]. Both experts confirmed that results were reflective of their clinical experiences and this provides validation for a number of the clinical inputs informing the economic modelling.[85, 211]

Further validation can be derived from a comparison of the total costs predicted for TNFα inhibitors and for conventional care in this model and the York model produced for the MTA in AS. Table 110 presents a summary comparison of these results, which are based on similar time horizons (58 years in this model versus 60 years in the York model).

Table 110. Comparison of total costs by intervention in submission model and York model in AS

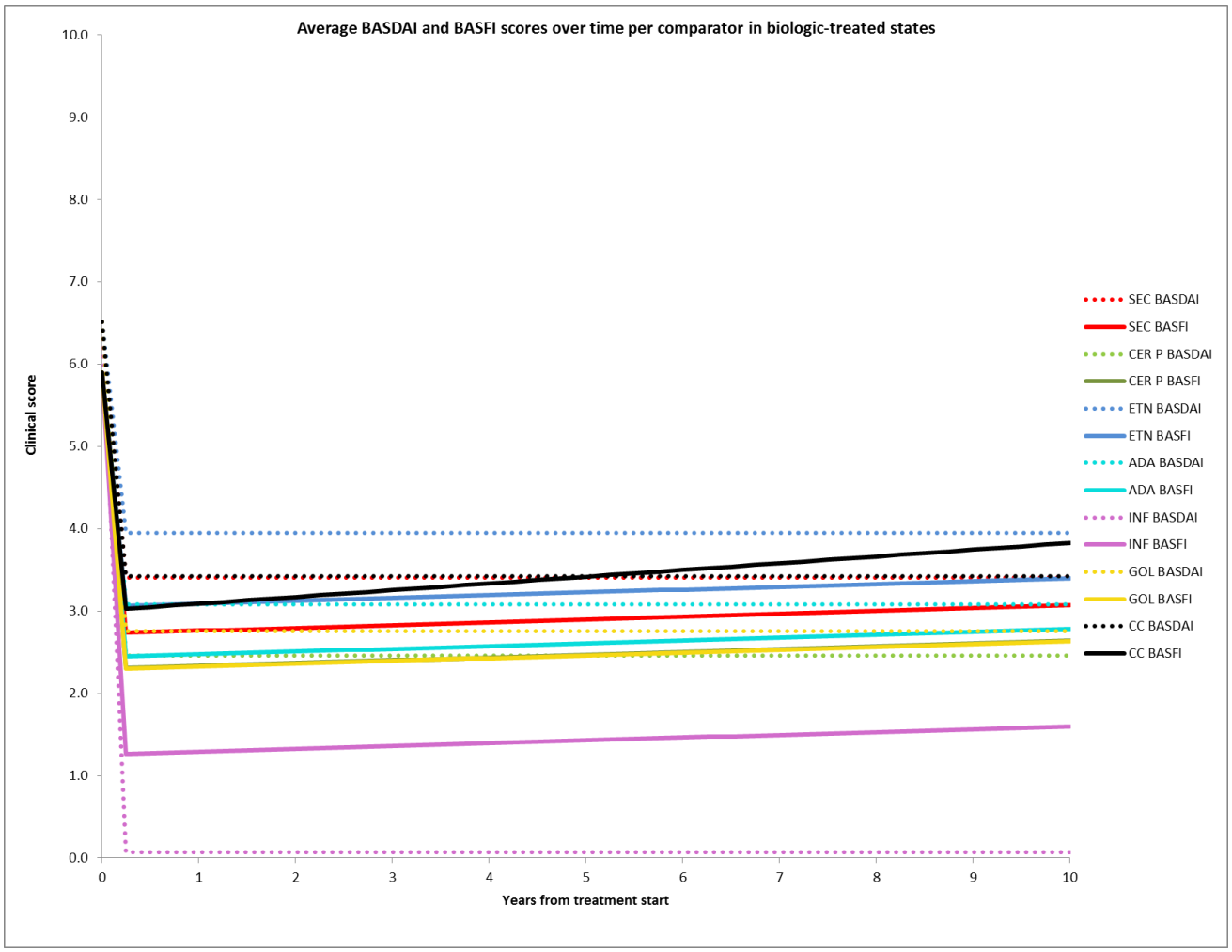
	Total costs – model presented in this submission	Total costs – York model in AS (base case)
Conventional care	£91,823	£110,821
Etanercept	£115,779	£130,630
Certolizumab pegol	£124,557	£128,485
Adalimumab	£127,919	£130,257
Golimumab	£131,157	£130,173
Infliximab	£139,598	£148,073

As can be seen, the model presented in this submission presents relatively similar total costs for each intervention to those that are predicted by the York model. The comparison in Table 110 therefore provides support for the validity of the presented model.

An additional validation of the model is provided by a comparison of predicted model outcomes with long-term registry data from the BSR Biologics Register in AS (BSRBR-AS), which acts as a source of UK-based real-world data on AS patients who have received biologic therapy.[227] Data from this registry is available that provides information on BASDAI and BASFI scores over 4 years of biologic treatment, which can be compared to model outcomes. Figure 40, below, shows the average BASDAI and BASFI

scores amongst patients in the biologic treated health states over 10 years of the model, hence aligning to the registry data which is based on patients who continue on biologic treatment.

Figure 40. Average BASDAI and BASFI scores from the economic model (over 10 years)



The available data from the BSRBR-AS registry suggests that patients on biologics in clinical practice might be expected to maintain constant BASDAI scores whilst on biologic treatment.[227] For secukinumab, the maintenance of BASDAI scores up to 2 years is supported up by data presented in Table 22 (MEASURE 2) and Table 34 (MEASURE 1), which shows that BASDAI changes from baseline are sustained from Week 52 to Week 104.

In terms of BASFI scores, the model similarly predicts relatively constant BASFI scores for patients remaining on biologic therapy, with slight increases in score for patients on biologic treatments over the course of the 10 years shown in Figure 40. Once again, this is validated against real-world outcomes from the BSRBR-AS registry, which showed relatively sustained BASFI scores following the introduction of biologic treatment.[227] In addition, as with the BASDAI outcome, data from the MEASURE 1 trial of secukinumab supported that BASFI scores observed at 2 years were consistent with those observed at 1 year (Table 38; data to 2 years unavailable for MEASURE 2).

5.11. Interpretation and conclusions of economic evidence

The economic model provides estimates of the cost-effectiveness of secukinumab across the populations of biologic naïve and biologic experienced patients, in line with the final NICE scope for this appraisal. Cost and resource use inputs are sourced from UK data sources, and utility values are based on a linear model informed by EQ-5D estimates as per the NICE reference case.

The results of the base case analysis demonstrate that secukinumab represents a cost-effective treatment option compared to all TNFα inhibitor comparators in the biologic naïve population and compared to conventional care in the biologic experienced population. Secukinumab is the lowest cost biologic licensed for the treatment of ankylosing spondylitis. It dominates adalimumab, certolizumab pegol and etanercept in the base case analysis of the biologic naïve population, having both lower costs and greater QALY gains. In comparison with golimumab and infliximab the QALY gains are marginally lower with secukinumab, however there are substantial cost savings, which result in ICERs in excess of £250,000 saved per QALY lost. In situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. We can therefore conclude that secukinumab represents a cost-effective treatment option for patients with ankylosing spondylitis who are naïve to biologic therapy.

In the biologic experienced population, robust comparisons versus the biologic therapies are not possible due to an absence of randomised controlled data on efficacy in this population. The base case analysis therefore compares secukinumab with conventional care alone, based on the results of the MEASURE 1 and MEASURE 2 studies. The ICER for secukinumab versus conventional care in this population is £2,245. Hence secukinumab also represents a cost-effective treatment option for patients with ankylosing spondylitis whose disease has responded inadequately to, or who are intolerant to TNFα inhibitors.

These findings are robust to changes in key assumptions as part of scenario analyses, and exploration of combined uncertainty in model parameters explored through probabilistic sensitivity analysis. It is also relevant to note that in the recent MTA of biologics for AS, the preferred approach by the assessment group was to assume “exchangeable effects across treatments” and in their analysis “the differences between each of the treatments are driven entirely by their respective acquisition, administration and monitoring costs”.[20] In addition, the network meta-analyses described in Section 4.10 largely indicate no significant differences between secukinumab and the TNFα inhibitors.

One limitation within the modelling is a lack of conditional data for all comparators i.e. changes from baseline in BASDAI and BASFI for patients meeting the BASDAI 50 response criteria. Assumptions, validated with UK clinicians, were therefore required. These were tested in a scenario analysis (scenario 3) without conditional response estimates in which secukinumab dominated all comparators, with the exception of etanercept, which was associated with marginally lower costs for considerable QALY loss.

Attempts to incorporate the use of second-line biologics into the model as part of exploratory analyses are limited by the requirement for assumptions regarding the efficacy of comparator biologics in the biologic experienced population due to a lack of comparator data. Nonetheless, these exploratory analyses allow a reasonable estimation of the cost-effectiveness of secukinumab when considering sequential use of two biologics (see Table 103). Exploratory analyses in the biologic experienced population provide estimates of the cost-effectiveness of secukinumab versus biologic comparators in this population. However, lack of comparator data means these analyses rest on an assumption of the same relative decline in efficacy for both secukinumab and the TNFα inhibitors. Nonetheless they indicate secukinumab is cost-effective treatment option for biologic experienced patients (see Table 104), further supporting the findings of the base case analysis.

In summary, secukinumab is a cost-effective treatment option compared to TNFα inhibitors in a biologic naïve population and compared to conventional care in a biologic experienced population.

6. Assessment of factors relevant to the NHS and other parties

Summary of Budget Impact Analysis

- An analysis was conducted to explore the budget impact of the introduction of secukinumab between 2016-2020.
- The analysis was based on predicted market share estimates and discontinuation rates of secukinumab and the following comparators: adalimumab (Humira®); certolizumab pegol (Cimzia®); etanercept (Enbrel®); golimumab (Simponi®); infliximab (Remicade®) and biosimilar versions, Remsima® and Inflectra®.
- Introduction of secukinumab 150 mg with the offered PAS is anticipated to be associated with a significant negative budget impact resulting in a cost saving each year rising from [redacted] in Year 1 to [redacted] in Year 5.
- There are no additional service implications resulting from the introduction secukinumab.

Prevalence and Incidence of AS in England and Wales

A single population was considered in this Budget Impact Analysis: the number of patients who will receive biologic therapy for AS in England and Wales. The population considered is representative of current and expected future clinical practice in the UK, considering both the proportion of patients who have responded inadequately to conventional treatment for AS and the proportion that will receive biologic therapy based on commissioning practice.

Estimations of the total projected population in England and Wales were taken from the Office for National Statistics.[41] From these population estimates, the projected adult population (≥ 18 years) in England and Wales were calculated and summed to give a projected adult population in England & Wales between 2016 and 2020 (a five year time horizon).

In order to calculate the number of patients with AS in England and Wales, a prevalence rate of 0.238% was taken from a study by Dean *et al.* which reported a mean European prevalence of AS of 23.8 per 10,000.[51] The incidence rate reported in the BSR guidelines of 7.3 per 100,000 person years was approximated to 0.01% and used to calculate the annual incidence of AS in England and Wales.

The projected prevalence and incidence of AS in England and Wales between 2016 and 2020 are presented in Table 111 and Table 112, respectively.

Table 111. Projected Prevalent Population of AS in England and Wales 2016-2020

Year	2016	2017	2018	2019	2020
Population in England aged ≥18 years (at end of year)	43,482,704	43,818,066	44,130,533	44,413,044	44,672,000
Population in Wales aged ≥18 years (at end of year)	2,484,908	2,494,638	2,502,874	2,509,965	2,515,368
Population in England and Wales aged ≥18 years (at end of year)	45,967,612	46,312,704	46,633,407	46,923,009	47,187,368

Prevalence of AS	0.238%	0.238%	0.238%	0.238%	0.238%
Prevalence of AS in England and Wales	109,403	110,224	110,988	111,677	112,306

Abbreviations: AS, ankylosing spondylitis.

Table 112. Projected Incident Population of AS in England and Wales 2016-2020

Year	2016	2017	2018	2019	2020
Population in England and Wales aged ≥18 years (at end of year)	45,967,612	46,312,704	46,633,407	46,923,009	47,187,368
Incidence of AS	0.01%	0.01%	0.01%	0.01%	0.01%
Incidence of AS in England and Wales	3,172	3,196	3,218	3,238	3,256

Abbreviations: AS, ankylosing spondylitis.

Additional Mortality Rate of Patients with AS

The mortality rate of males and females aged 45-50 was taken from the National Life Tables, and averaged to give a mortality rate for each gender in this age group (0.26% and 0.17% in males and females, respectively). This age range was selected to approximately reflect the mean age of patients in the MEASURE 2 and MEASURE 1 trials and the likely average age of patients in clinical practice. The mortality rate was subsequently adjusted based on the relative risk of death for AS per gender and the background mortality rate subtracted to give an additional mortality rate for males and females with AS (0.16% and 0.06% for males and females, respectively).[83] These additional mortality rates were then weighted according to the European gender ratio in AS of 3.8:1 (males: females) to give an average additional mortality rate for patients with AS of 0.14%.[51] Application of this additional mortality rate to the estimates of the prevalence and incident populations resulted in a net number of patients with AS as shown below.

The details of the additional mortality rate calculation and the resulting net number of patients with AS are presented in Table 113.

Table 113. Mortality Rate Calculation for Patients with AS

Year	2016	2017	2018	2019	2020
General mortality rate (males, age 45-50)	0.26%	0.26%	0.26%	0.26%	0.26%
General mortality rate of (females, age 45-50)	0.17%	0.17%	0.17%	0.17%	0.17%
Relative risk of death for AS patients (male)	1.63	1.63	1.63	1.63	1.63
Relative risk of death for AS patients (female)	1.38	1.38	1.38	1.38	1.38
Proportion of patients with AS (male)	0.77	0.77	0.77	0.77	0.77
Proportion of patients with AS (female)	0.23	0.23	0.23	0.23	0.23
Additional mortality rate for patients with AS (male)	0.16%	0.16%	0.16%	0.16%	0.16%
Additional mortality rate for patients with AS (female)	0.06%	0.06%	0.06%	0.06%	0.06%
Additional mortality rate for patients with AS (weighted per gender)	0.14%	0.14%	0.14%	0.14%	0.14%
Estimated number of patients with AS	112,575	113,420	114,205	114,914	115,562
Net number of patients with AS, taking into account additional AS-related mortality	**112,419**	**113,263**	**114,047**	**114,755**	**115,402**

Abbreviations: AS, ankylosing spondylitis.

Estimated Number of AS Patients Receiving Treatment with Biologics in Each Year

The number of patients eligible for treatment with secukinumab was calculated based on 40% of patients not responding to conventional treatment and thus being eligible for biologic therapy.[19] Subsequently 60% of these patients were considered to receive biologic therapy based on clinical expert opinion resulting in 24% of patients being eligible for, and subsequently treated with, biologics.[85] Details of these calculations are shown in Table 114 below.

Table 114. Estimated Number of Patients Receiving Biologic Therapy 2016-2020

Year	2016	2017	2018	2019	2020
Net number of patients with AS	112,419	113,263	114,047	114,755	115,402
Proportion of patients eligible for and subsequently treated with biologics	24.00%	24.00%	24.00%	24.00%	24.00%
Number of patients eligible for and subsequently treated with biologics	**26,981**	**27,183**	**27,371**	**27,541**	**27,696**

Abbreviations: AS, ankylosing spondylitis.

Predicted Uptake of Secukinumab

Internal market share estimates were applied to determine the number of eligible patients predicted to receive secukinumab. Market shares were estimated based on current market shares, change in market shares over the previous three years and anticipated market changes including the introduction of biosimilars. The uptake of secukinumab was assumed to increase over time from [redacted] in 2016 to [redacted] in 2020, in doing so displacing current biologic therapies used for the treatment of AS in England and Wales: adalimumab, etanercept, infliximab (Remicade®) and biosimilar versions (Inflectra® and Remsima®), golimumab and certolizumab pegol.

The market share estimates used in the budget impact analysis are presented in Table 115 below.

Table 115. Market Share Estimates by Regimen 2016-2020

Year	2015	2016	2017	2018	2019	2020
NHS without secukinumab						
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NHS with secukinumab						
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biosimilar infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition, the withdrawal rates used in the cost-effectiveness model described above (please see Table 76) were applied, to calculate the number of patients expected to be treated with each biologic in each year.

Additional Costs

No additional costs are expected as there are no service implications associated with the introduction of secukinumab. Treatment of secukinumab will not require additional monitoring or testing in comparison to the comparator biologic treatments.

Unit Cost Assumptions and Calculations

As there are no additional costs associated with the introduction of secukinumab, the only costs considered in the budget impact analysis were the costs of the drugs and associated administration costs. The dosing regimens detailed in the relevant SmPCs of the included biologics were applied in the budget impact analysis, consistent with their respective marketing authorisation, for further details please see Section 5.2.3.

For infliximab (Remicade®) and the infliximab biosimilars, it was assumed that, following the initial 3 doses at Weeks 0, 2 and 6, patients received each subsequent maintenance dose every 8 weeks. This is a conservative approach as the licence for infliximab notes maintenance dosing every 6-8 weeks, and hence maintenance dosing may be more frequent (and therefore costly) in practice. Since infliximab is dosed by weight, the average number of vials required by each patient was calculated based on a mean weight of 78.20 kg (SD 16.88 kg) – the pooled average weight of all patients in the MEASURE 2 and MEASURE 1 trials – and it was assumed that weight was normally distributed. The calculation performed was that presented previously in Table 83, resulting in acquisition costs per dose for infliximab (Remicade®) and the infliximab biosimilars of £1,850.59 and £1,665.54, respectively.

In addition to treatment acquisition costs, the administration cost of each drug was also included. For those therapies administered subcutaneously (all included therapies with the exception of infliximab), this was assumed to consist of a one-off training cost after which there is no administration cost because patients are able to self-inject. This training cost was assumed to be £43.00, based on the cost of 1 hour of nurse training (including qualifications) from the Personal and Social Services Research Unit Costs 2015.[224] In contrast, infliximab is considered to incur a £326.46 administration cost per dose due to the intravenous formulation of this drug. This cost is sourced from the NHS Reference Costs 2014-15 (health resource group [HRG] code SB15Z).[222]

A summary of the details of the unit costs and corresponding calculated three-monthly and annual costs used in the budget impact analysis are presented in Table 116 and Table 117 below.

Table 116. Details of unit costs used in the budget impact analysis

Drug	Dose	Pack size	Cost per pack	Cost per dose
Secukinumab with PAS	150mg at Baseline, W1, W2, W3, W4 then monthly	150mg x2	[redacted]	[redacted]
Adalimumab	40mg every 2 weeks	40mg	£352.14	£352.14
Certolizumab Pegol with PAS	400mg at W0, W2, W4 then 200mg every 2 weeks	200mg	£357.50	£357.50
Etanercept	50mg once/week	50mg	£178.75	£178.75
Golimumab	50mg once/month	100mg	£762.97	£762.97
Infliximab	5mg/kg at W0, W2, W6 then every 6-8 weeks	100mg	£419.62	£1,850.59
Biosimilar Infliximab	5mg/kg at W0, W2, W6 then every 6-8 weeks	100mg	£377.66	£1,665.54

Abbreviations: PAS, Patient Access Scheme.

Table 117. Calculated costs used in the budget impact analysis

			Months 1-3		Months 4-6		Months 6-12		Year 1	Year 2+	
Drug	Cost per dose	Admin cost	No. of doses required	Cost	No. of doses required	Cost	No. of doses required	Cost	Total cost	No. of doses required	Total cost
Secukinumab with PAS	[redacted]	£43.00	7.00	[redacted]	3.00	[redacted]	6.00	[redacted]	[redacted]	12.00	[redacted]
Adalimumab	£352.14	£43.00	6.52	£2,339.77	6.52	£2,296.77	13.04	£4,593.54	£9,230.08	26.09	£9,187.08
Certolizumab Pegol with PAS	£357.50	£43.00	9.78	£43.00	6.52	£2,331.73	12.00	£4,290.00	£6,664.73	24.00	£8,580.00
Etanercept	£178.75	£43.00	13.00	£2,366.75	13.00	£2,323.75	26.08	£4,661.80	£9,352.30	52.16	£9,323.60
Golimumab	£762.97	£43.00	3.00	£2,331.91	3.00	£2,288.91	6.00	£4,577.82	£9,198.64	12.00	£9,155.64
Infliximab	£1,850.59	£326.46[a]	3.00	£6,531.15	2.00	£4,354.10	3.26	£6,035.07	£16,920.32	6.52	£14,199.42
Biosimilar Infliximab	£1,665.54	£326.46[a]	3.00	£5,976.00	2.00	£3,984.00	3.26	£5,431.59	£15,391.59	6.52	£12,992.46

Abbreviations: PAS, Patient Access Scheme.
[a]Infliximab administration cost is a cost per dose; all other administration costs are a one-off cost. [b]Month 1-3 costs for certolizumab pegol incorporate a PAS, where patients receive the first 3 months of treatment (10 vials of 200 mg) free of charge.

Costs were then weighted according to the prevalent and incident populations, assuming that for secukinumab all patients would initially receive first year costs in Year 1, and subsequently incident populations would receive first year costs while the prevalent population would receive Year 2+ costs. For comparator treatments, incident populations were assumed to receive first year costs, and prevalent populations assumed to receive Year 2+ costs in all five years. The weighted costs per treatment are presented in Table 118.

Table 118. Weighted unit costs per patient

Weighted Costs	2016	2017	2018	2019	2020
Secukinumab with PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	£9,188.29	£9,188.29	£9,188.29	£9,188.29	£9,188.29
Etanercept	£9,324.41	£9,324.41	£9,324.41	£9,324.41	£9,324.41
Infliximab	£14,276.08	£14,276.08	£14,276.08	£14,276.08	£14,276.08
Biosimilar Infliximab	£13,060.06	£13,060.06	£13,060.06	£13,060.06	£13,060.06
Certolizumab Pegol	£8,526.04	£8,526.04	£8,526.04	£8,526.04	£8,526.04
Golimumab	£9,156.85	£9,156.85	£9,156.85	£9,156.85	£9,156.85

Abbreviations: PAS, patient access scheme.

Additional Resource Savings

There is a cost saving associated with the subcutaneous administration of secukinumab in comparison to the i.v. administration of infliximab. This has been incorporated into the above unit costs. No other additional resource savings are anticipated.

Annual Budget Impact

The annual budget impact anticipated following the introduction of secukinumab with a PAS applied is presented in Table 119. Secukinumab (with PAS) is anticipated to result in a negative budget impact each year i.e. annual cost saving rising from [redacted] in Year 1 to [redacted] in Year 5.

Table 119. Budget impact results 2016-2020 - with PAS

Year	2016	2017	2018	2019	2020
NHS without secukinumab					
Adalimumab	£94,296,632	£99,528,570	£107,050,809	£114,591,079	£122,150,872
Etanercept	£48,966,069	£45,538,774	£40,122,353	£34,604,160	£28,999,263
Infliximab	£23,481,930	£16,265,023	£12,208,797	£10,187,242	£9,340,698
Biosimilar Infliximab	£8,354,019	£12,174,206	£16,072,267	£18,090,800	£19,019,663
Certolizumab Pegol	£18,414,516	£18,552,759	£18,681,232	£18,797,246	£18,903,147
Golimumab	£29,942,852	£32,488,230	£32,713,202	£32,916,357	£33,101,804
Total	**£223,456,019**	**£224,547,561**	**£226,848,659**	**£229,186,883**	**£231,515,448**
NHS with secukinumab					
Secukinumab with PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	£92,051,474	£92,742,531	£93,384,748	£93,964,684	£89,884,604
Etanercept	£48,966,069	£41,743,876	£36,301,176	£28,836,800	£19,332,842
Infliximab	£23,481,930	£16,265,023	£12,208,797	£9,055,326	£8,302,842
Biosimilar Infliximab	£8,354,019	£12,174,206	£16,072,267	£16,080,711	£16,906,367
Certolizumab Pegol	£16,368,459	£14,429,924	£12,454,155	£12,531,497	£8,401,399
Golimumab	£25,336,260	£25,526,466	£23,366,573	£21,160,515	£16,550,902
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Budget Impact (with PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, patient access scheme.
[a]Negative values indicate a negative budget impact i.e. cost saving each year

Limitations of the Budget Impact Analysis

The primary limitation of the budget impact analysis described is that it does not consider sequential treatment of biologics. As there is no clear guidance on the sequence of treatments, switching between biologic therapies has not been considered in this model, but should be noted in the interpretation of these results.

Summary of Results

The budget impact of using secukinumab with the PAS resulted in a substantial estimated cost saving every year ranging from [redacted] in Year 1 to [redacted] in Year 5. The results assume market share estimates of [redacted] in Year 1 rising to [redacted] in Year 5, and higher levels of secukinumab uptake would be associated with even greater cost savings. These findings confirm the significant economic benefit conferred by secukinumab, adding further support to this submission.

7. References

1. Gordeev VS, Maksymowych WP, Schachna L, et al. Understanding presenteeism in patients with ankylosing spondylitis: contributing factors and association with sick leave. Arthritis Care Res (Hoboken) 2014;66:916-24.
2. Julide Ö, BAŞOĞLU F, Kuran B. Work Absenteeism and Its Determinant Factors in Patients with Ankylosing Spondylitis: A Cross-Sectional Study. Archives of Rheumatology 2014;29:001-007.
3. Zink A, Braun J, Listing J, et al. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis--results from the German rheumatological database. German Collaborative Arthritis Centers. J Rheumatol 2000;27:613-22.
4. Machado P, Landewe R, Braun J, et al. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:1465-70.
5. European Medicines Agency (EMA). Cosentyx 150 mg powder for solution for injection. Summary of Product Characteristics. 2016. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf. Last accessed 12th January 2016.
6. Isailovic N, Daigo K, Mantovani A, et al. Interleukin-17 and innate immunity in infections and chronic inflammation. J Autoimmun 2015;60:1-11.
7. Konya C, Paz Z, Apostolidis SA, et al. Update on the role of Interleukin 17 in rheumatologic autoimmune diseases. Cytokine 2015.
8. Li D, Guo B, Wu H, et al. Interleukin-17 in systemic lupus erythematosus: A comprehensive review. Autoimmunity 2015:1-9.
9. European Medicines Agency (EMA). Simponi 50 mg solution for injection in pre-filled pen. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000992/WC500052368.pdf. Last accessed 15th December 2015.
10. European Medicines Agency (EMA). Enbrel 25 mg powder and solvent for solution for injection. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf. Last accessed 15th December 2015.
11. European Medicines Agency (EMA). Humira 40 mg/0.8 ml solution for injection. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf. Last accessed 15th December 2015.
12. European Medicines Agency (EMA). Remicade 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf. Last accessed 12th January 2016.
13. European Medicines Agency (EMA). Cimzia 200 mg solution for injection. Summary of Product Characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

_Product_Information/human/001037/WC500069763.pdf. Last accessed 15th December 2015.
14. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med 2015a;373:2534-48.
15. Novartis Data on File: MEASURE 2– Week 104 Analysis Tables.
16. Novartis Data on File: MEASURE 1 Clinical Study Report – Week 104 Analysis.
17. European Medicines Agency (EMA). Inflectra 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002778/WC500151489.pdf. Last accessed 12th January 2016.
18. European Medicines AE. Remsima 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002576/WC500150871.pdf. Last accessed 12th January 2016.
19. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA383]. Multiple Technology Appraisal (MTA): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. 2016. Available at https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077. Last accessed 2nd February 2016.
20. National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233): Assessment Report. 2014. Available at https://www.nice.org.uk/guidance/gid-tag355/documents/ankylosing-spondylitis-and-axial-spondyloarthritis-nonradiographic-adalimumab-etanercept-infliximab-and-golimumab-inc-rev-ta143-and-ta233-assessment-report-2. Last accessed 13th January 2016.
21. Office for National Statistics - Statistical Bulletin. Estimates of the Very Old (including Centenarians) for England and Wales, United Kingdom, 2002 to 2013). Available at: http://www.ons.gov.uk/ons/dcp171778_378107.pdf [Last accessed 20.11.2015].
22. Baeten D, Baraliakos X, Braun J, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:1705-13.
23. Baeten D, Braun J, Sieper J, et al. Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis: 2-Year Efficacy and Safety Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheumatol 2015b;67.
24. Novartis Data on File: MEASURE 1 Clinical Study Report – Week 52 Analysis.
25. Novartis Data on File: MEASURE 2 Clinical Study Report – Week 52 Analysis.
26. Baraliokos X, Deodhar A, Braun J, et al. Effect of Interleukin-17A Inhibition on Spinal Radiographic Changes through 2 Years in Patients with Active

Ankylosing Spondylitis: Results of a Phase 3 Study with Secukinumab. Arthritis Rheumatol 2015a;67.
27. Sieper J, Braun J, Baraliakos X, et al. Secukinumab Efficacy in Anti-TNF-Naive Patients and Patients Previously Exposed to Anti-Tnf Therapy: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study (MEASURE 2) in Active Ankylosing Spondylitis. Poster presented at EULAR 2015.
28. Baeten D, Blanco R, Geusens P, et al. Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis in Anti-TNF-Naïve Patients and Those Previously Exposed to Anti-TNF Therapy: 52-Week Results from Two Randomized, Double-Blind, Placebo-Controlled Phase 3 Trials. Arthritis Rheumatol 2015c;67.
29. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 2010;30:1437-40.
30. Smith JA, Colbert RA. Review: The interleukin-23/interleukin-17 axis in spondyloarthritis pathogenesis: Th17 and beyond. Arthritis Rheumatol 2014;66:231-41.
31. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:2127-37.
32. Xueyi L, Lina C, Zhenbiao W, et al. Levels of circulating Th17 cells and regulatory T cells in ankylosing spondylitis patients with an inadequate response to anti-TNF-alpha therapy. J Clin Immunol 2013;33:151-61.
33. Kim HR, Lee SH, Kim HY. Elevated serum levels of soluble receptor activator of nuclear factors-kappaB ligand (sRANKL) and reduced bone mineral density in patients with ankylosing spondylitis (AS). Rheumatology (Oxford) 2006;45:1197-200.
34. Kirkham BW, Kavanaugh A Fau - Reich K, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis.
35. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. Nat Rev Drug Discov 2012;11:763-776.
36. National Institute for Health and Care Excellence (NICE). Secukinumab for treating moderate to severe plaque psoriasis. TA350. 2015. Available at https://www.nice.org.uk/guidance/ta350/resources/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-82602661589701. Last accessed 12th January 2016.
37. National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis [TA143]. 2008. Available at https://www.nice.org.uk/guidance/ta143/resources/adalimumab-etanercept-and-infliximab-for-ankylosing-spondylitis-82598252597701. Last accessed 15th December 2015.
38. National Institute for Health and Care Excellence (NICE). Golimumab for the treatment of ankylosing spondylitis [TA233]. 2011. Available at https://www.nice.org.uk/guidance/ta233/resources/golimumab-for-the-treatment-of-ankylosing-spondylitis-82600368913861. Last accessed 15th December 2015. .
39. Keat A, Barkham N, Bhalla A, et al. BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. Rheumatology (Oxford) 2004;44:939-47.

40. Lai Y, Dong C. Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases. Int Immunol 2015.
41. O'Connor W, Jr., Zenewicz LA, Flavell RA. The dual nature of T(H)17 cells: shifting the focus to function. Nat Immunol 2010;11:471-6.
42. DeLay ML, Turner MJ, Klenk EI, et al. HLA–B27 misfolding and the unfolded protein response augment interleukin-23 production and are associated with Th17 activation in transgenic rats. Arthritis & Rheumatism 2009;60:2633-2643.
43. Glatigny S, Fert I, Blaton MA, et al. Proinflammatory Th17 cells are expanded and induced by dendritic cells in spondylarthritis-prone HLA–B27–transgenic rats. Arthritis & Rheumatism 2012;64:110-120.
44. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- entheseal resident T cells. Nat Med 2012;18:1069-76.
45. Sarin R, Wu X, Abraham C. Inflammatory disease protective R381Q IL23 receptor polymorphism results in decreased primary CD4+ and CD8+ human T-cell functional responses. Proc Natl Acad Sci U S A 2011;108:9560-5.
46. Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis & Rheumatism 2009;60:1647-1656.
47. Bowness P, Ridley A, Shaw J, et al. Th17 cells expressing KIR3DL2+ and responsive to HLA-B27 homodimers are increased in ankylosing spondylitis. J Immunol 2011;186:2672-80.
48. Kenna TJ, Davidson SI, Duan R, et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive gamma/delta T cells in patients with active ankylosing spondylitis. Arthritis Rheum 2012;64:1420-9.
49. Appel H, Maier R, Wu P, et al. Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther 2011;13:R95.
50. Noordenbos T, Yeremenko N, Gofita I, et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondylarthritis. Arthritis Rheum 2012;64:99-109.
51. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford) 2014;53:650-7.
52. Hamilton-West KE, Quine L. Living with Ankylosing Spondylitis: the patient's perspective. J Health Psychol 2009;14:820-30.
53. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol 2015;29:1082-90.
54. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. BMJ 2006;333:581-5.
55. Sieper J. How to screen for axial spondyloarthritis in primary care? Curr Opin Rheumatol 2012;24:359-62.
56. Sieper J, Rudwaleit M. How early should ankylosing spondylitis be treated with tumour necrosis factor blockers? Ann Rheum Dis 2005;64 Suppl 4:iv61-4.

57. El-Gabalawy H, Guenther Lc Fau - Bernstein CN, Bernstein CN. Epidemiology of Immune-Mediated Inflammatory Diseases: Incidence, Prevalence, Natural History, and Comorbidities. J Rheumatol 2010:2-10.
58. El Maghraoui A. Extra-articular manifestations of ankylosing spondylitis: prevalence, characteristics and therapeutic implications. Eur J Intern Med 2011;22:554-60.
59. Elewaut D, Matucci-Cerinic M. Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice. Rheumatology (Oxford) 2009;48:1029-35.
60. Momeni M, Taylor N, Tehrani M. Cardiopulmonary manifestations of ankylosing spondylitis. Int J Rheumatol 2011;2011:728471.
61. Husain MJ, Brophy S, Cooksey R, et al. 211. The Cost of Ankylosing Spondylitis to the UK NHS. Rheumatology 2014;53:i138.
62. Husain MJ, Brophy S, Cooksey R, et al. 216. The Work-Related Costs of Ankylosing Spondylitis in a UK Cohort. Rheumatology 2014;53:i140-i141.
63. Ara RM, Packham JC, Haywood KL. The direct healthcare costs associated with ankylosing spondylitis patients attending a UK secondary care rheumatology unit. Rheumatology (Oxford) 2008;47:68-71.
64. Brophy S, Davies H, Dennis MS, et al. Fatigue in ankylosing spondylitis: treatment should focus on pain management. Semin Arthritis Rheum 2013;42:361-7.
65. Dagfinrud H, Kjeken I, Mowinckel P, et al. Impact of functional impairment in ankylosing spondylitis: impairment, activity limitation, and participation restrictions. J Rheumatol 2005;32:516-23.
66. Zink A, Thiele K, Huscher D, et al. Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol 2006;33:86-90.
67. Kotsis K, Voulgari PV, Drosos AA, et al. Health-related quality of life in patients with ankylosing spondylitis: a comprehensive review. Expert Rev Pharmacoecon Outcomes Res 2014;14:857-72.
68. Tam LS, Gu J, Yu D. Pathogenesis of ankylosing spondylitis. Nat Rev Rheumatol 2010;6:399-405.
69. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
70. Raychaudhuri SK, Saxena A, Raychaudhuri SP. Role of IL-17 in the pathogenesis of psoriatic arthritis and axial spondyloarthritis. Clin Rheumatol 2015;34:1019-23.
71. Reveille JD. Biomarkers for diagnosis, monitoring of progression, and treatment responses in ankylosing spondylitis and axial spondyloarthritis. Clin Rheumatol 2015;34:1009-18.
72. Department of Health. The Musculoskeletal Services Framework. 2006.
73. Worcester S. Prevalence, diagnosis of ankylosis spondylitis still elusive. Rheumatology News 2011.
74. Hamilton L, Gilbert A, Skerrett J, et al. Services for people with ankylosing spondylitis in the UK--a survey of rheumatologists and patients. Rheumatology (Oxford) 2011;50:1991-8.
75. Adshead R, Tahir H, Donnelly S. A UK BEST PRACTICE MODEL FOR DIAGNOSIS AND TREATMENT OF AXIAL SPONDYLOARTHRITIS.
76. National Institute for Health and Care Excellence (NICE). Clinical Knowledge Summary (CKS): Ankylosing spondylitis Available at:

http://cks.nice.org.uk/ankylosing-spondylitis#!topicsummary [Last accessed: 06/05/2015].
77. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
78. Lopez-Ferrer A, Vilarrasa E, Puig L. Secukinumab (AIN457) for the treatment of psoriasis. Expert Rev Clin Immunol 2015;11:1177-88.
79. Haroon N. Ankylosis in ankylosing spondylitis: current concepts. Clin Rheumatol 2015;34:1003-7.
80. Cooper C, Carbone L, Michet CJ, et al. Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 1994;21:1877-82.
81. Davey-Ranasinghe N, Deodhar A. Osteoporosis and vertebral fractures in ankylosing spondylitis. Curr Opin Rheumatol 2013;25:509-16.
82. Rafia R, Ara R, Packham J, et al. Healthcare costs and productivity losses directly attributable to ankylosing spondylitis. Clin Exp Rheumatol 2012;30:246-53.
83. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921-5.
84. National Institute for Health and Care Excellence. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology - Commissioning guide. October 2012. Available at: http://www.nice.org.uk/resource/CG153/html/p/biologic-drugs-for-the-treatment-of-inflammatory-disease-in-rheumatology-dermatology-and-gastroenterology?id=2p5mv5d7njrtuw3fyu4wp2tl4a [Last accessed 06/01/16].
85. Novartis Data on File: Summary of Teleconference with Clinical Expert. 9th December 2015.
86. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896-904.
87. Lord PA, Farragher TM, Lunt M, et al. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49:563-70.
88. Gaffney K, Elender F, Hamilton L, et al. An Open Label, Pilot, Multi-Centre, Step-Down, Randomized Controlled Trial to Examine Whether Etanercept 25 mg Once Weekly is Effective in Maintaining a Clinical Response in Patients with Ankylosing Spondylitis who have Responded to 50 mg Once Weekly. Rheumatology 2014;53:i42.
89. Braun J, van der Horst-Bruinsma IE, Huang F, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum 2011;63:1543-51.
90. Braun J, Pavelka K, Ramos-Remus C, et al. Clinical efficacy of etanercept versus sulfasalazine in ankylosing spondylitis subjects with peripheral joint involvement. J Rheumatol 2012a;39:836-40.
91. Moots RJ, Ostor AJ, Loft AG, et al. Reduction of direct and indirect costs in patients with AS receiving etanercept: results from an open-label 36-week extension of the ASCEND study in four European countries. Rheumatology (Oxford) 2012;51:393-6.

92. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.
93. Braun J, van der Heijde D, Doyle MK, et al. Improvement in hemoglobin levels in patients with ankylosing spondylitis treated with infliximab. Arthritis Rheum 2009;61:1032-6.
94. Braun J, Landewe R, Hermann KG, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum 2006;54:1646-52.
95. Braun J, Deodhar A, Dijkmans B, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. Arthritis Rheum 2008;59:1270-8.
96. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136-46.
97. van der Heijde D, Breban M, Halter D, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. Rheumatology (Oxford) 2015;54:1210-9.
98. Sieper J, van der Heijde D, Dougados M, et al. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71:700-6.
99. Maksymowych WP, Gooch KL, Wong RL, et al. Impact of age, sex, physical function, health-related quality of life, and treatment with adalimumab on work status and work productivity of patients with ankylosing spondylitis. J Rheumatol 2010;37:385-92.
100. van der Heijde DM, Revicki DA, Gooch KL, et al. Physical function, disease activity, and health-related quality-of-life outcomes after 3 years of adalimumab treatment in patients with ankylosing spondylitis. Arthritis Res Ther 2009a;11:R124.
101. van der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 2009b;68:922-9.
102. Revicki DA, Luo MP, Wordsworth P, et al. Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS). J Rheumatol 2008;35:1346-53.
103. van der Heijde D, Pangan AL, Schiff MH, et al. Adalimumab effectively reduces the signs and symptoms of active ankylosing spondylitis in patients with total spinal ankylosis. Ann Rheum Dis 2008a;67:1218-21.
104. Davis JC, Jr., Revicki D, van der Heijde DM, et al. Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. Arthritis Rheum 2007;57:1050-7.
105. Sieper J VDHD, Varothai NA, Anderson JK,. Comparison of baseline extra-articular manifestations, comorbidities, and long-term safety in patients treated with adalimumab for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis Rheumatol 2014a;66:S242-3.

106. van der Heijde D, Dijkmans B, Schiff M, et al. Maintenance of reduction in disease activity and partial remission in patients with ankylosing spondylitis (AS) - 3 year results from the adalimumab (Humira) trial evaluating long-term efficacy and safety in AS (ATLAS). Arthritis Rheum 2008b:S579.
107. Inman RD, Maksymowych WP. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol 2010;37:1203-10.
108. Maksymowych WP, Salonen D, Inman RD, et al. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol 2010;37:1728-34.
109. Inman R, Shojania K, Keystone E, et al. CANaDian evaluation of Low dosE infliximab in ankylosing spondylitis (CANDLE). J Rheumatol 2008a;35:1213-4.
110. Maksymowych W, Salonen D, Inman R, et al. CANaDian evaluation of Low dosE Infliximab in Ankylosing Spondylitis (CANDLE) - 12 week magnetic resonance imaging evaluation of spinal inflammation with the SPARCC MRI method. J Rheumatol 2008;35:1211-2.
111. Inman RD, Davis JC, Jr., Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008b;58:3402-12.
112. Deodhar A, Braun J, Inman RD, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. Ann Rheum Dis 2015a;74:757-61.
113. van der Heijde D, Deodhar A, Braun J, et al. The effect of golimumab therapy on disease activity and health-related quality of life in patients with ankylosing spondylitis: 2-year results of the GO-RAISE trial. J Rheumatol 2014;41:1095-103.
114. Braun J, Baraliakos X, Hermann KG, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis 2014;73:1107-13.
115. van der Heijde D, Braun J, Deodhar A, et al. Comparison of three enthesitis indices in a multicentre, randomized, placebo-controlled trial of golimumab in ankylosing spondylitis (GO-RAISE). Rheumatology (Oxford) 2013a;52:321-5.
116. Braun J, Baraliakos X, Hermann KG, et al. Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo- controlled GO-RAISE study. Ann Rheum Dis 2012b;71:878-84.
117. Braun J, Deodhar A, Inman RD, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 104-week results of the GO-RAISE study. Ann Rheum Dis 2012c;71:661-7.
118. Deodhar A, Braun J, Inman RD, et al. Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: results from a randomized, placebo-controlled trial. Arthritis Care Res (Hoboken) 2010;62:1266-71.
119. van der Heijde D, Deodhar A, Braun J, et al. Achieving ankylosing spondylitis disease activity score c-reactive protein major improvement and inactive disease in patients with ankylosing spondylitis after treatment with golimumab is associated with normalized health-related quality of life: 2-year results from GO-RAISE. , In Rheumatology, Oxford Univ Press Great Clarendon St, Oxford OX2 6DP, England, 2013b.
120. Deodhar A, Braun J, Inman R, et al. Long-term safety and efficacy of golimumab in the treatment of ankylosing spondylitis: results through 5 years of the go-raise trial. Ann Rheum Dis 2013;72.

121. Braun J, Van Der Heijde D, Hermann KG, et al. The effect of anti-tumor necrosis factor therapy with golimumab on radiographic progression in definite ankylosing spondylitis: 4-year results. Ann Rheum Dis 2013;71.
122. Deodhar A, Braun J, Inman R, et al. Long-term safety and efficacy of golimumab in the treatment of ankylosing spondylitis: Results through 5 years of a randomized, placebo-controlled trial. Rheumatology (United Kingdom). Volume 53, 2014a:i142.
123. Inman R, Deodhar A, Braun J, et al. Achieving ankylosing spondylitis disease activity score-c-reactive protein major improvement and inactive disease in patients with ankylosing spondylitis after treatment with golimumab is associated with normalized health related quality of life: 2-year results from go-raise. J Rheumatol 2013;40:1012.
124. Van Der Heijde D. Deodhar A. Braun J. Mack M. Hsu B. Gathany T. Han C. Inman R. Achieving ASDAS-CRP major improvement and inactive disease in patients with ankylosing spondylitis after treatment with golimumab is associated with normalized health related quality of life: Two-year results from the go-raise trial. Ann Rheum Dis 2013c;71.
125. Kay J, Fleischmann R, Keystone E, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis 2015;74:538-46.
126. Gorman J, Sack K, Davis JJ. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346:1349-56.
127. Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.
128. Huang F, Zhang J, Huang J, et al. A multicenter, double-blind, placebo-controlled, randomized, phase III clinical study of etanercept in treatment of ankylosing spondylitis. Zhonghua Nei Ke Za Zhi. 2010 Sep;49(9):741-5. (In Chinese) (Reference number: 195). 2010.
129. Huang F, Zhang J, Zheng Y, et al. A multicenter, double-blind, randomized, placebo-controlled clinical trial of etanercept treatment of Chinese patients with active ankylosing spondylitis. Zhonghua Nei Ke Za Zhi. 2011 Dec;50(12):1043 7. (In Chinese) (Reference number: 132). 2011.
130. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 2014;73:587-94.
131. Navarro-Sarabia F, Fernandez-Sueiro JL, Torre-Alonso JC, et al. High-dose etanercept in ankylosing spondylitis: results of a 12-week randomized, double blind, controlled multicentre study (LOADET study). Rheumatology (Oxford) 2011;50:1828-37.
132. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64:1568-75.
133. Baeten D, Braun J, Baraliakos X, et al. Secukinumab, a Monoclonal Antibody to Interleukin-17a, Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: Results of a 52-Week Phase 3 Randomized Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Arthritis Rheumatol. 2014;66(Suppl 10). 2014b.

134. Deodhar AA, Baeten DL, Braun J, et al. Secukinumab, a Monoclonal Antibody to Interleukin-17A, Significantly Improves Physical Function and Quality of Life in Subjects with Active Ankylosing Spondylitis: Results of a Phase 3 Randomized, Placebo-Controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Arthritis & Rheumatology 2014b;66:S233-S234.
135. Deodhar A, Baeten D, Sieper, et al. Safety and Tolerability of Secukinumab in Patients with Active Ankylosing Spondylitis: Pooled Safety Analysis of Two Phase 3, Randomized, Controlled Trials. Arthritis Rheumatol. 2015; 67 (suppl 10). 2015b.
136. Baraliakos X, Braun J, Sieper J, et al. Secukinumab Reduces Sacroiliac Joint and Spinal Inflammation in Patients with Ankylosing Spondylitis: MRI Data from a Phase 3 Randomized, Double-Blind, Placebo-Controlled Study (MEASURE 1). Annals of the Rheumatic Diseases 2015b;74:281.
137. Wei JCC, Baeten DL, Geusens P, et al. Intravenous Loading and Subcutaneous Maintenance with Secukinumab Provides Sustained Improvement in Multiple Measures of Disease Activity in Subjects with Active Ankylosing Spondylitis: 52-Week Data From the Randomized, Double-Blind, Placebo-Controlled, Phase 3 Measure 1 Study. Annals of the Rheumatic Diseases 2015;74:1146-1147.
138. Sieper J, Braun J, Baraliakos X, et al. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a phase 3, randomized, placebo-controlled trial with subcutaneous loading and maintenance dosing. American College of Rheumatology 2014 Congress; Boston, MA. 14-19 November 2014. Poster 536. 2014b.
139. Braun J, Deodhar A, Sieper J, et al. Secukinumab Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: 52-Week Results from a Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing. Arthritis Rheumatol 2015;67.
140. Braun J, Sieper J, Aelion J, et al. Secukinumab Improves Multiple Parameters of Disease Activity in Subjects with Active Ankylosing Spondylitis Through 52 Weeks of Subcutaneous Therapy: Data From the Phase 3 Measure 2 Study. Ann Rheum Dis 2015;74:1147.
141. Deodhar A, Sieper J, Emery P, et al. Secukinumab Significantly Improves Physical Function, Quality of Life, and Work Productivity Through 52 Weeks in Subjects with Active Ankylosing Spondylitis in the Phase 3 Measure 2 Study. Ann Rheum Dis 2015c;74:1144.
142. Sieper J, Braun J, Baraliakos X, et al. Secukinumab Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: 52-Week Data from MEASURE 2, A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing. Abstract presented at EULAR 2015. Ann Rheum Dis 2015;74:132-133.
143. Lambert RG, Salonen D, Rahman P, et al. Adalimumab Significantly Reduces Both Spinal and Sacroiliac Joint Inflammation in Patients with Ankylosing Spondylitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheum. 2007;56(12):4005-4014.

144. van der Heijde D, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009c;11:R127.
145. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39-47.
146. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. Arthritis Rheumatol 2015b;67:668-77.
147. Landewe R, Rudwaleit M, van der Heijde D, et al. Effect of certolizumab pegol on signs and symptoms of ankylosing spondyltitis and non-radiographic axial spondyloarthritis: 24 week results of a double blind randomized placebo-controlled phase 3 axial spondyloarthritis study, In Arthritis Rheum. , 2012.
148. Sieper J, Kivitz A, van Tubergen A, et al. Long-Term Maintenance of Improvements in Patient-Reported Outcomes With Certolizumab Pegol in Patients With Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis: 96-Week Results of the Rapid-Axspa Study. Value in Health 2014d;7:A385-A386.
149. Maksymowych W LR, Rudwaleit M, van der Heijde D, Dougados M, Mease P, et al. . Effect of certolizumab pegol over 48 weeks in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis. . J Rheumatol. 2014;41:1495-6.
150. Sieper JR, M. van der Heijde, D. Maksymowych, W. Dougados, M. Mease, PJ. et al. . Long-term safety and efficacy of certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 96-week outcomes of the RAPID-axSpA trial. Ann Rheum Dis. 2014e;73.
151. Mease P, Dougados M, Davies O, et al. Certolizumab pegol rapidly reduces peripheral enthesitis and the incidence of tender and swollen joints in patients with active axial spondyloarthritis, including both ankylosing spondylitis and non-radiographic axial spondyloarthritis. , In Ann Rheum Dis. , 2014.
152. Van Der Heijde D, Maksymowych WP, Landewe R, et al. Effect of certolizumab pegol on inflammation of spine and sacroiliac joints in patients with axial spondyloarthritis: 12-week magnetic resonance imaging results of rapid-axSpA study. Annals of the Rheumatic Diseases 2013d;72 Suppl 3.
153. Landewé R, Rudwaleit M, van der Heijde D, et al. Effect of certolizumab pegol on signs and symptoms of axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 24-week results of RAPID-axSpA study. Ann Rheum Dis 2013a;72:86-87.
154. Sieper J, Kivitz A, van Tubergen A, et al. Rapid improvements in patient-reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis: 24-week results of RAPID-axSpA study. Ann Rheum Dis 2013a;72:287-287.
155. Sieper J, Kivitz A, van Tubergen A, et al. Rapid Improvements In Patient-Reported Outcomes With Certolizumab Pegol In Patients With Axial Spondyloarthritis, Including Ankylosing Spondylitis And Non-Radiographic Axial Spondyloarthritis: 24-Week Results Of A Phase 3 Double Blind Randomized Placebo-Controlled Study. Value in Health 2013b;16:A227.

156. Landewe RBM, Rudwaleit M, Van Der Heijde DM, et al. Effect of certolizumab pegol over 48 weeks in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis and Rheumatism 2013b;65 Suppl 10:S767.
157. Sieper J. RM, Van Der Heijde D. M., Maksymowych W. P.,Dougados M., Mease P., Braun J., Deodhar A. A., Hoepken B., Nurminen T., Landewe R. B. M,. Safety and efficacy of certolizumab pegol over 96 weeks in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis. Arthritis and Rheumatology 2014f;66:S376-7.
158. Rosenbaum J. Rudwaleit M. Landewe R. Marzo-Ortega H. Sieper J. Van Der Heijde D. M. Davies O. Stach C. Nurminen T. Deodhar A. Observed incidence rates of uveitis over 96 weeks of certolizumab pegol treatment in patients with axial spondyloarthritis. Arthritis Rheumatol 2014;66:S237.
159. Rudwaleit M, Landewe R, Marzo-Ortega H, et al. Observed incidence rates of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. Clin Exp Rheumatol 2014;32:787.
160. Sieper J RM, Van Der Heijde D, Maksymowych WP, Dougados M,Mease PJ. Reveille J, Braun J, Deodhar A, Arledge T, Nurminen T, Landewe R,. Long-term safety and efficacy of certolizumab pegol in patients with axial spondyloarthritis: 96-week outcomes of the rapid-axSpA trial. Clin Exp Rheumatol 2014g;32:785-6.
161. Sieper J, Kivitz A, van Tubergen A, et al. Impact of Certolizumab Pegol on Patient-Reported Outcomes in Patients With Axial Spondyloarthritis. Arthritis Care Res (Hoboken) 2015c;67:1475-80.
162. Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 2011;70:799-804.
163. Dougados M, Braun J, Szanto S, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. Rheumatology (Oxford) 2012;51:1687-96.
164. Tam LS, Shang Q, Kun EW, et al. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis-a randomized, placebo-controlled pilot trial. Rheumatology (Oxford) 2014;53:1065-74.
165. Zhang J, Zhang Y, Zhang J, et al. Efficacy of etanercept in patients with ankylosing spondylitis: a double-blind, randomized, placebo controlled trial [Chinese]. Chin J New Drugs 2009;18:1846-9.
166. Zhang J, Huang F, Zhang J, et al. The efficacy of etanercept in enthesitis in ankylosing spondylitis and an evaluation method for enthesitis [Chinese]. Zhonghua Nei Ke Za Zhi 2012;51:376-9.
167. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1-44.
168. Lukas C, Landewe R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18-24.
169. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.

170. Rudwaleit M, Listing J, Brandt J, et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis 2004;63:665-70.
171. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
172. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.
173. Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 1997;13:63-74.
174. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127-32.
175. Creemers MC, Franssen MJ, van't Hof MA, et al. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127-9.
176. EMEA (CHMP): Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis, 2009.
177. Sieper J, Braun J, Baraliakos X, et al. Secukinumab Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis: 52-Week Data from MEASURE 2, a Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial With Subcutaneous Loading and Maintenance Dosing. Presentation Number: OP0168. Presented at EULAR Annual Congress 2015.
178. European Medicines Agency (EMA). Assessment report. Cosentyx. Procedure No. EMEA/H/C/003729/II/0002. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003729/WC500199574.pdf. Last accessed 16th January 2016. .
179. Garrett S, Jenkinson T, Kennedy LG, et al. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. The Journal of rheumatology 1994;21:2286-2291.
180. Calin A, Nakache J-P, Gueguen A, et al. Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? Rheumatology 1999;38:878-882.
181. Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 2003;62:817-24.
182. Eyres S, Tennant A, Kay L, et al. Measuring disability in ankylosing spondylitis: comparison of bath ankylosing spondylitis functional index with revised Leeds Disability Questionnaire. J Rheumatol 2002;29:979-86.
183. Baeten D BJ, Sieper J, Dougados M, Deodhar AA, Baraliakos X, Porter B, Gong Y, Richards H. Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Ankylosing Spondylitis: 2-Year Efficacy and Safety Results from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial. Poster presented at ACR Annual Meeting September 2015. Available at http://novartis.medicalcongressposters.com/Default.aspx?doc=7a83b. Accessed on 2/12/15. 2015d.

184. Baeten D BJ, Sieper J, Dougados M, Deodhar AA, Baraliakos X, Porter B, Gong Y, Richards H. Secukinumab, a Monoclonal Antibody to Interleukin-17A Significantly Improves Signs and Symptoms of Active Ankylosing Spondylitis Results of a 52-week Phase 3 Randomized Placebo-controlled Trial with Intravenous Loading and Subcutaneous Maintenance Dosing. Presentation number: 819. Presented at ACR Annual Meeting 2014. 2014a.
185. Baraliakos X, Braun J, Sieper J, et al. Secukinumab Reduces Sacroiliac Joint and Spinal Inflammation in Patients with Ankylosing Spondylitis: MRI Data from a Phase 3 Randomized, Double-Blind, Placebo-Controlled Study (MEASURE 1). Poster presented at EULAR 2015. 2015c.
186. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. 2015. Available at https://www.nice.org.uk/article/pmg24/resources/non-guidance-single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf. Last accessed 13th January 2016.
187. Dias S, Welton NJ, Suttone AJ, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-analysis of Randomised Controlled Trials. Available at: http://www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%2015April2014.pdf (Accessed 16.10.15). 2014.
188. Bongartz T SA, Sweeting MJ, Buchan I, Matteson EL, Montori V. . Anti-TNF Antibody Therapy in Rheumatoid Arthritis and the Risk of Serious Infections and Malignancies: Systematic Review and Meta-analysis of Rare Harmful Effects in Randomized Controlled Trials. . JAMA 2006;295:2275-2285.
189. Ryan C, Leonardi CL, Krueger JG, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. Jama 2011;306:864-71.
190. Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. J Eur Acad Dermatol Venereol 2013;27:622-7.
191. Deodhar A, Baeten D, Sieper, et al. Safety and Tolerability of Secukinumab in Patients with Active Ankylosing Spondylitis: Pooled Safety Analysis of Two Phase 3, Randomized, Controlled Trials. Poster presented at Poster presented at the American College of Rheumatology Congress, November 6–11, 2015, San Francisco, USA. Available at http://novartis.medicalcongressposters.com/Default.aspx?doc=7a43e. Last accessed 16th January 2016. 2015b.
192. Blauvelt A, Armstrong AW, Krueger GG. Essential Truths for the Care and Management of Moderate-to-Severe Psoriasis. J Drugs Dermatol 2015;14:805-12.
193. Boonen A, van der Heijde D, Landewe R, et al. Costs of ankylosing spondylitis in three European countries: The patient's perspective. Ann Rheum Dis 2003;62:741-7.
194. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med 2014;371:326-38.
195. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj 1996;313:275-83.

196. Ara RM, Reynolds AV, Conway P. The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK. Rheumatology (Oxford) 2007;46:1338-44.
197. Armstrong N, Joore M, Asselt T, et al. Golimumab for the Treatment of Ankylosing Spondylitis: A NICE Single Technology Appraisal. PharmacoEconomics 2013;31:415-425.
198. Botteman MF, Hay JW, Luo MP, et al. Cost effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom. Rheumatology (Oxford) 2007;46:1320-8.
199. Kobelt G, Andlin-Sobocki P, Brophy S, et al. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology (Oxford) 2004;43:1158-66.
200. Kobelt G, Sobocki P, Sieper J, et al. Comparison of the cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in the United Kingdom based on two different clinical trials. Int J Technol Assess Health Care 2007;23:368-75.
201. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-158, iii-iv.
202. Scottish Medicines Consortium (SMC). Etanercept 25mg vial of powder for subcutaneous injection (Enbrel) (No. 212/05). 2005. Available at http://www.scottishmedicines.org.uk/files/etanercept__Enbrel___for_ank_spond__212-05_.pdf. Last accessed 13th January 2016.
203. Scottish Medicines Consortium (SMC). Adalimumab, 40mg/0.8mL, solution for injection (Humira®). SMC No. (858/13). 2013. Available at https://www.scottishmedicines.org.uk/files/advice/adalimumab_Humira_FINAL_March_2013_for_website.pdf. Last accessed 15th December 2015.
204. Scottish Medicines Consortium S. Golimumab 50mg solution for injections prefilled pen (auto-injector) or prefilled syringe (Simponi®). SMC No. (721/11). 2011. Available online at https://www.scottishmedicines.org.uk/files/advice/golimumab_Simponi_FINAL_August_2011_for_website.pdf. Last accessed 12th January 2016.
205. Scottish Medicines Consortium (SMC). Certolizumab pegol 200mg/mL solution for injection in pre-filled syringe (Cimzia®). SMC No. (960/14). 2014. Available at https://www.scottishmedicines.org.uk/files/advice/certolizumab_pegol_Cimzia_FINAL_April_2014_for_website.pdf. Last accessed 15th December 2015.
206. Scottish Medicines Consortium (SMC). Infliximab, 100mg, powder for concentrate for solution for infusion (Remsima®). SMC No. (1006/14). 2015. Available at https://www.scottishmedicines.org.uk/files/advice/infliximab_Remsima_FINAL_November_2014_amended_240205_for_website.pdf. Last accessed 15th December.
207. Scottish Medicines Consortium (SMC). Infliximab, 100mg, powder for concentrate for solution for infusion (Inflectra®). SMC No. (1007/14). 2015. Available at https://www.scottishmedicines.org.uk/files/advice/infliximab_Infectra_FINAL_November_2014_Amended_240215_for_website.pdf. Last accessed 15th December 2015.

208. Mustur D, Vesovic-Potic V, Stanisavljevic D, et al. Assessment of functional disability and quality of life in patients with ankylosing spondylitis. Srp Arh Celok Lek 2009;137:524-8.
209. Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev 2015;4:Cd005468.
210. Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119-30.
211. Novartis Data on File: Summary of Teleconference with Clinical Expert. 29th January 2016.
212. Landewe R, Dougados M, Mielants H, et al. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis 2009;68:863-7.
213. Ramiro S, Stolwijk C, van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. Annals of the Rheumatic Diseases 2013.
214. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.
215. Juckett DA, Rosenberg B. Comparison of the Gompertz and Weibull functions as descriptors for human mortality distributions and their intersections. Mech Ageing Dev 1993;69:1-31.
216. Rodgers M ED, Bojke L, et al. . Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: A Systematic Review and Economic Evaluation. Southampton (UK): NIHR Journals Library; 2011 Feb. (Health Technology Assessment, No. 15.10.) Appendix 19, All-cause mortality. Available from: http://www.ncbi.nlm.nih.gov/books/NBK109486/.
217. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011:Cd008794.
218. Bath Ankylosing Spondylitis Disease Activity Index. 2005. Available at http://basdai.com/. Last accessed 13th January 2016.
219. The National Ankylosing Spondylitis Society. The Bath Indices. Outcome measures for use with ankylosing spondylitis patients. 2009. Available at nass.co.uk/download/4c4da6b17854b. Last accessed 13th January 2016.
220. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
221. Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. Value Health 2015;18:425-31.
222. Department of Health. NHS Reference Costs 2014-2015. National schedule of reference costs: the main schedule. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Last accessed 19th January 2016.
223. Department of Health. NHS Reference Costs 2013-2014. National schedule of reference costs: the main schedule. Available at https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. Last accessed 19th January 2016.

224. Curtis L. PSSRU. Unit costs of Health & Social Care 2015. 2015. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php. Last accessed 19th January 2016.
225. National Institute for Health and Care Excellence (NICE). Adalimumab for the treatment of adults with psoriasis. TA146. Costing template. 2008. Available at http://www.nice.org.uk/guidance/ta146/resources. Last accessed 19th January 2016.
226. National Institute for Health and Care Excellence (NICE). Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: a Systematic Review and Economic Evaluation. Available at https://www.nice.org.uk/guidance/TA199/documents/psoriatic-arthritis-etanercept-infliximab-adalimumab-review-acd-assessment-report3. Last accessed 19th January 2016.
227. The British Society for Rheumatololgy Biologics Register for Ankylosing Spondylitis (BSRBR-AS): Online Presentation. Available at: http://www.rheumatology.org.uk/includes/documents/cm_docs/2012/1/1130_inbank_bsr_registers_and_the_new_information_age.pdf [Last accessed 03.02.2016].
228. Boonen A, Van Der Heijde D, Severens JL, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. Annals of the Rheumatic Diseases 2006;65:201-208.
229. Tran-Duy A, Boonen A, van de Laar MA, et al. A discrete event modelling framework for simulation of long-term outcomes of sequential treatment strategies for ankylosing spondylitis. Ann Rheum Dis 2011;70:2111-8.
230. Tran-Duy A, Boonen A, Van De Laar MA, et al. Simultaneously forecasting burden of illness and cost-effectiveness: The case of tumour necrosis factor-alpha antagonist for ankylosing spondylitis in the dutch society. Annals of the Rheumatic Disease 2013;71 SUPPL. 3.
231. Gonzalez Alvarez A, Gomez Barrera M, Borras Blasco J, et al. [Analisis of the budget impact of adalimumab and etanercept in rheumatoid arthritis and spondyloarthropathies]. Farm Hosp 2013;37:192-7.
232. Ji X, Joshi A, Vidal Perez-Campoamor S, et al. A cost-effectiveness model of adalimumab (ADA) in non-radiographic axial spondyloarthritis in Spain. Annals of the Rheumatic Diseases 2014;73 SUPPL. 2.
233. Kobelt G, Sobocki P, Mulero J, et al. The cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in Spain. Comparison of clinical trial and clinical practice data. Scand J Rheumatol 2008;37:62-71.
234. Scaccabarozzi L, Author A, Janssen SPB, et al. Cost-minimization analysis of anti-TNF biologics in the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis under the Brazilian private health care system perspective. Value in Health 2014;17:A229.
235. Zavada J, Uher M, Sisol K, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. Ann Rheum Dis 2014.
236. Kobelt G, Andlin-Sobocki P, Maksymowych WP. The cost-effectiveness of infliximab (Remicade) in the treatment of ankylosing spondylitis in Canada. J Rheumatol 2006;33:732-40.

237. Fautrel B, Benhamou M, Breban M, et al. Cost effectiveness of two therapeutic regimens of infliximab in ankylosing spondylitis: economic evaluation within a randomised controlled trial. Ann Rheum Dis 2010;69:424-7.
238. Neilson AR, Sieper J, Deeg M. Cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in Germany. Rheumatology. Volume 49, 2010:2122-34.
239. Codreanu C, Mogosanu C, Joita M, et al. Cost-effectiveness of certolizumab pegol in the treatment of active rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis in Romania. Value in Health 2014;17:A379.
240. Ivakhnenko O, Rebrova O, Avxentyeva M, et al. Three TNF-a-inhibitors for treatment of rheumat oid arthritis, ankylosing spondylitis and psoriatic arthritis. Value in Health 2013;16:A564.
241. Akkoc N, Direskeneli H, Erdem H, et al. Direct and indirect costs associated with ankylosing spondylitis and related disease activity scores in Turkey. Rheumatol Int 2015;35:1473-8.
242. Ariza-Ariza R, Hernandez-Cruz B, Navarro-Sarabia F. Physical function and health-related quality of life of Spanish patients with ankylosing spondylitis. Arthritis Rheum 2003;49:483-7.
243. Ariza-Ariza R, Hernandez-Cruz B, Lopez-Antequera G, et al. [Cross-cultural adaptation and validation of a Spanish version of a specific instrument to measure health-related quality of life in patients with ankylosing spondylitis]. Reumatol Clin 2006;2:64-9.
244. Ariza-Ariza R, Hernandez-Cruz B, Lopez-Antequera G, et al. Variables related to utility in patients with ankylosing spondylitis. Clin Rheumatol 2009;28:207-11.
245. Boonen A, Severens JL, Van Tubergen A, et al. Willingness of patients with ankylosing spondylitis to pay for inpatient treatment is influenced by the treatment environment and expectations of improvement. Annals of the Rheumatic Diseases 2005;64:1650-1652.
246. Boonen A, Heijde D, Landewé R, et al. How do the EQ-5D, SF-6D and the well-being rating scale compare in patients with ankylosing spondylitis? Annals of the rheumatic diseases. Volume 66, 2007:771-7.
247. Boonen A, Patel V, Traina S, et al. Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept. Journal of Rheumatology 2008;35:662-667.
248. Braun J, McHugh N, Singh A, et al. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology 2007;46:999-1004.
249. Brox JI, Helle A, Sorensen R, et al. Functional outcome after lumbar closing wedge osteotomy in ankylosing spondylitis. Int Orthop 2009;33:1049-53.
250. Choi CB, Kim TJ, Park HJ, et al. Safety and clinical responses in ankylosing spondylitis after three months of etanercept therapy. Journal of Korean Medical Science 2008;23:852-856.
251. Cooksey R, Husain MJ, Brophy S, et al. The Cost of Ankylosing Spondylitis in the UK Using Linked Routine and Patient-Reported Survey Data. PLoS One 2015;10:e0126105.
252. De Oliveira Junior HA, Dos Santos JB, Acurcio FA, et al. Poorer functionality is related to better quality of life response following the use of biological drugs: 6-month outcomes in a prospective cohort from the Public Health System

(Sistema Unico de Saude), Minas Gerais, Brazil. Expert Review of Pharmacoeconomics and Outcomes Research 2015;15:403-412.
253. Forejtova S, Zavada J, Uher M, et al. A comparison of baseline characteristics and real-life effectiveness of anti-TNF therapy in non-radiographic axial spondyloarthritis versus ankylosing spondylitis-a single center cohort study. Arthritis and Rheumatology 2014;66:S1128.
254. Gordeev VS, Maksymowych WP, Evers SM, et al. Role of contextual factors in health-related quality of life in ankylosing spondylitis. Ann Rheum Dis 2010;69:108-12.
255. Haglund E, Bremander A, Bergman S, et al. Work productivity in a population-based cohort of patients with spondyloarthritis. Rheumatology (Oxford) 2013;52:1708-14.
256. Haywood KL, Garratt AM, Dziedzic K, et al. Generic measures of health-related quality of life in ankylosing spondylitis: reliability, validity and responsiveness. Rheumatology (Oxford) 2002;41:1380-7.
257. Haywood KL, Garratt AM, Dziedzic K, et al. Patient centered assessment of ankylosing spondylitis -specific health related quality of life : Evaluation of the Patient Generated Index. J Rheumatol 2003;30:764-73.
258. Healey EL, Haywood KL, Jordan KP, et al. Patients with well-established ankylosing spondylitis show limited deterioration in a ten-year prospective cohort study. Clinical Rheumatology 2013;32:67-72.
259. Jacobsson LT, Husmark T, Theander E, et al. Quality of life in patients with axial spondyloarthritis in clinical practice in Sweden: Baseline results from a longitudinal study. Value in Health 2014;17:A386.
260. Karlsson JA, Kapetanovic MC, Petersson IF, et al. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients: Baseline characteristics and development of clinical variables during 3 years of anti-TNF therapy in clinical practice. Scandinavian Journal of Rheumatology 2014;43 SUPPL. 127:70.
261. Kimel M, Revicki D, Rao S, et al. Norms-based assessment of patient-reported outcomes associated with adalimumab monotherapy in patients with ankylosing spondylitis. Clinical and experimental rheumatology. Volume 29, 2011:624-32.
262. Kobelt G, Andlin-Sobocki P, Maksymowych WP. Costs and quality of life of patients with ankylosing spondylitis in Canada. J Rheumatol 2006;33:289-95.
263. Kobelt G, Sobocki P, Mulero J, et al. The burden of ankylosing spondylitis in Spain. Value in Health 2008;11:408-415.
264. Kvamme MK, Kristiansen IS, Lie E, et al. Identification of cutpoints for acceptable health status and important improvement in patient-reported outcomes, in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Journal of Rheumatology 2010;37:26-31.
265. Kydd AS, Chen JS, Makovey J, et al. Smoking did not modify the effects of anti-TNF treatment on health-related quality of life among Australian ankylosing spondylitis patients. Rheumatology (Oxford) 2015;54:310-7.
266. Lee TJ, Park BH, Kim JW, et al. Cost-of-illness and quality of life in patients with ankylosing spondylitis at a tertiary hospital in Korea. J Korean Med Sci 2014;29:190-7.
267. Miranda L, Negreiro F, Queiroz MJ, et al. [RAISE study observational and cross sectional study to evaluate the actual reality of the socio-economic impact of ankylosing spondylitis]. Acta Reumatol Port 2008;33:189-97.

268. Park YS, Kim HS, Baek SW, et al. Preoperative computer-based simulations for the correction of kyphotic deformities in ankylosing spondylitis patients. Spine Journal 2014;14:2420-2424.
269. Pimentel-Santos FM, Pinto T, Santos H, et al. Portuguese version of the bath indexes for ankylosing spondylitis patients: a cross-cultural adaptation and validation. Clin Rheumatol 2012;31:341-6.
270. Sedova L, Stolfa J, Suchy D, et al. Qualityof life, productivity impairment, disease severity and health care costs in relation to functional impairment in ankylosing spondylitis patients in the Czech Republic. Arthritis and Rheumatism 2013;65 SUPPL. 10:S433-S434.
271. Sedova L, Urbanova M, Stolfa J, et al. Long-term quality of life, productivity impairment, disease severity and health care costs in relation to functional impairment in ankylosing spondylitis patients in the czech republic. Arthritis and Rheumatology 2014;66:S509-S510.
272. Verstappen SM, Jacobs JW, van der Heijde DM, et al. Utility and direct costs : ankylosing spondylitis compared with rheumatoid arthritis. Ann Rheum Dis 2007;66:727-31.
273. Wade AG, Crawford GM, Pumford N, et al. Baseline characteristics and patient reported outcome data of patients prescribed etanercept: web-based and telephone evaluation. BMC medical research methodology 2011;11:91.
274. Zavada J, Uher M, Sisol K, et al. A tailored approach to reduce dose of anti-TNF drugs is equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over one year: A propensity score-matched cohort study. Arthritis and Rheumatology 2014;66:S376.
275. Husain MJ, Brophy S, Macey S, et al. HERALD (Health Economics using Routine Anonymised Linked Data). BMC Med Inform Decis 2012;12:24.
276. Jha A, Upton A, Dunlop WC, et al. The Budget Impact of Biosimilar Infliximab (Remsima) for the Treatment of Autoimmune Diseases in Five European Countries. Adv Ther 2015.
277. Jois RN, Leeder J, Gibb A, et al. Low-dose infliximab treatment for ankylosing spondylitis - clinically- and cost - effective. Rheumatology (Oxford) 2006;45:1566-9.

A matching-adjusted indirect comparison (MAIC) of secukinumab versus adalimumab in ankylosing spondylitis (AS)

Description of methods

Prepared for
Novartis Pharma AG
Steffen Jugl
Global Patient Access Immunology & Dermatology

Date: 1st of February 2016

Table of contents

Table of tables

Abbreviations

AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis international Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
CI	Confidence intervals
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
EULAR	European League Against Rheumatism
GEE	Generalized Estimating Equation
IPD	Individual patient data
ITC	Indirect treatment comparison
MAIC	Matching-adjusted indirect comparison
MTC	Mixed-treatment comparison
NMA	Network meta-analysis
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds ratio
PBO	Placebo
PSO	Psoriasis
QoL	Quality of Life
RA	Rheumatoid Arthritis

RR	Relative risks
SD	Standard deviation
SE	Standard error
TNF-alfa	Tumour Necrosis Factor-alfa inhibitors
UK	United Kingdom
US	United States
Wk	Week

1 Introduction

1.1 Background

1.1.1 Ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a chronic inflammatory disease that affects the axial skeleton and is manifested by back pain and progressive stiffness of spine [1]. The disease is prevalent in 0.2 to 1% of the whole population in Europe [2].

Treatment of the disease can decrease pain, symptoms and prevent complications and deformities. As recommended in the updated Assessment of Spondyloarthritis international society (ASAS)/European League Against Rheumatism (EULAR) guidelines on AS management, the treatment of ankylosing spondylitis consists of non-steroidal anti-inflammatory drugs (NSAIDs), including Coxibs as first-line [3]. Disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids and anti-TNF therapy can also be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations. In 2010, ASAS/EULAR guidelines on the management of AS were updated. Physical therapy contributes enormously towards pain relief and flexibility. Surgery is recommended in only rare cases [3, 4].

1.1.2 Secukinumab

Secukinumab is a first in class recombinant high-affinity, fully human monoclonal anti-human antibody of the IgG1/kappa isotype that selectively targets interleukin 17A (IL-17A).

Secukinumab offers a new mode of action therapy for the treatment of active AS. Two pivotal, randomised, double-blind, placebo-controlled studies were conducted (MEASURE-1 Study: CAIN457F2305 and MEASURE-2 Study: CAIN457F2310) among patients with active AS, to confirm the efficacy and characterise the safety of secukinumab in AS [5]. Both MEASURE 1 and MEASURE 2 trials evaluated secukinumab 75 mg and 150 mg versus placebo. In the MEASURE 1 study, patients received an intravenous loading dose of 10 mg/kg every two weeks for the first four weeks of treatment followed by monthly subcutaneous doses that aimed to provide high exposure for induction of response in order to confirm the clinical benefit observed in an initial proof-of-concept study; MEASURE 2 evaluated subcutaneous loading regimens on the other hand. For ethical reasons, placebo-treated patients

who did not meet predefined response criteria were re-randomised 1:1 at week 16 to receive active treatment.

In MEASURE 1, the ASAS20 response rates at week 16 were 61%, 60%, and 29% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively (P<0.001 for both comparisons with placebo). ASAS40 response rates at week 16 were 42% and 33% in the groups that received subcutaneous secukinumab at the higher and lower doses, respectively, as compared with 13% in the placebo group (P<0.001 for both comparisons with placebo) [6].

In MEASURE 2, ASAS 20 response rates were 61%, 41%, and 28% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively (P<0.001 for the 150-mg dose and P=0.10 for the 75-mg dose). ASAS40 response rates at week 16 were 36% with subcutaneous secukinumab at a dose of 150 mg and 26% with subcutaneous secukinumab at a dose of 75 mg, as compared with 11% with placebo (P<0.001 and P = 0.10, respectively, with placebo) [6]. The significant improvements were sustained through 52 weeks.

1.1.3 Adalimumab

Adalimumab is a human anti-tumor necrosis factor (TNF) monoclonal antibody and was approved by the FDA in June 2006 for reducing signs and symptoms in patients with AS.

In the phase 3 ATLAS trial, subcutaneous injection of adalimumab 40 mg every other week was compared with placebo for 24 weeks. Patients who did not achieve an ASAS20 response at weeks 12, 16 or 20 were eligible for early escape open label treatment with adalimumab every other week [7].

At week 12, 58.2% of adalimumab-treated patients achieved a 20% response according to the Assessment in Ankylosing Spondylitis International Working Groupc criteria for improvement (ASAS20), compared with 20.6% of patients treated with placebo. At least a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50) at week 12 was achieved by 45.2% of patients in the adalimumab arm and 15.9% in the placebo arm, respectively. Patients treated with adalimumab also had significant improvements in the ASAS 40 response and the response according to the ASSAS5/6 criteria at weeks 12 and 24 [7].

The percentage of patients achieving ASAS20, ASAS40, ASAS 5/6 and ASAS partial remission responses was sustained from week 24 to up to 2 years [8].

1.2 Rationale

Whereas both, adalimumab and secukinumab have demonstrated superiority against placebo, to date, no comparative studies of adalimumab and secukinumab have been published in AS.

In the absence of head-to-head trials, meta-analytic techniques can be used to synthetise all evidence from various sources to estimate indirect relative treatment effects. In cases where three or more treatment options are being compared, a mixed-treatment comparison (MTC), also called network meta-analysis, becomes a more relevant method. MTC evidence synthesis is a generalisation of a series of pairwise meta-analyses for A vs. B trials to data structures including multiple treatment arms.

In some cases though, MTC or indirect treatment comparison (ITC) can be biased by cross-trial differences that is not possible to correct (e.g. difference in study designs, eligibility criteria, outcome definition or time assessment). In 2010, Signorovitch et al. proposed to carry out a matching-adjusted indirect comparison (MAIC) using both, aggregated data available in the literature, and individual patient data (IPD) from randomised clinical trials to solve of these issues [9]. This technique was used in the recent years in several indications including psoriasis and psoriatic arthritis [9-11]. Unlike standard MTC methods, MAIC can compare treatments even if the evidence network is not connected.

The objective of this analysis was to carry out a MAIC comparing primary efficacy outcomes between patients receiving secukinumab in the MEASURE 2 trial and patients receiving adalimumab in the ATLAS trial at week 16. As patients in the placebo arm of the ATLAS trial could receive open label treatment with adalimumab as early as 12 weeks after randomisation, the indirect treatment comparison between secukinumab and adalimumab at week 16 was non-placebo-adjusted. In addition to comparison of outcomes at week 16, additional analyses were carried out for long-term outcomes reported at week 24 and week 52. Furthermore, outcomes at week 12 were calculated using both, a placebo-adjusted and a non-placebo-adjusted comparison.

Further analyses are planned using MEASURE 1 study for secukinumab following the same method.

1.3 Objectives

The objectives of this study were as follows:

- Carry out MAIC analyses in AS for primary efficacy outcomes at week 16
- Carry out additional analyses on outcomes reported at week 12, week 24 and week 52

2 Methods

2.1 Population

The population considered was the intention-to-treat population from MEASURE-2 and ATLAS respectively.

Patients from the two pooled secukinumab arms were matched to reflect the patient characteristics from the adalimumab arm from ATLAS. Patients from the placebo arm in MEASURE-2 were matched to reflect the patient characteristics from placebo arm from ATLAS.

Whereas patients who had previously received anti-TNF therapy, cyclosporine, azathioprine, or disease-modifying antirheumatic drugs (DMARDs) were excluded from the ATLAS trial, previous use of DMARDs and anti-TNF agents was allowed in MEASURE-2.

2.2 Matching-adjusted indirect comparison

The objective of the matching was to re-weight individual patients from the available MEASURE-2 trial to match the mean baseline characteristics reported in the literature in the ATLAS trial. The methods presented below are based on the Signorovitch et al. (2010) publication [10].

2.2.1 Statistical principles

The matching is accomplished by re-weighting patients in the MEASURE-2 trial by their odds of having been enrolled in the ATLAS trial. The approach is very similar to propensity score weighting with the difference that IPD are not available for the ATLAS trial so that the usual maximum likelihood approach cannot be used to estimate the parameters of the propensity score model. Instead, a method of moments must be used. After the matching is complete and weights have been added to the IPD, it is then possible to estimate the weighted outcomes and compare the results across. IPD data was accessed using the statistical software SAS v9.2 and the matching using R v3.2.1.

The mapping approach can be described as follows:

Let’s assume that each trial has one arm. In this case each patient can be characterised by the following random triple (X, T, Y) where:

- X: baseline characteristics (e.g. age, weight, mean BASDAI score at baseline)
- T: Treatment of interest (e.g. T = 0 for secukinumab and T = 1 for adalimumab)
- Y: outcomes of interest (e.g. ASAS20)

In this situation, for each patient we have the following random triple (x_i, t_i, y_i) with i=1 to N but only when IPD is available, i.e. when t_i = 0. In case where t_i = 1, only the mean baseline characteristics $\bar{x}_1$ and mean outcome $\bar{y}_1$ is observed.

Given the observed data, the causal effect of treatment T = 0 versus T = 1 on the mean of Y can be estimated as follows:

$$\hat{\theta} = \frac{\sum_{i=1}^{N} y_i(1-t_i)w_i}{\sum_{i=1}^{N}(1-t_i)w_i} - \bar{y}_1 \qquad \textbf{(Equation 1)}$$

Where weight $w_i = \frac{\Pr(T_i=1|x_i)}{\Pr(T_i=0|x_i)}$ is the odds that patient *i* receives treatment T= 1 versus T = 0 (i.e. enrolls in ATLAS versus MEASURE 2) given baseline characteristics x_i.

As you can see in Equation 1, the weighted outcome estimates are calculated based on the weights the patients receiving T = 0 (e.g. secukinumab) to match the distribution of patients receiving T = 1 (e.g. adalimumab). This estimator has been used previously in the literature in the situation where observational data are fully available for individual patients receiving either treatment [12].

As above-mentioned, it is important to first estimate the weight w_i for each patient where IPD is available to match the observed aggregated data. The individual weights can be estimated using a logistic regression model as shown below following matching methods based on propensity scoring [13].

$$w_i = \exp(\alpha + x_i'\beta) \quad \textbf{(Equation 2)}$$

However, since IPD are not available for the ATLAS trial, the usual maximum likelihood approach cannot be used to estimate the parameters of the propensity score model. Instead, a method of moments must be used. To apply the methods of moments to estimate β as shown in Equation 2, we re-weighted the IPD of patients receiving T = 0 (e.g. secukinumab) by $w_i = \exp(x_i'\beta)$ to exactly match their mean baseline characteristics to the aggregate data available in the literature (e.g. adalimumab). β is estimated solving the following equation:

$$0 = \frac{\sum_{i:t_i=0} x_i \exp(x_i'\hat{\beta})}{\sum_{i:t_i=0} \exp(x_i'\hat{\beta})} - \overline{x_1} \quad \textbf{(Equation 3)}$$

It is possible to use this estimator since a logistic regression model for the odds of receiving T=1 vs. T=0 would, by definition, provide the correct weights for balancing the trial populations. If the x_i's contains all confounders and the logistic model for w_i is correctly specified, then $\hat{\theta}$ in Equation 4 provides a consistent estimate of the causal effect of treatment T=0 vs. T=1 on the mean of Y among patients actually receiving treatment T=1.

$$\hat{\theta} = \frac{\sum_{i:t_i=0} y_i \exp(x_i'\hat{\beta})}{\sum_{i:t_i=0} \exp(x_i'\hat{\beta})} - \bar{y}_1 \quad \textbf{(Equation 4)}$$

Now that by applying these weights, we match perfectly the patient characteristics of the aggregated data (e.g. adalimumab for ATLAS). It is possible to do the same for placebo using the same methodology. After matching both treatment and placebo arms to match the aggregated baseline characteristics from the comparator trial arms, it is then possible to estimate the relative treatment effect between T = 1 and T = 0 (e.g. secukinumab versus adalimumab) by using the method presented by Bucher et al.[14].

To assess the impact of re-weighting the IPD, an effective sample size can be computed as the square of the summed weights divided by the sum of the squared weights [9]. If the weights are treated as fixed, this effective sample size provides the correct sample size for converting the standard deviation of the re-weighted outcome to a standard error. The maximum effective sample size occurs when all patients have equal weight.

2.2.2 Matching optimisation algorithm

It can be shown that $\hat{\beta}$ in equation (2) can be obtained by minimizing equation $Q(\beta) = \sum_{i:t_i=0} \exp(x_i^T \beta)$ where x_i^T is the vector of baseline characteristics used for the matching for individual *i*. In this study, $Q(\beta)$ was minimized using the function `optim` and specifying the "`BFGS`" method in R. This function is based on a so called general-purpose optimization using the quasi-Newton method as developed by Broyden, Fletcher, Goldfarb and Shanno (1970).

2.2.3 Practical steps for the MAIC in this study

The matching-adjusted indirect comparisons performed during this study followed the following steps:

- Identify the matching variables to use from the Novartis trial (MEASURE-2) in SAS (see 2.5)
- Create a file containing patient subject ID and matching variables
- Export file to be read in R
- Run matching algorithm in R for both secukinumab and placebo respectively to match the reference trial treatment and placebo arm
- Export weights obtained from the matching to be read in SAS
- Import weights in SAS
- Estimated weighted outcomes of interest, including risk differences, relative risks and odds ratios
- Present results in Excel

2.3 Outcomes of interest

Different efficacy outcomes were considered in this analysis. In both trials, patients were assessed at different points in time and recorded the proportion of patients with an ASAS20 response and an ASAS40 response. Additional endpoints might be considered in future analyses.

Both endpoints were derived using non-responder imputation (NRI). Both, the primary and the secondary endpoint for ASAS response rate from MEASURE-2 were analysed:

- ASAS20 at week 12, 16, 24 and 52
- ASAS40 at week 12, 16, 24 and 52

All ASAS responses were considered binary outcomes.

2.4 Analyses

In general, all efficacy outcomes for adalimumab together with their standard errors and confidence intervals were estimate from the published numbers of patients

reported to have a response, and the number of patients randomized to each treatment arm. In a single randomised clinical trial, these outcomes can be displayed by means of the following 2x2 contingency table:

Table 1. Outcome data from a single randomised clinical trial

	Success	Failure
New treatment	a	b
Placebo	c	d

Efficacy outcomes for secukinumab were estimated using weighted averages as well as regression models that take into account the different weights obtained by the matching adjustment. To obtain these weighted estimates, the statistical software SAS was used.

2.4.1 Comparison of secukinumab and adalimumab at week 12

Indirect treatment comparisons between secukinumab and adalimumab at week 12 were placebo-adjusted, i.e. after reweighting patients in the MEASURE-2 trial, relative efficacy outcomes of secukinumab vs. placebo in MEASURE-2 were compared to relative efficacy outcomes of adalimumab vs. placebo in ATLAS.

2.4.1.1 Risk differences

Risk differences were calculated as the absolute difference in relative response frequencies between adalimumab and placebo, and secukinumab and placebo, respectively.

Risk differences between adalimumab and placebo in the ATLAS trial were calculated from the contingency table as follows:

$$RD = \frac{a}{a+b} - \frac{c}{c+d}$$

The variance can then be calculated as follows:

$$Var(RD) = \frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}$$

Where p_1 and p_2 are the observed rates of occurrence of the given event in the treatment and comparator arm, respectively.

A 95% confidence interval around this risk difference was calculated using the Normal approximation, i.e. lower and upper limits were calculated as follows:

$$RD \pm z_{0.975}\sqrt{\frac{p_1(1-p_1)}{n_1}+\frac{p_2(1-p_2)}{n_2}}$$

Where $z_{0.975}$ is the 0.975 quantile of the standard normal distribution.

Risk differences between secukinumab and placebo in the reweighted MEASURE population were estimated using the `RISKDIFF` option in the `TABLE` statement of `PROC FREQ` in SAS with patient weights entered through the `WEIGHT` option.

P-values for the difference of risk differences between secukinumab vs. placebo and adalimumab vs. placebo were calculated from the following z statistic, which divides the difference in risk differences by the combined standard error:

$$z = \frac{RD_{SEC\ vs.PBO} - RD_{ADA\ vs.PBO}}{\sqrt{Var(RD_{SEC\ vs.PBO}) + Var(RD_{ADA\ vs.PBO})}}$$

2.4.1.2 Odds ratios

An odds ratio is defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. In this study, the odds ratio provides a relative measure of change of the event of interest (e.g. reaching ASAS20) by calculating the ratio of the odds of a response in the active treatment arm by the odds of a response in the placebo arm. An OR above 1 would constitute an improvement compared to placebo.

Odds ratios for response in the adalimumab arm vs. the placebo arm in the ATLAS trial were calculated using the following formula:

$$OR = \frac{ad}{bc},$$

where a, b, c and d refers to Table 1.

Confidence intervals around the OR for adalimumab vs. placebo were based on the assumption that log odds ratio approximately follow a normal distribution.

The variance of the log odds ratio was estimated as follows:

$$Var\big(log(OR)\big) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

Thus, the 95% confidence interval of the log OR was estimated as follows:

$$\log OR \pm z_{0.975}\sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

When no events will have been reported, a continuity correction factor will be applied by adding 0.5 to each cell in Table 1.

Odds ratios for response in the secukinumab arm vs. the placebo arm in the reweighted MEASURE-2 population were derived from a logistic regression model estimated by using generalized estimating equations (GEEs). These GEEs were fitted using `PROC GENMOD` in SAS as suggested by Signorovitch et al. [9]. In this regression model, patient weights were again entered through the `WEIGHT` option, and the `REPEATED` statement was used to ensure that the weights are correctly interpreted in the estimation of standard errors.

2.4.1.3 Relative risks

Relative risks are defined as the probability of an event in the treatment group (a/(a+b)) divided by the probability of the same event to occur in the comparator group (c/(c+d)). RRs can be interpreted in a similar way as ORs.

Relative risks for adalimumab vs. placebo were estimated from the 2x2 contingency table shown in Table 1 as follows:

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

As for OR, RRs were transformed by taking the natural logarithm and assume that log relative risk follows a normal distribution. The variance of the log RR can be calculated as follows:

$$Var\big(log(RR)\big) = \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}.$$

The 95% confidence interval of the log RR was estimated as follows:

$$\log(RR) \pm z_{0.975}\sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$$

Relative risks of response for secukinumab vs. placebo in the reweighted MEASURE-2 population were derived from the same logistic regression model that was used to estimate odds ratios described in 2.4.1.2.

2.4.2 Frequentist indirect comparison (Bucher method)

Matching-adjusted indirect treatment comparisons between secukinumab and adalimumab were conducted using the Bucher method.

In the publication by Bucher et al. (1997), the authors presented a simple method to estimate - using a frequentist approach - the relative treatment effect of treatment A and C using treatment B (usually placebo) as common comparator.

Usually, outcomes of interest such as odds ratio or relative risk are transformed by taking the natural logarithm.

The method is as follows:

Let's assume:

- δ_{AC} is the meta-analytic estimate of the difference between treatment A and C, usually the
- δ_{BC} is the meta-analytic estimate of the difference between treatment B and C

Then, the indirect estimate of the difference between A and B can be estimated as follows:

$$\delta_{AB} = (\delta_{AC} - \delta_{BC})$$

The standard error (SE) can then be estimated:

$$SE(\delta_{AB}) = \sqrt{Var(\delta_{AC}) + Var(\delta_{BC})}$$

And the 95% confidence interval (CI), assuming that δ_{AB} follows a normal distribution:

$$95\%\ CI\text{: } \delta_{AB} \pm z_{0.975}\ x\ SE(\delta_{AB})$$

This method was applied to estimate matching-adjusted log odds ratios and matching-adjusted log relative risks for secukinumab vs. adalimumab. Log odds ratios, log relative risks, and corresponding standard errors for adalimumab vs. placebo and secukinumab vs. placebo, respectively, were obtained from the ATLAS trial and the reweighted MEASURE-2 data as described in 2.4.1.2 and 2.4.1.3.

P-values for indirect treatment comparisons based on relative risks were again derived from the corresponding z statistic, which divides the difference in log odds ratios by the combined standard error:

$$z = \frac{logRR_{SEC\ vs.PBO} - logRR_{ADA\ vs.PBO}}{\sqrt{Var(logRR_{SEC\ vs.PBO}) + Var(logRR_{ADA\ vs.PBO})}}$$

The same approach was used to obtain p-values for odds ratios.

2.4.3 Comparison of secukinumab and adalimumab at week 16, week 24 and week 52

As patients in the placebo arm of the ATLAS trial could receive open label treatment with adalimumab as early as 12 weeks after randomisation, the indirect treatment comparisons between secukinumab and adalimumab after week 12 were non-placebo-adjusted.

Thus, for week 16, 24 and 52, outcomes from the adalimumab arm in ATLAS were directly compared with outcomes in the reweighted secukinumab arm of MEASURE-2. As a complement to placebo-adjusted comparisons, non-placebo-adjusted comparisons at week 12 were calculated, too.

2.4.3.1 Comparison of response rates

The response rate for patients in the adalimumab arm of the ATLAS trial was estimated as $p_{ADA=}\frac{a}{a+b}$, with standard error $SE(p_{ADA}) = \sqrt{\frac{p_{ADA}*(1-p_{ADA})}{a+b}}$, and 95% confidence interval $p_{ADA} \pm z_{0.975} * SE(p_{ADA})$.

The response rate for patients in the secukinumab arm of the reweighted MEASURE-2 population was estimated as a weighted mean, using `PROC MEANS` option in SAS

with patient weights entered through the `WEIGHT` option. Confidence intervals were estimated based on the normal approximation using the `LCL` and `UCL` options in `PROC MEANS`.

P-values for the difference in response rates between secukinumab vs. placebo and adalimumab vs. placebo were calculated from the following z statistic, which divides the difference in risk response rates by the combined standard error:

$$z = \frac{p_{SEC} - p_{ADA}}{\sqrt{Var(p_{SEC}) + Var(p_{ADA})}}$$

2.4.3.2 Odds ratios and relative risks

For non-placebo-adjusted comparisons, odds ratios were calculated as the odds of a response in the active adalimumab arm of the ATLAS trial by the odds of a response in the secukinumab arm of the reweighted MEASURE-2 population.

$$OR = \frac{p_{SEC}/(1 - p_{SEC})}{p_{ADA}/(1 - p_{ADA})}$$

Relative risks were estimated accordingly, i.e. as the ratio of response rates.

Standard errors for odds ratios and relative risks were estimated based on the information provided by a fictitious 2x2 contingency table that shows outcomes in the adalimumab arm of the ATLAS trial and outcomes in the reweighted secukinumab arm of MEASURE-2.

For the estimation of standard errors and confidence intervals, the effective sample size after matching was used as the total number of patients in the reweighted secukinumab arm:

$$SE(\ln(OR)) = \sqrt{\frac{1}{N_{eff} * p_{SEC}} + \frac{1}{N_{eff}(1-p_{SEC})} + \frac{1}{N_{ADA} * p_{ADA}} + \frac{1}{N_{ADA} * (1-p_{ADA})}},$$

$$SE(\ln(RR)) = \sqrt{\frac{1-p_{SEC}}{N_{eff} * p_{SEC}} + \frac{1-p_{ADA}}{N_{ADA} * p_{SEC}}},$$

where

N_{eff} is the effective sample size in the secukinumab arm of MEASURE-2 after reweighting, and

N_{ADA} is the total number of patients in the adalimumab arm of the ATLAS trial.

A 95% confidence interval was constructed using the normal approximation on the log scale.

2.5 Scenarios

The different set of matching variables (scenarios) considered are presented in Table 2. In all scenarios, the pooled secukinumab arms from MEASURE-2 were matched to the adalimumab arm from ATLAS and the placebo arm from MEASURE-2 was matched to the one in ATLAS, respectively.

All three scenarios used age, sex, mean C-reactive protein, and previous use of anti-TNF agents as matching variables. The first scenario further included the mean BASFI score at baseline, whereas the second scenario further included the mean BASDAI score at baseline. The third scenario finally included both, mean BASFI and mean BASDAI scores at baseline.

Table 2. Matching variables

Baseline characteristics	ATLAS		Analyses		
Demographics	**ADA 40mg (N=208)**	**PBO (N=107)**	**#1**	**#2**	**#3**
Age (yrs), mean (SD)	41.7 (11.7)	43.4 (11.3)	x	X	X
Female, n (%)	51 (24.5%)	28 (26.2%)	x	X	X
Disease characteristics					
BASDAI at baseline, mean (SD)	6.3 (1.7)	6.3 (1.7)		X	X
BASFI at baseline, mean (SD)	5.2 (2.2)	5.6 (2.2)	X		X
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.2 (2.9)	X	X	X
TNF-naïve, n (%)	208 (100%)	107 (100%)	X	X	X

ADA: Adalimumab; PBO; Placebo; yrs: years; SD: standard deviation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; TNF: Tumor necrosis factor

3 References

1. Mayoclinic. *Ankylosing spondylitis*. 11/02/2014; Available from: http://www.mayoclinic.org/diseases-conditions/ankylosing-spondylitis/basics/definition/con-20019766.
2. Dougados, M. *Ankylosing spondylitis*. Available from: https://www.orpha.net/data/patho/GB/uk-Ankylosing-spondylitis.pdf.
3. Braun, J., et al., *2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis.* Ann Rheum Dis, 2011. **70**(6): p. 896-904.
4. Mayoclinic. *Ankylosing Spondylitis: treatments and drugs*. 11/02/2014; Available from: http://www.mayoclinic.org/diseases-conditions/ankylosing-spondylitis/basics/treatment/con-20019766.
5. Novartis. *Novartis announces new one-year results demonstrating sustained secukinumab efficacy in ankylosing spondylitis patients*. 2015; Available from: https://www.novartis.com/news/media-releases/novartis-announces-new-one-year-results-demonstrating-sustained-secukinumab.
6. Baeten, D., et al., *Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis.* N Engl J Med, 2015. **373**(26): p. 2534-48.
7. van der Heijde, D., et al., *Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial.* Arthritis Rheum, 2006. **54**(7): p. 2136-46.
8. van der Heijde, D., et al., *Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial.* Ann Rheum Dis, 2009. **68**(6): p. 922-9.
9. Signorovitch, J.E., et al., *Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept.* Pharmacoeconomics, 2010. **28**(10): p. 935-45.
10. Signorovitch, J.E., et al., *Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research.* Value Health, 2012. **15**(6): p. 940-7.
11. Kirson, N.Y., et al., *Matching-adjusted indirect comparison of adalimumab vs etanercept and infliximab for the treatment of psoriatic arthritis.* J Med Econ, 2013. **16**(4): p. 479-89.
12. Hirano, K., G.W. Imbens, and G. Ridder, *Efficient estimation of average treatment effects using the estimated propensity score.* Econometrica, 2003. **71**(4): p. 1161-89.
13. Rosembaum, P. and D. Rubin, *Reducing bias in observational studies using subclassification on the propensity score.* J Am Stat Assoc, 1984. **79**(387): p. 516-24.
14. Bucher, H.C., et al., *The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials.* J Clin Epidemiol, 1997. **50**(6): p. 683-91.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors [ID719]

Dear Anna

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have now had an opportunity to take a look at the submission received on 8 February 2016 from Novartis. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter). The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **15 March 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/11699.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact [redacted] Technical Lead [redacted]. Any procedural questions should be addressed to [redacted] Project Manager [redacted]

Yours sincerely

[redacted]
Technical Adviser – Appraisals
Centre for Health Technology Evaluation
Encl. checklist for in confidence information

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

Section A: Clarification on effectiveness data

Definitions

A1. **Priority request:** Please provide definitions for 1) mild, 2) moderate and 3) severe ankylosing spondylitis as used in the submission.

- Please state how many people had mild, moderate and severe ankylosing spondylitis in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).
- Please provide data separately for people with mild, moderate and severe ankylosing spondylitis, for all outcomes specified in the scope (after 12 and 16 weeks) for each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).

A2. Please provide a definition of conventional care, in both the biologic experienced and biologic naïve populations. Does conventional care include physiotherapy and/or non-steroidal anti-inflammatory drugs (NSAIDS)?

- Please provide an overview of the concomitant therapies that were permitted in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available), as well as the prior medications received before starting the trial.

A3. Section 3.1 of the company submission provides UK specific prevalence estimates.

- What is the time frame for the “estimated 200,000 cases of AS [that] have been diagnosed in the UK”?
- What is the denominator used to calculate prevalence?

Literature searching

A4. Please supply the date span of the individual databases searched for the clinical systematic literature review and the cost effectiveness systematic literature review.

A5. Please supply the search strategies for the searches conducted in clinicaltrials.gov and the International Clinical Trials Registry (ICTRP).

A6. Inclusion and exclusion criteria:

- Please explain why combination therapies were included in the cost effectiveness inclusion/exclusion criteria (footnote a in table 65) but were not included for clinical effectiveness (table 6).

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

- Please explain why non-biologic treatments have been excluded from both the clinical and cost effectiveness inclusion/exclusion criteria.

Secukinumab trial design and baseline characteristics

A7. According to table 131 in appendix E of the company submission, concomitant medicines were allowed in MEASURE 1 and MEASURE 2. Please provide details of how many patients were on concomitant medication.

A8. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients whose disease had not responded to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

A9. Please state how intolerance was defined in each of the trials included in the network meta-analysis. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients who, at baseline, were intolerant to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

A10. Please provide additional detail for the category ‘other’ in table 15 (baseline characteristics of participants in MEASURE 1 and MEASURE 2) i.e. which ethnic group represented 13.9% and 21.6% of the secukinumab and placebo arms, respectively, in MEASURE 1?

A11. The baseline characteristics for patients in MEASURE 1 appear to differ from the baseline characteristics for patients in MEASURE 2. For example: ethnicity, average weight, time since diagnosis and number of prior TNF-alpha inhibitors. Please discuss the impact these differences may have.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

Secukinumab trial results

A12. Please provide an interpretation as to why ASAS20 response improves between weeks 12 and 16, but ASAS40 response deteriorates during this time period, for people receiving secukinumab in the MEASURE 2 trial (section 4.7.1, figures 11 and 13).

A13. Please provide patient-level Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores from MEASURE 1 and MEASURE 2 for biologic naïve and experienced patients separately.

A14. Please provide details of the statistical analysis methods used for subgroup analyses (section 4.8). The p-values in table 44, table 45 and all subgroup analyses in section 4.8 appear to be for the treatment comparison within each subgroup and not from an interaction test between subgroups. Please report the results of a test for an interaction between treatment and the subgroup.

Statistical analysis of secukinumab trials

A15. According to table 14, “the impact of missing data on the analysis results of ASAS20 response was assessed by repeating the logistic regression model using different ways to handle missing data, including multiple imputation and observed data analysis.”

None of these results appear to be reported, please provide them for the binary outcomes or clarify why using different assumptions about missing data did not alter the results.

Network meta-analysis

A16. **Priority request:** According to table 8 of the company submission the study by Marzo-Ortega et al. 2005 was excluded from the network meta-analysis on the basis that the study did not connect to the network. This study is a comparison of infliximab with placebo and therefore it is unclear why this study cannot be connected to the network via the placebo arm.

Please provide further details to explain the reason why this study was excluded, or provide revised results from the network meta-analyses including this study.

A17. **Priority request:** According to section 4.10.9 of the company submission, both fixed effects and random effects models were applied to all networks. The results for the random effects models are not included in the company submission. Please provide the random effects model results for all networks listed in table 59.

A18. Section 4.10.2 of the company submission states that ASAS 5/6 and SF-36 PCS outcomes were analysed. Please provide these results.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

A19. According to section 4.10.6 the Markov Chain Monte Carlo simulations appear to have been implemented in two different software packages: OpenBUGS and JAGS. Please clarify why 2 different software packages were employed and specify which package was used for which analysis.

A20. Section 4.10.7.1 of the company submission reports the predicted absolute response for each treatment for 5 outcomes (ASAS20, ASAS40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline). The analysis methods do not describe how the absolute response was calculated. Please provide full details of how this was calculated.

A21. Section 4.10.8 states that no evidence of inconsistency was found for the base case network. It is unclear from the text which outcome this refers to. According to the network diagrams provided in appendix K there is potential for inconsistency in both the whole population and the biologic naïve population in the ASAS20 networks and the ASAS40 networks (Figures 51-54). In addition, the cited reference describes several methods for the assessment of inconsistency.[1]

- Please specify which method of inconsistency assessment was used.
- Please provide the full results of the inconsistency assessment for each network where inconsistency may be present.

A22. According to page 140 "...there were very few situations [in this network meta-analysis] in which multiple trials informed a comparison, no formal assessment of heterogeneity was performed."

Please report the I^2 values for comparisons involving 2 or more trials, especially MEASURE 1 and 2. For example, the comparison of adalimumab with placebo contained 3 trials so heterogeneity should have been assessed.

A23. According to page 25, "insufficient data was available to conduct an network meta-analysis in the biologic-experienced only population; outside of the MEASURE 1 and MEASURE 2 studies there is no reported data for TNF-alpha inhibitors in the biologic-experienced population."

Please provide results for MEASURE 1 and MEASURE 2 in the biologic experienced population.

Matched adjusted indirect comparison

A24. Section 4.10.11 and appendix J report the results of a matching adjusted indirect comparison. Please clarify the following points:

- Why were other studies of adalimumab not considered in this analysis?
- Why were other comparators not considered for this type of analysis?

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

- Why was only MEASURE 2 included, but not MEASURE 1?

Section B: Clarification on cost-effectiveness data

Model structure and assumptions

B1. **Priority question:** In the base case model, response at 12 weeks was defined as an improvement of 50% or more in BASDAI score from baseline (BASDAI 50). A scenario analysis defined response as a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more.

- In TA383, the appraisal committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British Society of Rheumatology (BSR) guidelines and the previous technology appraisal[2]: a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more. Please present the results of an additional scenario analysis, where the response assessment for treatment continuation takes into consideration the response definition that was adopted in NICE guidance[2], which also includes 2 cm reduction in spinal pain VAS. Please also provide the details regarding the extent to which data on spinal VAS are missing, and what method was used to adjust for the missing data.

B2. For people who whose disease has not responded to treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, are biologics used as the next line of treatment? If so:

- What proportion of the ankylosing spondylitis population in England use a second biologic after the first has failed?

- What proportion use 'conventional' treatment after the first biologic has failed?

B3. **Priority question:** When modelling treatment sequencing, an efficacy reduction of 0.55 for the second biologic treatment in the sequence was assumed (Excel model, "Clinical Inputs" sheet, Cell F26). Please explain how the value of 0.55 was derived. Please provide and justify the other assumptions in the modelling of second-line biologics. Include the baseline BASDAI/BASFI values used at the start of second-line treatment and the values used for change from baseline.

B4. On pages 185-186, the company submission highlights a "lack of robust clinical data to support use of the TNF-alpha inhibitors in this setting" as a reason for not comparing secukinumab to TNF-alpha inhibitors in the biologic experienced population. Please explain why non-randomised data was not used to compare secukinumab with TNF-alpha inhibitors in the biologic experienced population in an exploratory analysis.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

B5. The model includes an infliximab biosimilar as a comparator, but not the recently approved etanercept biosimilar (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004007/WC500196736.pdf). Please rerun the analyses including the etanercept biosimilar.

Treatment effect in cost effectiveness model

B6. **Priority request:** Different values for the change from baseline in BASDAI scores for biologic naïve patients are reported in table 73 and the Excel model (worksheet "Clinical inputs", Cells "F49:L50").

- Please explain which values are the correct ones and why there is a discrepancy.
- Please explain in detail the calculations in the "Subgroup data" sheet, formulae in columns "M:CU". How were the BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline calculate? Which regression coefficients were used?

B7. **Priority request:** Baseline BASDAI, BASDAI 50 and absolute BASDAI change from baseline are correlated parameters. BASDAI 50 and absolute BASDAI change from baseline were modelled separately; the dependence of these 2 parameters was not reflected in the probabilistic sensitivity analysis. By contrast, the assessment group for TA383 (herein referred to as York) used joint modelling approaches for BASDAI and BASFI-related treatment outcomes (approaches B and C, see sections 6.1.4 and 6.1.5 as well as appendix 9 of the assessment report for TA383).[3]

Please rerun the economic model using input data based on the results of the network meta-analysis models (including secukinumab), which incorporate dependencies between BASDAI, BASDAI 50 and BASFI. Please follow the approaches B1, B2, C1 and C2 (independent treatment effects) in the York assessment report for TA383.[3]

B8. In TA383, the appraisal committee concluded that TNF-alpha inhibitors were clinically effective compared with placebo and that they should be considered as a class with broadly similar, even if not completely identical, effects.[2] In the company submission for secukinumab there were no statistically significant differences between secukinumab and TNF-alpha inhibitors (except infliximab) for all trial outcomes in the network meta-analyses.

Please rerun the economic model using input data based on the results of the network meta-analysis models, which assume that all TNF-alpha inhibitors have the same treatment effect. Please follow the approaches A3, A4 and A5 in section 6.1.3 and appendix 9 of the York assessment report for TA383.[3]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

B9. Please provide all relevant input data for the model so that the other approaches described in the York assessment report for TA383 (A1-5, B3-5, C3-5) can be conducted.

B10. According to table 70, BASDAI 50 responses for biologic naïve patients are obtained from the network meta-analysis results (figure 26). However, results reported in table 70 differ from the results in figure 26. Please explain these differences and clarify how average values were calculated when corresponding outcomes for a comparator were lacking in the network meta-analysis.

B11. The BASDAI 50 responses for TNF-alpha inhibitors (Table 70) appear to be inconsistent with the results in the York assessment report for TA383 (Table 7).[3] Please explain why they are different.

B12. In TA383, recommendations were based on severe active ankylosing spondylitis. However, the inclusion criteria for MEASURE 1 and MEASURE 2 were not limited only to "severe" active ankylosing spondylitis. The scope for secukinumab is for adults with active ankylosing spondylitis.

Were any of the values used in the company model, which came from TA383[2] or the York assessment report[3] adjusted for the severity of the ankylosing spondylitis?

B13. The text above table 71 suggests that the difference in baseline BASDAI and BASFI scores between responders and non-responders was based on response at week 12. However, the text following table 72 suggest that response was derived from pooled data from the MEASURE 1 and MEASURE 2 trials, which suggests that response at week 16 was used.

- Please specify the definition, including time point, of response used to differentiate between responders and non-responders when estimating baseline BASDAI and BASFI scores in table 72.
- Please provide the number of patients (n) for each result in table 72.
- Please provide response-based BASDAI and BASFI figures not differentiated by treatment.

In the Excel model, the same baseline BASDAI and BASFI scores (given in table 72) are used even though different secukinumab trial data (week 12 and week 12-16) were chosen (sheet "Settings", range "E60:F60").

- Please provide BASDAI 50 response specific baseline BASDAI and BASFI scores based on different (week 12 or week 12-16) time point responses.

B14. Section 5.3.3.1 is difficult to follow. Please provide a step by step explanation showing all formulae used to calculate mean change in BASDAI and BASFI from the

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

various sources (MEASURE 1 & 2 trials, network meta-analyses, York assessment report[3], TA383[2] and any other sources).

B15. By definition, the absolute BASDAI change from baseline at 3 months for the BASDAI 50 responders should be at least 50% of their baseline BASDAI. However, this does not appear to be the case for some of the model inputs (e.g. etanercept, adalimumab and conventional care; (tables 72 and 73).

Please explain this discrepancy for BASDAI 50 responders.

B16. In the Excel model, differing baseline BASDAI and BASFI scores are used in subgroup (biologic experienced and biologic naïve) and scenario (only MEASURE 2 trial data as a data source for secukinumab) analyses.

Please justify why other baseline characteristics (age, weight and percentage males) are not varied in these subgroup/scenario analyses.

B17. BASDAI and BASFI change from baseline of TNF-alpha inhibitors in tables 73 and 74 appear to be inconsistent with the results reported in the York assessment report for TA383 (for example table 69 on page 167 of the York report).[3] Please explain these differences.

B18. Please provide details of the methods used to derive the values in table 73 of the company submission (especially for etanercept, certolizumab pegol and infliximab).

B19. Please explain how the value of 0.15 for the annual BASFI progression rate for secukinumab (section 5.3.3.2, second paragraph on page 193) was derived from Ramiro et al. and MEASURE 1 week 104 rates.[4]

Adverse events

B20. Please justify why switching to a second TNF-alpha inhibitor was not allowed following an adverse event.

Utilities

B21. **Priority request:** Please provide the details of the methods used to generate the utility regression equation (section 5.4.5.4, page 198) used for mapping to EQ-5D.

- Please provide details of the regression models considered, the explanatory variables assessed, and the variable selection method used to obtain the final model.
- Please provide all related regression outputs, e.g. coefficients, test scores and goodness of fit.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

- Please provide a Q-Q plot for all 3 utility regression methods (MEASURE 1-2 model, Wailoo et al. 2015 method and McLeod et al. 2007 method) to compare the 3 utility mapping models.[5, 6]

Costs

B22. Please update the cost regression (section 5.5.5, page 157) used for active disease health state according to 2016 NHS prices.

Please check the study on which this regression method is based and whether the assumptions of the regression model are still relevant for the UK clinical setting.[7]

B23. The drug acquisition costs are the same as those in the York assessment report for TA383, from 2014.[3] Please verify that these drug prices have not changed since 2014.

B24. Please explain the calculation methods for the number of doses for all interventions (especially for certolizumab pegol) (Excel Model Sheet ”Resource Use Inputs”, Range G15:I20).

B25. According to the NHS choices website, surgery is part of the treatment pathway. The model does not include costs related to surgeries. Please justify the assumption of excluding surgery costs.

Validation

B26. Please provide a table similar to table 110 for the comparison of total QALYs in the company model for secukinumab and the York model for TA383. Please provide a comparison for disaggregated costs in table 110.

B27. Please provide a figure that compares the average BASDAI and BASFI scores at different time points from the model with average BASDAI and BASFI scores at different time points from relevant clinical trials.

B28. In the excel model, it seems that the model estimates are not the same for total QALYs and LYs, even though a utility of 1 is used for each alive state (and no disutilities for adverse events were considered). Please confirm if this is a programming error. If this is the case, please provide a corrected version.

B29. In the excel model it appears that the discount rate for costs was used when discounting both costs and health outcomes. Please confirm if this is a programming error and if so, provide a corrected version.

B30. In the excel model it seems that variations in non-responder BASFI baseline value, and in non-responder change in BASDAI and BASFI, have no effect at all on costs and QALYs. Please confirm if this is meant to be the case and provide an explanation.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

B31. In the excel model, there is a big difference between the averages from probabilistic sensitivity analyses (PSA) and base case deterministic results, especially in QALYs. Please explain the underlying reasons for this.

B32. In the excel model, some of the model input parameters were not included in the PSA (e.g. relative risk of BASDAI 50 response for biologic experienced patients). Please justify the inclusion criteria that were applied to the input parameters for PSA.

B33. Please provide the BASDAI and BASFI changes from baseline used in Scenario 3 described in section 5.8.3 (page 232).

Section C: Textual clarifications and additional points

C1. Table 6: The inclusion criteria list patients with intolerance or inadequate response. However, the exclusion criteria list “treatment-naïve patients”. Please explain this discrepancy.

C2. Details of how many patients remain in MEASURE 2 at different time points were provided. However, outcomes reported in tables and appendices do not always reflect these numbers. For example, table 139 reports on 68 patients at 16 weeks in the secukinumab arm yet there were only 66 patients in study at this point. Please add reasons for any differences in the patient numbers to each table.

C3. Cross-references are missing on page 58 and 213 (the text says “please see section 0”). Please confirm the correct section numbers that should be referenced here.

10 Spring Gardens
London
SW1A 2BU
United Kingdom
+44 (0)845 003 7780

References

[1] Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. *NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials [Internet]*. Sheffield, 2014 [accessed 24.2.16]. 41p. Available from: http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series%282391675%29.htm

[2] National Institute for Health and Care Excellence. *TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance TA383 [Internet]*, 2016 [accessed 24.2.16]. 70p. Available from: https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077

[3] Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, et al. *TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233*. York: CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, 2014. 371p.

[4] Ramiro S, van Tubergen A, van der Heijde D, van den Bosch F, Dougados M, Landewe R. How to deal with missing items in BASDAI and BASFI. *Rheumatology (Oxford)* 2014;53(2):374-6.

[5] McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess* 2007;11(28):1-158, iii-iv.

[6] Wailoo A, Hernandez M, Philips C, Brophy S, Siebert S. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. *Value Health* 2015;18(4):425-31.

[7] Boonen A, van der Heijde D, Landewe R, Guillemin F, Rutten-van Molken M, Dougados M, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. *Ann Rheum Dis* 2003;62(8):732-40.

Novartis Clarification Questions Response:

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors [ID719]

Contents

Section A: Clarification on effectiveness data

Definitions

A1. **Priority request**: Please provide definitions for 1) mild, 2) moderate and 3) severe ankylosing spondylitis as used in the submission.

There is currently no consensus on the definitions of mild, moderate or severe ankylosing spondylitis (AS).[1] The classification of AS continues to be a topic of debate and the absence of agreed terminology means that the relevance and importance of this classification is unclear.[2] The inclusion criteria of the MEASURE 2 and MEASURE 1 trials specified that patients had been diagnosed with moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI≥4 (0-10), spinal pain as measured by VAS≥4 (0-10) on BASDAI question 2, and total back pain as measured by VAS≥40 (0-100mm).[3, 4] No further criteria were used to determine whether patients had moderate to severe AS or to distinguish between these classes. This is in line with the approved indication for secukinumab, the population in the final NICE scope, with the British Society for Rheumatology guidelines for prescribing biologics in AS and the EMA CHMP Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis (2005).[5, 6]

- Please state how many people had mild, moderate and severe ankylosing spondylitis in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).

In both MEASURE trials, patients were required to have prior documented radiologic evidence fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI≥4 and spinal pain as measured by VAS≥4 cm, meaning that all patients in the study had active AS, in line with the approved indication for secukinumab and the population in the final NICE scope.

Please see above statements regarding the definitions and available data for MEASURE 1 and MEASURE 2.

Furthermore, this data does not exist for the other trials included in the network meta-analysis (NMA), indicating that such classification lacks clinical relevance.

- Please provide data separately for people with mild, moderate and severe ankylosing spondylitis, for all outcomes specified in the scope (after 12 and 16 weeks) for each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).

See above, these data are not available.

A2. Please provide a definition of conventional care, in both the biologic experienced and biologic naïve populations. Does conventional care include physiotherapy and/or non-steroidal anti-inflammatory drugs (NSAIDS)?

As described in Section 3.5 of the submission, conventional care is defined as treatment with NSAIDs alongside non-pharmacological interventions to help relieve pain and stiffness (e.g. physiotherapy).[5] Therefore, conventional care is considered to include both NSAIDs and physiotherapy. This treatment is variably referred to in the submission as conventional therapy or conventional care; the two terms are considered interchangeable.

- Please provide an overview of the concomitant therapies that were permitted in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available), as well as the prior medications received before starting the trial.

Concomitant Therapies – MEASURE 2 and MEASURE 1

Information on permitted concomitant therapies within the MEASURE 1 and MEASURE 2 trials was provided in Tables 11 and Appendix E (Table 131) of the submission; “Inclusion criteria” and “Guidelines for the use of concomitant medicines”, respectively.

Please find below a summary of the concomitant therapies that were permitted in other trials included in the network meta-analysis.

Concomitant Therapies – Other Trials Included in the NMA

Details of concomitant therapies used in other trials included in the NMA are presented in Table 1 below.

Table 1: Summary of the concomitant therapies that were permitted in other trials included in the NMA

Trial	Treatment	Concomitant Medications
ATLAS[7]	Adalimumab	Remain on the following treatments if dosage has remained stable for at least 4 weeks before the baseline visit: • Sulfasalazine (≤3gm/day) • Methotrexate (≤25mg/week) • Hydroxychloroquine (≤400mg/day) • Prednisone or prednisone equivalent (≤10mg/day) • NSAIDS
Hu (2012)[8]	Adalimumab	Patients could remain taking the following treatments if dosage has remained stable for at least 4 weeks before the baseline visit: • Sulfasalazine (≤3gm/day) • Methotrexate (≤25mg/week) • Prednisone and/or prednisone equivalents (≤10mg/day) and/or NSAIDs
Huang (2014)[9]	Adalimumab	The following treatments were allowed, however dose adjustments, induction and/or discontinuation of therapies was only permitted during the open-label period: • Methotrexate (≤25mg/week) • Sulfasalazine (≤3gm/day) • Prednisone (≤10mg/day) • NSAIDs and/or analgesics
RAPID-axSpA[10]	Certolizumab	NSAIDs DMARDs
Giardina (2010)[11]	Etanercept	NSAIDs
SPINE[10]	Etanercept	NSAIDs – doses had to remain stable for the 2 weeks prior to study entry DMARD (sulfasalazine and methotrexate) – doses had to remain stable in the 4 weeks prior to study entry
ASSERT[12]	Infliximab	Patients could receive concomitant stable doses of: • NSAIDs • Acetaminophen (paracetamol) • Tramadol
GO-RAISE[13]	Golimumab	Patients were allowed to continue the following concomitant treatments at stable doses: • Methotrexate • Sulfasalazine • Hydroxychloroquine • Corticosteroids • NSAIDs Patients receiving NSAIDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3month course of full dose NSAID therapy because of intolerance, toxicity or contraindications

Abbreviations: DMARD, Disease modifying anti-rheumatic drug; NSAID, Non-steroidal anti-inflammatory drug.
Source: as indicated.

Prior Medications

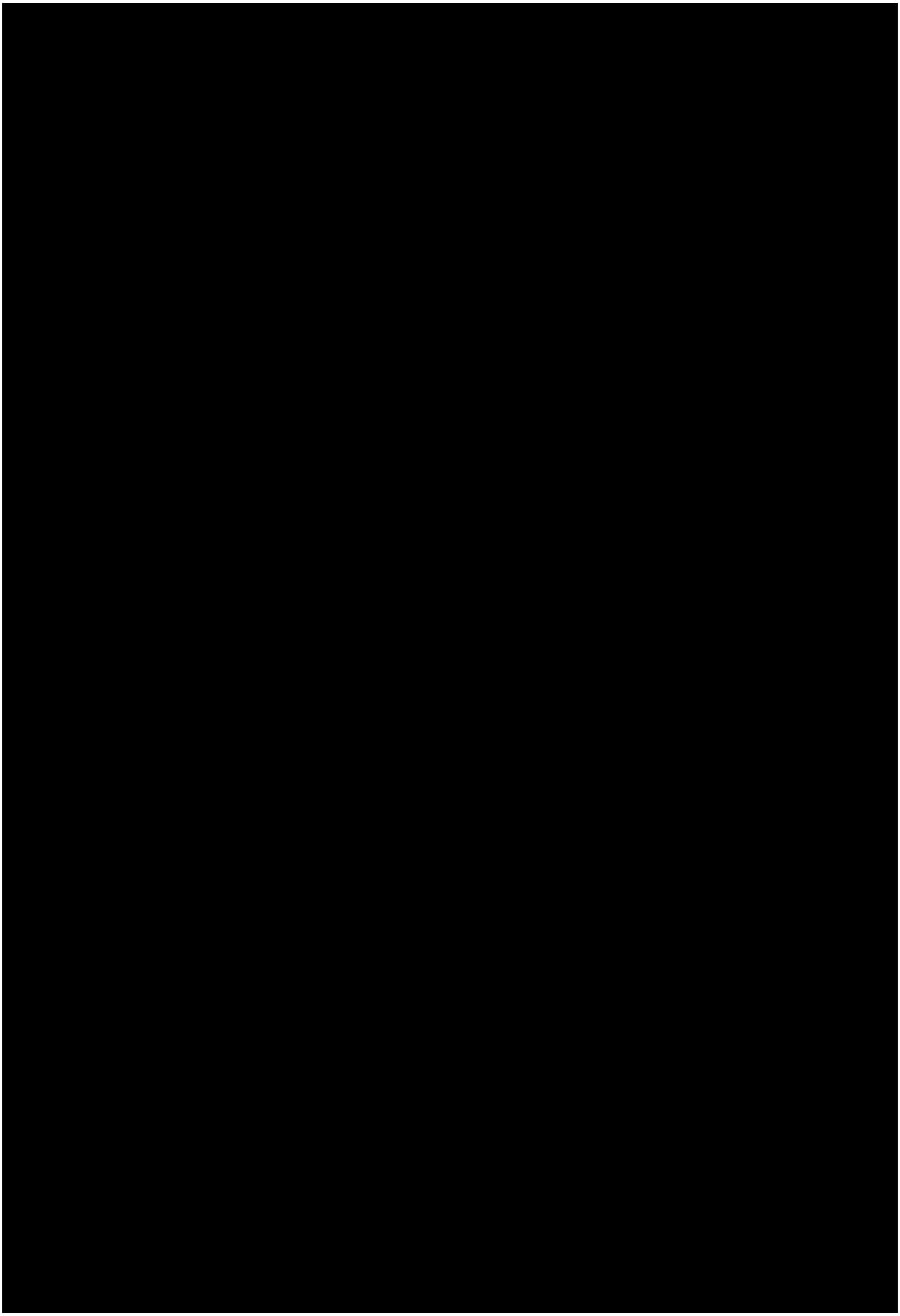
In MEASURE 1 and 2 Prior medications were reported in similar proportions of patients across the treatment groups:

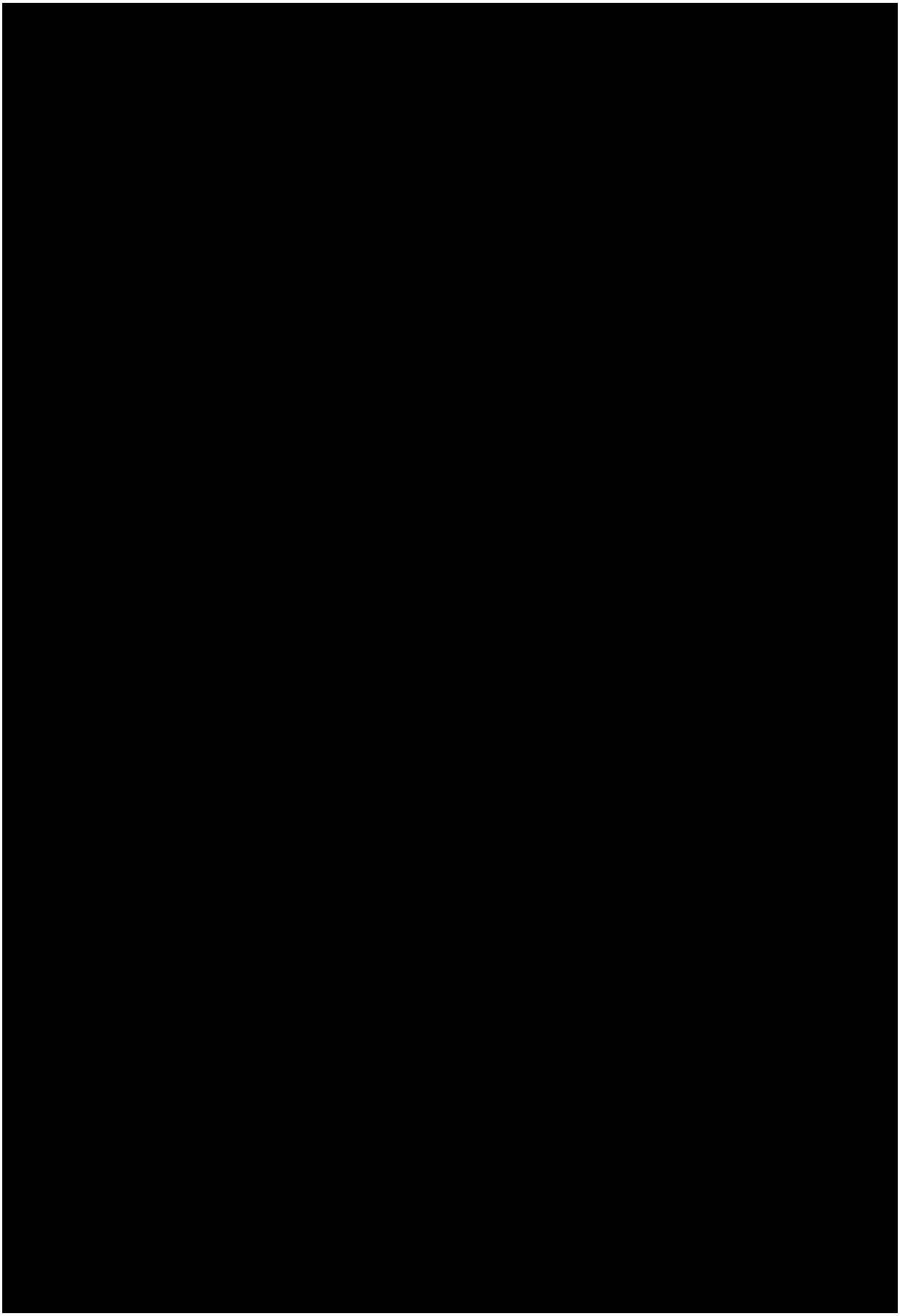
- MEASURE 1: [redacted] and [redacted] for the secukinumab IV-150 mg and placebo groups
- MEASURE 2: prior medications were reported in [redacted] and [redacted] of patients in the secukinumab 150 mg s.c. and placebo groups, respectively.

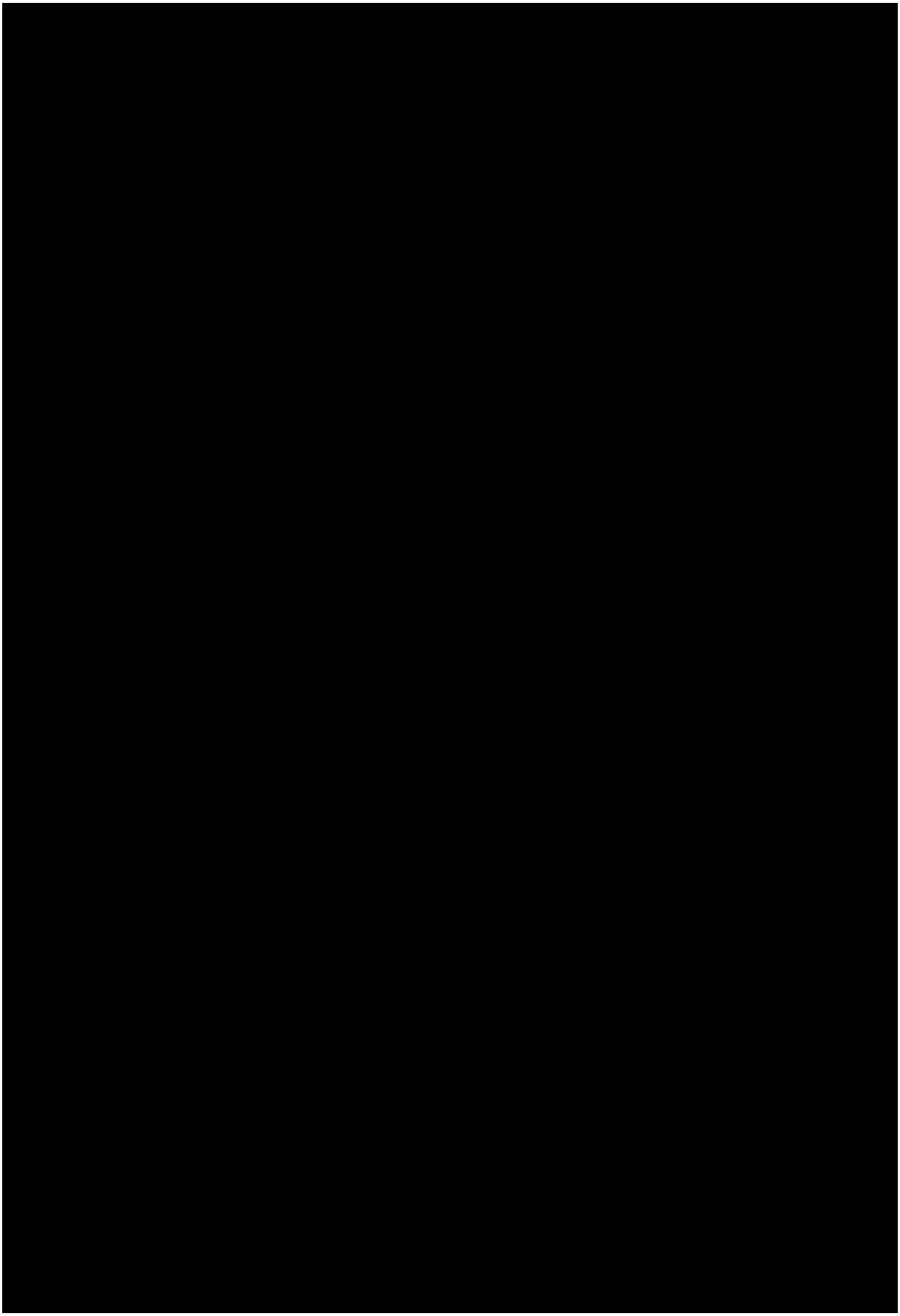
Please find in [redacted] 2 below a summary of the prior medications that patients in MEASURE 1 and 2 had received.

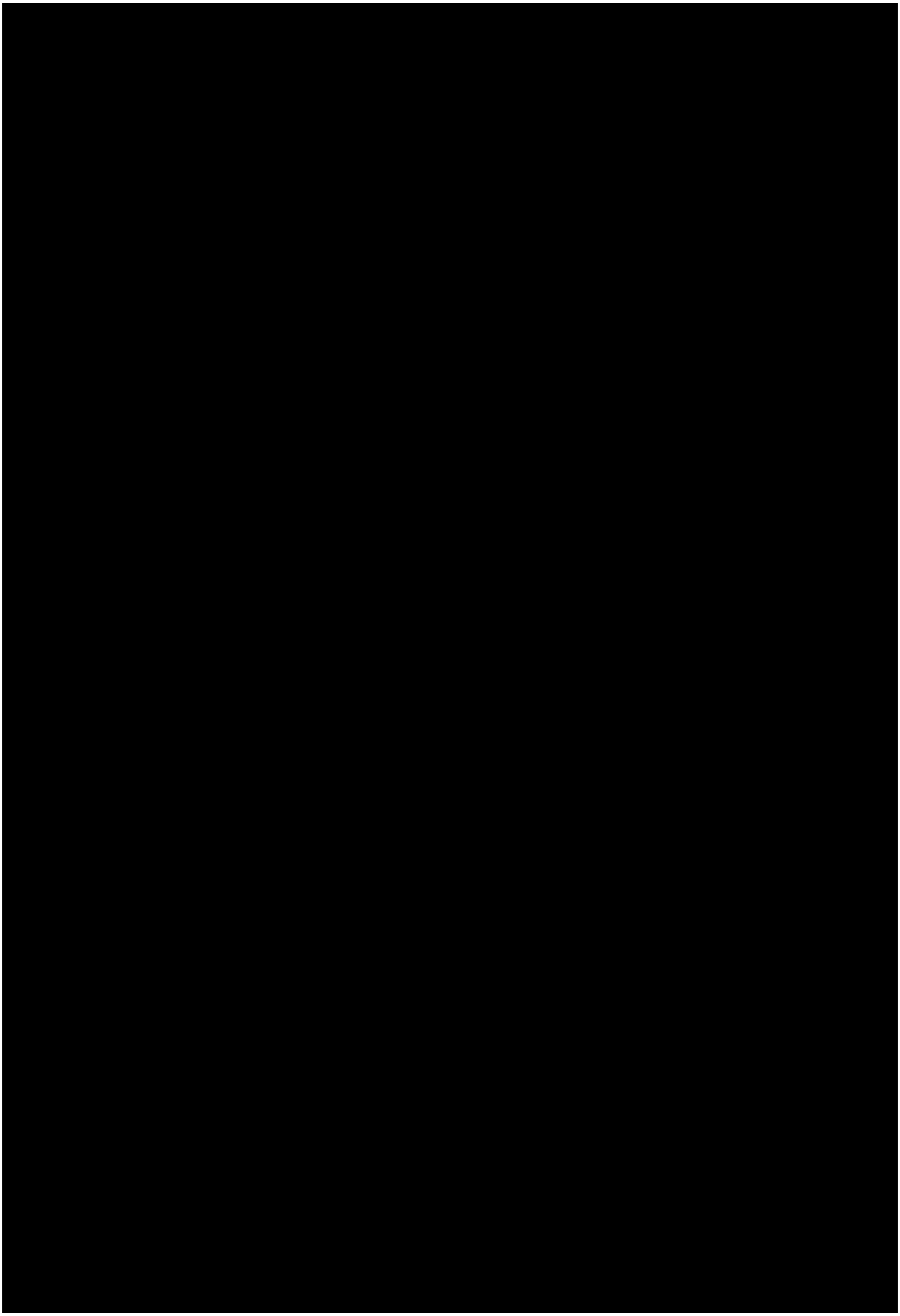
[redacted] 2

[redacted]









[redacted]

A3. Section 3.1 of the company submission provides UK specific prevalence estimates.

- What is the time frame for the "estimated 200,000 cases of AS [that] have been diagnosed in the UK"?

The prevalence estimate of 200,000 cases of AS was provided by the Department of Health in The Musculoskeletal Services Framework published on 12th July 2006.[14] The original source states that "upwards of 400,000 adults in the UK have rheumatoid arthritis, while about 200,000 have been diagnosed with ankylosing spondylitis…", which suggests the figure of 200,000 is an estimate of the number of patients in the UK who, at the time of reporting, had received a diagnosis of AS.

- What is the denominator used to calculate prevalence?

The prevalence estimate of 200,000 is quoted for adults in the UK and therefore, the denominator is assumed to be the adult population in the UK at the time of reporting.[14] Assuming a UK adult population of 47,469,500 as reported in 2006, this would be equivalent to a prevalence estimate of 42.1 cases per 10,000, which is a similar order of magnitude to the alternative European prevalence estimate of 23.8 cases per 10,000.[15, 16]

Literature searching

A4. Please supply the date span of the individual databases searched for the clinical systematic literature review and the cost effectiveness systematic literature review.

a) For the clinical systematic literature review, databases were searched from database inception up to 23rd January 2015 (PubMed, Cochrane), 26th January (Embase), and 27th January 2015 (BIOSIS) for the original review. For the update, all databases were searched from 1st January 2014 to 14th September 2015.

As described in Appendix C of the submission, in the original clinical systematic literature review, databases were searched from database inception up to 23rd January 2015 (PubMed, Cochrane), 26th January (Embase), and 27th January 2015 (BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

b) For the original economic systematic literature review, databases were searched from 1st January 1999 up to 22nd December 2014 (Embase, Cochrane Library), 23rd January 2015 (PubMed), and 27th January 2015 (EconLit, BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

As described in Appendix D of the submission, in the original economic systematic literature review, databases were searched from 1st January 1999 up to 22nd December 2014 (Embase, Cochrane Library), 23rd January 2015 (PubMed), and 27th January 2015 (EconLit, BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

Database inception dates for PubMed, EMBASE and BIOSIS are 1946, 1947 and 1926, respectively.

A5. Please supply the search strategies for the searches conducted in clinicaltrials.gov and the International Clinical Trials Registry (ICTRP).

Search Strategy for clinicaltrials.gov

The following search strategies, listed as Conditions | Interventions | Age Group, were conducted in clinicaltrials.gov:

- "ankylosing spondylitis" | secukinumab OR cosentyx | Adult, Senior
- "ankylosing spondylitis" | certolizumab OR cimzia | Adult, Senior
- "ankylosing spondylitis" | Etanercept OR Enbrel OR Avent OR BX2922 OR CHS-0214 OR ENIA11 OR Etacept OR Etanar OR GP2013 OR GP2015 OR HD203 OR LBEC0101 OR M923 OR PRX-106 OR SB4 OR tunex OR yisapu | Adult, Senior
- "ankylosing spondylitis" | Adalimumab OR Humira OR Trudexa OR ABP 501 OR BI695501 OR CHS-1420 OR GP2017 OR M923 OR PF-06410293 | Adult, Senior
- "ankylosing spondylitis" | infliximab OR Remicade OR CT-P13 OR Remsima OR Inflectra | Adult, Senior
- "ankylosing spondylitis" | Golimumab OR Simponi | Adult, Senior

Search Strategy for the International Clinical Trials Registry (ICTRP)

The following search strategies were conducted in the ICTRP:

- "ankylosing spondylitis" in condition, "Secukinumab" in intervention
- "ankylosing spondylitis" in condition, "certolizumab" in intervention
- "ankylosing spondylitis" in condition, "Etanercept" in intervention
- "ankylosing spondylitis" in condition, "Adalimumab" in intervention
- "ankylosing spondylitis" in condition, "Infliximab" in intervention
- "ankylosing spondylitis" in condition, "Golimumab" in intervention

A6. Inclusion and exclusion criteria:

- Please explain why combination therapies were included in the cost effectiveness inclusion/exclusion criteria (footnote a in table 65) but were not included for clinical effectiveness (table 6).

The clinical systematic literature review was designed to inform the NMA, which did not consider combination therapies as these were considered inappropriate comparators for the decision problem; therefore the inclusion of combination therapies was beyond the scope of the clinical literature review. The economic literature review was designed with broader inclusion criteria in order to allow the collection of data that may have been beneficial for the model design.

- Please explain why non-biologic treatments have been excluded from both the clinical and cost effectiveness inclusion/exclusion criteria.

Non-biologic treatments were excluded from both the clinical and cost effectiveness inclusion/exclusion criteria consistent with the final scope issued by NICE, which is presented in Table 1 of the submission. Whilst we acknowledge that the scope also defines "established clinical management without secukinumab" for the population whose disease has responded inadequately to, or who are intolerant to, TNFα inhibitors, we considered that no appropriate search strategy could be employed to capture this comparator and that this comparator would be addressed by the placebo arms of any clinical studies of biologic treatments identified by the SLR.

Secukinumab trial design and baseline characteristics

A7. According to Table 131 in appendix E of the company submission, concomitant medicines were allowed in MEASURE 1 and MEASURE 2. Please provide details of how many patients were on concomitant medication.

In MEASURE 1, up to Week 16, concomitant medications were used [redacted] in the placebo groups and by [redacted] in the secukinumab IV-150 mg group. In MEASURE 2, up to Week 16, concomitant medications were used by [redacted] in the secukinumab groups and [redacted] patients in the placebo group.

A8. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients whose disease had not responded to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

Feasibility for the above analyses was assessed by determining the patient numbers per sub-group. The results of these analyses are presented in Table 3 below.

Table 3: Patient numbers for sub-groups defined by inadequate response to prior medications

	MEASURE 1		MEASURE 2	
Patients with inadequate response to:	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs and TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs or TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **NSAID, non-steroidal anti-inflammatory drug; TNFα, tumour necrosis factor alpha**

Sub-group analyses were deemed feasible where a minimum of 20 patients were available for both arms of the studies. Based on the above analyses, the sub-group of patients with

inadequate response to both NSAIDs and TNFα inhibitors was deemed too small for meaningful sub-group analysis. Outcome data, on ASAS20, ASAS40, BASDAI 50, BASDAI change from baseline and BASFI change from baseline, for the other three sub-groups, is provided in Table 4 to Table 6 below. No data on these sub-groups is available for any of the other trials included in the network meta-analysis.

Table 4: Results for NSAID inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Results for TNFα inhibitor inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Results for NSAIDs or TNFα inhibitors inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	Secukinumab 150 mg	Placebo	Secukinumab 150 mg	Placebo
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]

A9. Please state how intolerance was defined in each of the trials included in the network meta-analysis. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients who, at baseline, were intolerant to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

Intolerance to prior medication was based on the individual investigator's assessment. Feasibility for the above analyses was assessed by determining the patient numbers per sub-group. The results of these analyses are presented in Table 7 below.

Table 7: Patient numbers for sub-groups defined by inadequate response to prior medications

	MEASURE 1		MEASURE 2	
Patients with intolerance to:	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs and TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs or TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **NSAID, non-steroidal anti-inflammatory drug; TNFα, tumour necrosis factor alpha**

Sub-group analyses were deemed feasible where a minimum of 20 patients were available for both arms of the studies. Based on the above analyses, no meaningful analyses of sub-groups with intolerance to prior medications were possible.

No data on these sub-groups is available in the public domain for any of the other trials included in the network meta-analysis.

A10. Please provide additional detail for the category 'other' in table 15 (baseline characteristics of participants in MEASURE 1 and MEASURE 2) i.e. which ethnic group represented 13.9% and 21.6% of the secukinumab and placebo arms, respectively, in MEASURE 1?

Please find the requested information in Table 8 below.

Table 8: Race data for MEASURE 1 participants

	Secukinumab 150 mg (N=125)	Placebo (N=122)
White, n (%)	69 (55.2)	81 (66.4)
Black or African American, n (%)	0 (0.0)	1 (0.8)
Asian, n (%)	21 (16.8)	19 (15.6)
American Indian or Alaska Native, n (%)	8 (6.4)	3 (2.5)
Native Hawaiian or other Pacific Islander, n (%)	0 (0.0)	1 (0.8)
Other, n (%)	[redacted]	[redacted]
Mestizo / Mestiza, n (%)	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]
North African, n (%)	[redacted]	[redacted]
Turkish, n (%)	[redacted]	[redacted]
Western European, n (%)	[redacted]	[redacted]

A11. The baseline characteristics for patients in MEASURE 1 appear to differ from the baseline characteristics for patients in MEASURE 2. For example: ethnicity, average weight, time since diagnosis and number of prior TNF-alpha inhibitors. Please discuss the impact these differences may have.

As described by study investigators, the primary publication of MEASURE 2 and MEASURE 1 findings by Baeten et al. (NEJM, 2015) states that the baseline demographic and disease characteristics were similar between MEASURE 2 and MEASURE 1 and among the groups within each study.[17] This manuscript was peer reviewed and approved by external experts outside the secukinumab study group prior to publication. Thus, no impact is expected from any of the above mentioned factors.

Of note, as patients treated with more than one TNF-alpha inhibitor were excluded from both studies, the number of patients exposed to more than 1 TNF-alpha inhibitor in either study was negligible. In addition, as described in the submission dossier, pooled subgroup analyses based on ethnicity and weight revealed no clinically meaningful differences in efficacy or safety results based on these subgroups.

Secukinumab trial results

A12. Please provide an interpretation as to why ASAS20 response improves between weeks 12 and 16, but ASAS40 response deteriorates during this time period, for people receiving secukinumab in the MEASURE 2 trial (section 4.7.1, figures 11 and 13).

ASAS 20 and ASAS 40 are binary clinical variables, and there is a likelihood of seeing variation in the visit-to-visit results of these variables in rheumatology studies. Similar variation was also observed in the ATLAS study for adalimumab, in which a continual improvement in ASAS 20 rate was seen throughout the study, but a slight decrease in ASAS 40 rate was seen between weeks 30-52, even when using the less conservative statistical analysis of observed data.

The numerical decrease in ASAS 40 response in the MEASURE 2 trial was less than 3% (38.9% at week 12 compared with 36.1% at week 16), which is clinically negligible. It is important to note

that after week 16, the ASAS 40 response rate for secukinumab 150 mg continues to improve up to Week 52 at 48.6%. These data for secukinumab 150 mg were analysed using the most conservative method for missing data: non-responder imputation. Any patient data that were missing at any of the time points were imputed as a non-response for ASAS 20 and ASAS 40.

The ASAS 40 response deterioration in the MEASURE 2 trial was less than 3% (38.9% at week 12 compared with 36.1% at week 16). It is important to note that after week 16 the ASAS 40 response rate for secukinumab 150 mg continues to improve through to 48.6% at 52 weeks. It should also be noted that the data for secukinumab 150 mg was analysed using the most conservative method for missing data: non-responder imputation. Any patient data that was missing at any of the time points was imputed as a non-response with baseline values.

BASDAI is a continuous efficacy variable, rather than a binary endpoint, and the data for secukinumab 150 mg during the same time period of MEASURE 2 shows continuous improvement through weeks 0 - 16 as demonstrated in [redacted]1 below.

[redacted]1

A13. Please provide patient-level Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores from MEASURE 1 and MEASURE 2 for biologic naïve and experienced patients separately.

The requested patient-level data is provided in separate excel files. [redacted]

A14. Please provide details of the statistical analysis methods used for subgroup analyses (section 4.8). The p-values in table 44, table 45 and all subgroup analyses in section 4.8 appear to be for the treatment comparison within each subgroup and not from an interaction test between subgroups. Please report the results of a test for an interaction between treatment and the subgroup.

The MEASURE 1 and MEASURE 2 studies were not powered to detect a difference between the TNFα inhibitor-naïve subgroup and the TNFα inhibitor-inadequate responder subgroup, and hence these analyses were not included in the pre-specified analysis plan. However, the test for interaction between treatment and subgroup on the primary endpoint has been carried out as requested. The results are shown in Table 9 and Table 10 below. Relatively small patient numbers in the TNFα inhibitor-inadequate responder subgroup mean that these results should not be relied upon. Anti-TNF-α naïve patients showed numerically higher ASAS 20 response rates at Week 16, and whilst the tests for interaction do not reach statistical significance, we consider them to be clinically meaningful. In addition, switching to an alternative TNFα inhibitor in axial spondyloarthropathies has been shown to be associated with lower response rates.[18] Please note that these analyses were carried out at a trial level, and thus included the unlicensed 75mg dose of secukinumab.

Within the allocated time frame it has not been possible to run tests of interaction for the secondary efficacy endpoints – we will endeavour to supply these by Friday 18th March.

Table 9: MEASURE 1 ASAS20 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 10: MEASURE 2 ASAS20 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.

Statistical analysis of secukinumab trials

A15. According to table 14, "the impact of missing data on the analysis results of ASAS20 response was assessed by repeating the logistic regression model using different ways to handle missing data, including multiple imputation and observed data analysis."

None of these results appear to be reported, please provide them for the binary outcomes or clarify why using different assumptions about missing data did not alter the results.

As stated in the submission the sensitivity analyses of the primary endpoint included:

- Same logistic regression model using multiple imputation to handle missing values, to assess the robustness of missing data handling
- Same logistic regression model with observed data (with no rescue penalty), to assess the robustness of missing data handling

Please find below the results of these different analyses for ASAS20 at Week 16 in Table 11.

Table 11: Sensitivity analyses on ASAS20 at Week 16 in MEASURE 1 and 2

Analysis	Response Rate	Comparator	Odds Ratio	95% CI	p-value
MEASURE 1					
Multiple imputation					
Secukinumab 150mg (n=125)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed data (with no rescue penalty)					
Secukinumab 150mg (n=125)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MEASURE 2					
Multiple imputation					
Secukinumab 150mg (n=72)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=74)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed data (with no rescue penalty)					
Secukinumab 150mg (n=66)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=63)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition, post-hoc analyses using last observation carried forward (LOCF) imputation for missing data have now been performed, and these are provided in Table 12.

Table 12: Post-hoc LOCF analyses on ASAS20 at Week 16 in MEASURE 1 and 2

Analysis	n	N	Response rate	95% CI
MEASURE 1				
LOCF				
Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
MEASURE 2				
LOCF				
Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IV, intravenous; LOCF, last observation carried forward

Network meta-analysis

A16. **Priority request:** According to table 8 of the company submission the study by Marzo-Ortega et al. 2005 was excluded from the network meta-analysis on the basis that the study did not connect to the network. This study is a comparison of infliximab with placebo and therefore it is unclear why this study cannot be connected to the network via the placebo arm.

Please provide further details to explain the reason why this study was excluded, or provide revised results from the network meta-analyses including this study.

In the Marzo-Ortega et al. 2005 study all patients were treated with methotrexate and were randomly assigned, in a ratio of 2:1, to receive five infusions of either 5 mg/kg infliximab or placebo over 30 weeks.[19] As such, all patients in the placebo arm were also receiving methotrexate as per the planned treatment regimen. As methotrexate is considered to have some benefit as a treatment in AS, and all patients within the placebo arm of the trial received methotrexate, it was considered inappropriate to use this treatment regimen as a proxy for placebo in the NMA; as such, the study was deemed to be disconnected from the network.

In reviewing the studies included in the network, two omissions from the original set of analyses were identified:

- The ATLAS study had been excluded from the BASFI change from baseline networks in error
- The Huang (2014) study had not been included in the biologic-naïve networks. Initially this study was categorised as being "unclear" regarding whether the population was biologic naïve or biologic experienced. On further review, the article includes the statement "Prior exposure to TNF-α inhibitors, natalizumab or efalizumab at any time, or use of traditional Chinese medicines within 28 days of baseline was not allowed". This indicates that the study was conducted amongst biologic naïve patients. Therefore revised analyses, including Huang (2014) in the biologic naïve networks are, presented in Section D:.

A17. **Priority request:** According to section 4.10.9 of the company submission, both fixed effects and random effects models were applied to all networks. The results for the random effects models are not included in the company submission. Please provide the random effects model results for all networks listed in table 59.

Please see Table 13 to Table 20 for random effects results from both overall and biologic naïve populations in the base case NMA as well as the three sensitivity analyses (excluding MEASURE 1, 12 week data only and both excluding MEASURE 1 and using 12 week data only). Please note that the random effects results presented below are for the updated analyses including ATLAS in the BASFI networks and Huang (2014) in the biologic naïve networks (see response to A16). As discussed in the submission (Section 4.10.9), of the submission, the assessment of model fit by Deviance Information Criterion (DIC) indicated no strong preference for either the FE or RE models in any of the analyses where both model types were possible. Furthermore, for some analyses in the biologic naïve population RE models were not mathematically feasible to conduct. Given this, combined with the low number of trials reporting in each arm and the fact

that no strong evidence of heterogeneity was observed in trial baseline characteristics, FE models were chosen.

Results of comparisons of relative treatment effects – Base case

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Base case)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 13.

Table 13: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Base case NMA: 12-16 weeks, MEASURE 1 & MEASURE 2)

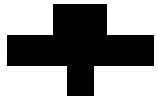
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Base case)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 14.

Table 14: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Base case NMA: 12-16 weeks, MEASURE 1 & MEASURE 2)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 1

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 1)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 15.

Table 15: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 1: 12-16 weeks, MEASURE 2 only)

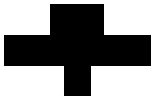
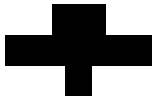
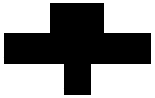
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Sensitivity Analysis 1)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 16.

Table 16: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 1: 12-16 weeks, MEASURE 2 only)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 2

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 2)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 17.

Table 17: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 2: 12 weeks, MEASURE 1 & MEASURE 2)

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Sensitivity Analysis 2)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 18.

Table 18: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 2: 12 weeks, MEASURE 1 & MEASURE 2)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

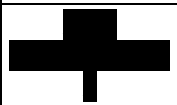
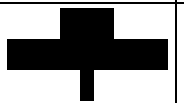
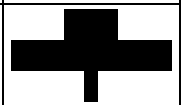
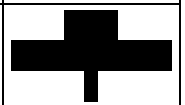
Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 3

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 3)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 19.

Table 19: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 3: 12 weeks, MEASURE 2 only)

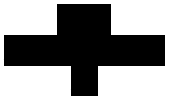
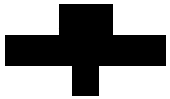
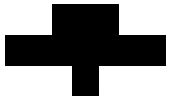
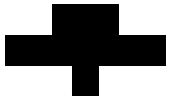
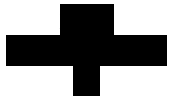
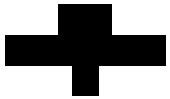
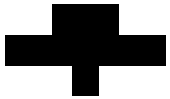
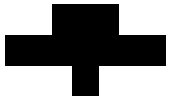
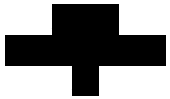
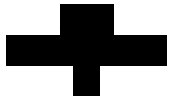
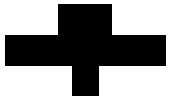
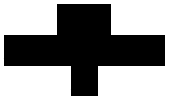
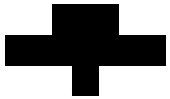
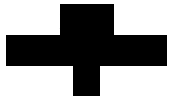
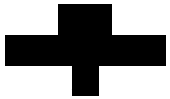
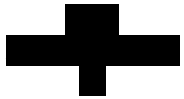
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Scenario 3)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 20.

Table 20: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 3: 12 weeks, MEASURE 2 only)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

A18. Section 4.10.2 of the company submission states that ASAS 5/6 and SF-36 PCS outcomes were analysed. Please provide these results.

Please find the ASAS 5/6 and SF-36 PCS results for both the base case NMA and scenario analyses in Table 21 to Table 28; Table 21 to Table 24 present results of fixed effects models, whilst Table 25 to Table 28 present results of random effects models. Further, please note that random-effects models were not feasible for SF-36 PCS. Cells shaded in light green indicate comparisons that are favourable to secukinumab. Cells shaded in purple indicate comparisons that are not favourable to secukinumab.

Table 21: Base case NMA (12-16 weeks, MEASURE 1 & MEASURE 2) – Fixed Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 22: Scenario 1 (12-16 weeks, MEASURE 2 only) – Fixed Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 23: Scenario 2 (12 weeks, MEASURE 1 & MEASURE 2) – Fixed Effects

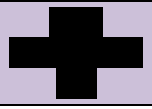
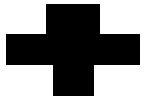
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 24: Scenario 3 (12 weeks, MEASURE 2 only) – Fixed Effects

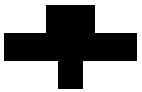
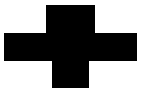
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 25: Base case NMA (12-16 weeks, MEASURE 1 & MEASURE 2) – Random Effects

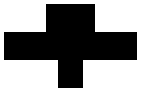
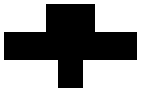
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 26: Scenario 1 (12-16 weeks, MEASURE 2 only) – Random Effects

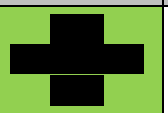
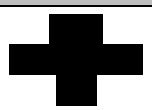
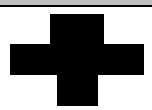
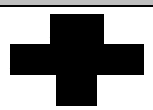
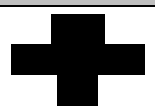
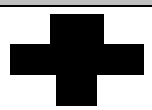
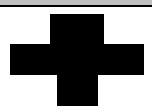
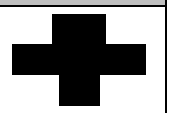
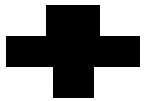
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 27: Scenario 2 (12 weeks, MEASURE 1 & MEASURE 2) – Random Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 28: Scenario 3 (12 weeks, MEASURE 2 only) – Random Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

A19. According to section 4.10.6 the Markov Chain Monte Carlo simulations appear to have been implemented in two different software packages: OpenBUGS and JAGS. Please clarify why 2 different software packages were employed and specify which package was used for which analysis.

The reference to two software packages is an oversight given that in the end all analyses were conducted in JAGS. In the early stages of the project, analyses for the ASAS outcomes were conducted in OpenBUGS, but by the end all analyses were conducted in JAGS.

A20. Section 4.10.7.1 of the company submission reports the predicted absolute response for each treatment for 5 outcomes (ASAS20, ASAS40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline). The analysis methods do not describe how the absolute response was calculated. Please provide full details of how this was calculated.

The primary outputs of Bayesian NMAs were posterior distributions of the relative treatment effects between all interventions in the network for each outcome. In addition, the expected absolute effect (change from baseline for continuous outcomes, proportion for dichotomous outcomes) for each of these outcomes by treatment was modelled by combining the relative treatment effect estimates versus placebo obtained from the NMA with the average outcome with placebo from placebo-controlled trials. For example, change from baseline in continuous outcomes for a given treatment was calculated by adding the mean placebo change from baseline to the posterior distribution of the relative difference between the treatment of interest and placebo. With dichotomous outcomes, transformations were required to go from log odds to proportions. The posterior distributions of modelled outcomes were summarized by the median and 95% credible intervals (CrIs), which were constructed from the 2.5th and 97.5th percentiles. This approach follows the guidance set forth by the NICE Decision Support Unit technical reports.[20, 21]

A21. Section 4.10.8 states that no evidence of inconsistency was found for the base case network. It is unclear from the text which outcome this refers to. According to the network diagrams provided in appendix K there is potential for inconsistency in both the whole population and the biologic naïve population in the ASAS20 networks and the ASAS40 networks (Figures 51-54). In addition, the cited reference describes several methods for the assessment of inconsistency.

- Please specify which method of inconsistency assessment was used.
- Please provide the full results of the inconsistency assessment for each network where inconsistency may be present.

Inconsistency was assessed by comparing direct and indirect evidence. Direct evidence was assessed through independent-means models where we simultaneously obtained pooled estimates for all the different direct comparisons.[22] The findings of a synthesis of direct evidence improved the understanding of the findings of the network meta-analysis where direct and indirect evidence were combined. The DIC was compared between the independent means model, which assumes no consistency, and NMA. Comparing these DICs served as a global test for the assumption of inconsistency. In all cases, the DIC was smaller for the NMA model and no concerns over inconsistency were raised.

In addition to a synthesis of direct evidence, we estimated relative treatment effects for all the possible comparisons in the network based on only indirect evidence using a technique that is called edge-splitting, more commonly referred to as node-splitting.[22] This allowed us to compare direct evidence with the indirect evidence to assess consistency. Edge-splitting was conducted in the ASAS20 and ASAS40 networks, as these were the only networks that contained closed loops of more than one trial. Plots of the estimated indirect and direct effects are provided in Appendix A: Figure 33 to Figure 48.

A22. According to page 140 "...there were very few situations [in this network meta-analysis] in which multiple trials informed a comparison, no formal assessment of heterogeneity was performed."

Please report the I2 values for comparisons involving 2 or more trials, especially MEASURE 1 and 2. For example, the comparison of adalimumab with placebo contained 3 trials so heterogeneity should have been assessed.

I^2 statistics and Cochran's Q statistics for each edge with multiple trials for each outcome have been calculated. Note that the test-based method of calculating confidence intervals for the I^2 statistic require at least three trials. Thus in such cases, no confidence intervals were produced for the I^2 statistic. As can be seen in both Table 29 and Table 30, there was no evidence of concerning heterogeneity outside of the ADA to placebo comparison for SF-36 PCS.

Table 29: Heterogeneity assessment of direct comparisons within the mixed population networks

Outcome	Trials	I^2	Cochran's Q	P-value
BASDAI CfB	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASDAI CfB	ATLAS, Hu (2012), Huang (2014)	[redacted]	[redacted]	[redacted]
BASDAI 50	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASDAI 50	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASFI	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASFI	Hu (2012), Huang (2014), ATLAS	[redacted]	[redacted]	[redacted]
ASAS20	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS20	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS40	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS40	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS 5/6	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS 5/6	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
SF-36	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
SF-36	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]

Table 30: Heterogeneity assessment of direct comparisons within the biologics-naïve population networks

Outcome	Trials	I^2	Cochran's Q	P-value
BASDAI CfB	MEASURE2, MEASURE1	[redacted]	[redacted]	[redacted]
BASDAI CfB	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASDAI 50	MEASURE2, MEASURE1	[redacted]	[redacted]	[redacted]
BASDAI 50	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASFI	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASFI	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS20	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS20	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS40	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS40	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS 5/6	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS 5/6	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
SF-36	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
SF-36	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]

A23. According to page 25, "insufficient data was available to conduct an network meta-analysis in the biologic-experienced only population; outside of the MEASURE 1 and MEASURE 2 studies there is no reported data for TNF-alpha inhibitors in the biologic-experienced population."

- Please provide results for MEASURE 1 and MEASURE 2 in the biologic experienced population.

- The results from MEASURE 1 and 2 in the biologic experienced population are provided in Section 4.8.1 and 4.8.2 of the submission.

We assume this request relates to a pair-wise meta-analysis of the MEASURE 1 and MEASURE 2 studies, results of which are provided in Table 31 and Table 32 below.

Table 31: Meta-analysis results comparing secukinumab to placebo at 12 weeks

Outcome	Effect of SEC relative to Placebo	I^2	Cochran's Q p-value
ASAS20	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]
ASAS 5/6	[redacted]	[redacted]	[redacted]
BASDAI 50	[redacted]	[redacted]	[redacted]
BASDAI CfB	[redacted]	[redacted]	[redacted]
BASFI CfB	[redacted]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects; RE: random effects; RR: relative risk; MD: mean difference; SEC: secukinumab.

Table 32: Meta-analysis results comparing secukinumab to placebo at 16 weeks

Outcome	Effect of SEC relative to Placebo	I2	Cochran's Q p-value
ASAS20	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]
ASAS 5/6	[redacted]	[redacted]	[redacted]
BASDAI 50	[redacted]	[redacted]	[redacted]
BASDAI CfB	[redacted]	[redacted]	[redacted]
BASFI CfB	[redacted]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects; RE: random effects; RR: relative risk; MD: mean difference; SEC: secukinumab.

Matched adjusted indirect comparison

A24. Section 4.10.11 and appendix J report the results of a matching adjusted indirect comparison. Please clarify the following points:

- Why were other studies of adalimumab not considered in this analysis?

Huang 2014 could potentially have been included, as it reports the ASAS20/40 outcomes. However, the MAIC method presented in the original Signorovitch papers focuses on a single trial per treatment. It is not clear that the meta-analysis method is appropriate, especially in cases where the baseline characteristics of the comparator trials (ATLAS and Huang, Table 201 of the submission) are not very similar. Furthermore, the single study comparison clearly compares adalimumab and secukinumab in the setting of the ATLAS trial but the setting of the meta-analysis comparison would be unclear. The ATLAS setting may be most appropriate as licensing/reimbursement decisions for adalimumab were based on its population.

- Why were other comparators not considered for this type of analysis?

Comparison of secukinumab versus adalimumab was prioritised since adalimumab currently has the largest share of the UK biologics market, with 39% of patients receiving adalimumab.

- Why was only MEASURE 2 included, but not MEASURE 1?

The MEASURE 1 trial used unlicensed intravenous administration and weight based dose (10mg/kg) of secukinumab for the loading dose, in contrast to the licensed subcutaneous secukinumab 150mg loading dose used in the MEASURE 2 trial. Since the ATLAS study of adalimumab used subcutaneous administration and MEASURE 2 was the only trial employing the licensed subcutaneous administration route and loading dose, inclusion of MEASURE 2 only was considered appropriate. However, as with the network meta-analyses sensitivity analyses with MEASURE 1 have now also been conducted and show similar results as with MEASURE 2 (see Appendix D: which represents an updated version of Appendix J from our original submission document).

Section B: Clarification on cost-effectiveness data

Model structure and assumptions

B1. **Priority question:** In the base case model, response at 12 weeks was defined as an improvement of 50% or more in BASDAI score from baseline (BASDAI 50). A scenario analysis defined response as a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more.

- In TA383, the appraisal committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British Society of Rheumatology (BSR) guidelines and the previous technology appraisal[23]: a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more. Please present the results of an additional scenario analysis, where the response assessment for treatment continuation takes into consideration the response definition that was adopted in NICE guidance[23], which also includes 2 cm reduction in spinal pain VAS. Please also provide the details regarding the extent to which data on spinal VAS are missing, and what method was used to adjust for the missing data.

The extent of missing data is indicated in Appendix Table 186 of the submission. The same N numbers are available at both 12 and 16 weeks in both MEASURE 1 and MEASURE 2 for classification according to either “BASDAI 50” or “BASDAI 50 or 2 unit drop in BASDAI” definitions. However, between 13% to 19% of patients cannot be included in the N for classification according to “BASDAI 50 or 2 unit drop in BASDAI and VAS reduction of 2cm or more”. This is due to the requirement for patients to have both BASDAI50 ***and*** VAS data available in the database for these analyses. BASDAI 50 analyses provided in Table 186 of the submission are based on observed data with no imputation for missing data.

Available analyses of conditional changes from baseline in BASDAI and BASFI within the sub-groups, based on the alternative definitions of response (“BASDAI 50 or a 2 unit reduction in BASDAI” as well as “BASDAI 50 or a 2 unit reduction in BASDAI plus a 2cm reduction in VAS”) are based on non-responder imputation i.e. patients unable to classified as responders due to missing VAS scores are classed as non-responders.

Pooled MEASURE 1 and MEASURE 2 efficacy data using alternative definitions of response amongst the biologic naïve and biologic experienced sub-groups are presented in Table 33 to Table 35 below.

Table 33: Response rate at week 12 according to alternative definitions of response

	Secukinumab 150mg			Placebo		
	n	N	%	n	N	%
Biologic naive						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: BASDAI change from baseline at week 12 according to alternative definitions of response

	Secukinumab 150mg		Placebo	
	n	CFB	n	CFB
Biologic naïve - responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]

Table 35: BASFI change from baseline at week 12 according to alternative definitions of response

	Secukinumab 150mg		Placebo	
	n	CFB	n	CFB
Biologic naïve - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]

From the above data, estimates of relative changes in efficacy parameters have been calculated and are provided in Table 36 below.

Table 36: Relative efficacy estimates for alternative definitions of response

	BASDAI 50 or 2 unit drop		BASDAI 50 or 2 unit drop + 2 cm VAS drop	
	Active treatment	Conventional care	Active treatment	Conventional care
Biologic naive				
Response rate	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced				
Response rate	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]

Please note two errors have been identified in the original response rate model inputs for Scenario 5:

- Week 16 data, rather than week 12 had been used to determine the proportion of responders
- The relative changes in response rate had been mis-calculated, resulting in reductions to the proportion of responders with the alternative definition of response, rather than increases.

The results of Scenario 5 have therefore been revised in the below results. The changes result in cost-effectiveness results that are further in favour of secukinumab; secukinumab now dominates all comparators except golimumab, whereas previously both golimumab and infliximab generated very slightly greater QALYs than secukinumab.

The results of cost-effectiveness analyses employing all three definitions of response are presented in Table 37 and Table 38, for biologic naïve and biologic experienced populations respectively.

Table 37: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population – comparison of alternative definitions of response

	Base Case – BASDAI 50			BASDAI 50 or 2 unit drop			BASDAI 50 or 2 unit drop + 2 cm VAS drop		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	£15,300	-0.359	SEC dominates	£23,265	-0.471	SEC dominates	£20,182	-0.429	SEC dominates
Certolizumab pegol – with PAS	£9,202	-0.359	SEC dominates	£14,903	-0.474	SEC dominates	£12,725	-0.430	SEC dominates
Etanercept	£2,033	-1.046	SEC dominates	£1,792	-1.378	SEC dominates	£2,027	-1.250	SEC dominates
Etanercept biosimilar	£1,018	-1.046	SEC dominates	£325	-1.378	SEC dominates	£738	-1.250	SEC dominates
Golimumab	£16,703	0.025	£674,914	£25,783	0.029	£874,073	£22,222	0.028	£798,038
Infliximab	£26,223	-0.216	SEC dominates	£37,686	-0.122	SEC dominates	£33,238	-0.153	SEC dominates
Infliximab biosimilar	£22,649	-0.216	SEC dominates	-£32,454	0.122	SEC dominates	£28,658	-0.153	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

Table 38: Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population – comparison of alternative definitions of response

	Conventional care		
	Incr. Costs	Incr. QALYs	ICER
Base Case – BASDAI 50	£1,747	0.778	£2,245
BASDAI 50 or 2 unit drop	£3,704	1.036	£3,574
BASDAI 50 or 2 unit drop + 2 cm VAS drop	£2,938	0.978	£3,004

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

B2. For people who whose disease has not responded to treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, are biologics used as the next line of treatment? If so:

- What proportion of the ankylosing spondylitis population in England use a second biologic after the first has failed?

There are limited data on the proportion of the ankylosing spondylitis population in England that use a second biologic after the first has failed, perhaps reflecting the lack of clear formal guidelines on the sequencing of biologic therapies in AS.

As noted in Section 5.2.2 of our submission, expert clinical feedback gathered during model development suggested that approximately 25% of patients might transition to conventional care rather than a biologic therapy, and that therefore 75% of patients would be expected to use a biologic therapy after failure of the first biologic.

- What proportion use 'conventional' treatment after the first biologic has failed?

As noted above, there are limited sources to estimate the proportion of patients who would go on to use conventional treatment after the first biologic has failed. As described in Section 5.2.2 of our original submission, clinical expert feedback has suggested that 25% of patients experiencing failure of their first-line biologic would be expected to use conventional care.

B3. **Priority question:** When modelling treatment sequencing, an efficacy reduction of 0.55 for the second biologic treatment in the sequence was assumed (Excel model, "Clinical Inputs" sheet, Cell F26). Please explain how the value of 0.55 was derived. Please provide and justify the other assumptions in the modelling of second-line biologics. Include the baseline BASDAI/BASFI values used at the start of second-line treatment and the values used for change from baseline.

Derivation of relative reductions in BASDAI 50, BASDAI change from baseline and BASFI change from baseline are explained in Table 39 to Table 41. Please refer to Tables 45 & 47 in the submission for sub-group data from MEASURE 1 and MEASURE 2.

Table 39: BASDAI 50 relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg			Placebo			Treatment effect (SEC response minus PBO response)	Relative reduction in BASDAI 50 response
	n	N	% response	n	N	% response		
Biologic naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. response rates in the experienced group are (1-0.45) = 0.55 x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 40: BASDAI change from baseline relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg		Placebo		Treatment effect (SEC response minus PBO response)	Relative reduction in BASDAI change from baseline
	n	Change from baseline	n	Change from baseline		
Biologic naive	132	-2.67	122	-0.87	-1.80	(-1.80 – (-1.04)/-1.80 = 41.9% i.e. response rates in the experienced group are (1-0.42) = 0.58 x those of the naïve group
Biologic experienced	56	-1.67	50	-0.62	-1.04	

Table 41: BASFI change from baseline relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg		Placebo		Treatment effect (SEC response minus PBO response)	Relative reduction in BASFI change from baseline
	n	Change from baseline	n	Change from baseline		
Biologic naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. response rates in the experienced group are (1-0.50) = **0.50** x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Another assumption underlying the modelling of second line biologics is that decline in efficacy with TNFα inhibitors when used in an experienced population is the same as that observed in MEASURE 1 and MEASURE 2. There is no randomised controlled data available on efficacy of the TNFα inhibitors when used in biologic experienced patients. Since secukinumab has a different mechanism of action to TNFα inhibitors it seems plausible to assume that the reduction in efficacy observed between naïve and experienced patients treated with secukinumab, all of whom are receiving their first IL-17A inhibitor, will be at least as large as the reduction in efficacy observed between naïve and experienced patients treated with TNFα inhibitors, some of whom will then be taking their second treatment from the same drug class. If the efficacy reduction between naïve and experienced patients is larger for the TNFα inhibitors than for secukinumab, our assumption of an equivalent reduction would disfavour secukinumab in the cost-effectiveness analyses.

B4. On pages 185-186, the company submission highlights a "lack of robust clinical data to support use of the TNF-alpha inhibitors in this setting" as a reason for not comparing secukinumab to TNF-alpha inhibitors in the biologic experienced population. Please explain why non-randomised data was not used to compare secukinumab with TNF-alpha inhibitors in the biologic experienced population in an exploratory analysis.

The NICE Guide to the Methods of Technology Appraisal 2013 states that data from non-randomised studies may be required to supplement RCT data.[24] Due to the considerable body of randomised data that was available for secukinumab and the comparator therapies, it was not felt necessary to supplement the RCT data with non-randomised studies and non-randomised data was not included in the search strategy for the clinical systematic literature review. Furthermore, the inclusion of randomised data sources only in the systematic literature review is consistent with the approach taken by the Assessment Group in the recent MTA of biologic therapies in AS.[25]

Although non-randomised data can be used in the absence of randomised data, and we acknowledge a lack of randomised data in biologic experienced populations, non-randomised data is associated with a number of well-established limitations. The NICE Guide to the Methods of Technology Appraisal 2013 notes a number of issues more frequently associated with non-randomised data, including confounding, lack of blinding and incomplete follow-up.[24] These limitations, amongst others, can result in biased estimates of treatment effect. Taking into account the uncertainty surrounding estimates from non-randomised data, and the methodological difficulties in incorporating this type of data into a NMA, it was considered appropriate to base the main cost-effectiveness analysis of secukinumab in the biologic experienced population on the MEASURE 1 and MEASURE 2 RCTs, and to compare versus conventional care only, based on the placebo arm of these trials.

B5. The model includes an infliximab biosimilar as a comparator, but not the recently approved etanercept biosimilar (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004007/WC500196736.pdf). Please rerun the analyses including the etanercept biosimilar.

At the time of submission, the UK list price for biosimilar etanercept was not available. This has subsequently become available and comparison versus biosimilar etanercept is included in the revised results (see Section E:). Secukinumab dominates biosimilar etanercept in the base case

and all scenarios except one; in which biosimilar etanercept falls in the south-west quadrant, with only a £1,701 saving per QALY lost.

We also omitted to include the certolizumab patient access scheme in our original analyses. The revised analyses incorporate the free loading doses of certolizumab available to the NHS through UCB's patient access scheme. These changes do not impact the overall conclusions of the cost-effectiveness analysis, as secukinumab continues to dominate certolizumab pegol,

Treatment effect in cost effectiveness model

B6. **Priority request:** Different values for the change from baseline in BASDAI scores for biologic naïve patients are reported in table 73 and the Excel model (worksheet "Clinical inputs", Cells "F49:L50").

- Please explain which values are the correct ones and why there is a discrepancy.

The discrepancy between the model and Table 73 in the submission was a mis-labelling issue in an early version of the NMA report. This mis-labelling issue was identified and the correction applied in the model, however, updates to Table 73 were overlooked. Therefore the values in the model were considered correct at the time of submission. Please note they have now been updated to reflect an error identified as a result of clarification question B15.

Revised versions of Table 73 and Table 74 from the submission, reflecting the corrections identified in response to clarification question B15, are presented below. We recognise that the BASDAI change from baseline with infliximab is now greater than the baseline value. This is due to the limitations of assuming a fixed ratio for responder to non-responder changes from baseline (see Estimation of conditional change from baseline in BASDAI and BASFI

), in the absence of conditional data for infliximab. BASDAI values less than zero will be treated as zero within the model.

Table 42. Change from baseline in BASDAI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-4.65	-5.63	-4.49	-4.61	-8.09	-5.35	-
BASDAI 50 non-responders	-1.09	-1.29	-1.03	-0.81	-1.85	-1.38	-
Biologic experienced population							
BASDAI 50 responders	-4.98	-	-	-	-	-	-3.81
BASDAI 50 non-responders	-0.94	-	-	-	-	-	-0.36

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

Table 43. Change from baseline in BASFI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-3.59	-3.96	-3.53	-3.22	-5.16	-4.18	-
BASDAI 50 non-responders	-1.12	-0.98	-0.87	-0.79	-1.27	-0.73	-
Biologic experienced population							
BASDAI 50 responders	-3.79	-	-	-	-	-	-2.73
BASDAI 50 non-responders	-0.73	-	-	-	-	-	0.06

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

- Please explain in detail the calculations in the "Subgroup data" sheet, formulae in columns "M:CU". How were the BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline calculate? Which regression coefficients were used?

Main analysis of biologic experienced population

Rows 11, 17, 51, 57, 91, 97, 131, 137, 171 and 177 relate to the biologic experienced population and utilise data from the pre-specified TNF-IR sub-groups of the MEASURE 1 and MEASURE 2 studies.

Rows 11 & 17 relate to the BASDAI 50 response:

- Column O is the BASDAI 50 response rate at 16 weeks pooled from MEASURE 1 and MEASURE 2 (see Tables 45 & 47 of the submission):
  - Secukinumab 150mg = (5+7)/(28+33) = 12/61 = 19.7%
  - Placebo = (1+1)/(29+33) = 2/62 = 3.2%
- Column P is the Log Odds ratio of BASDAI 50 treatment effect calculated as:
  - Secukinumab 150mg = (LN(19.7%/(1-19.7%))-(LN(3.2%/(1-3.2%))
  - Placebo = LN(3.2%/(1-3.2%)
- Column Q is the standard error of the Log Odds of BASDAI 50 response calculated as:
  - Secukinumab 150mg = 1/SQRT((61*19.7%*(1-19.7%)))
  - Placebo = 1/SQRT((62*3.2%*(1-3.2%)))

Rows 51, 57, 91 & 97 relate to the BASDAI changes from baseline; rows 51 & 57 amongst BASDAI 50 responders, and rows 91 & 97 amongst BASDAI 50 non-responders.

- Column O are weighted averages of change from baseline amongst patients identified as BASDAI 50 responders to secukinumab 150mg and placebo at week 12 in MEASURE 1 and MEASURE 2 (see conditional BASDAI change from baseline data in Table 44 below)
- Column P are the treatment effect coefficients calculated as the differences in change from baseline versus placebo

- Column Q is the standard error of the pooled, weighted changes from baseline for both secukinumab 150mg and placebo. Please note there was an error in the placebo calculations (SE values from MEASURE 2 used as SDs) which has resulted in corrections to the placebo SE values in the model (cells Q57, Q97, Q137, Q177 and equivalent cells in columns AB, AM and AX).

Table 44: Conditional BASDAI Change from baseline from MEASURE 1 and MEASURE 2

BASDAI Change from Baseline	Secukinumab 150mg			Placebo		
	n	Mean CFB	SD	n	Mean CFB	SD
BASDAI 50 responders at 12 weeks						
MEASURE 1	7	-4.48	1.265	3	-3.90	1.782
MEASURE 2	7	-5.48	2.459	2	-3.69	1.068
BASDAI 50 non-responders at 12 weeks						
MEASURE 1	25	-1.04	1.487	24	-0.29	2.143
MEASURE 2	19	-0.81	1.531	24	-0.43	1.499

Rows 131, 137, 171 & 177 relate to the BASFI changes from baseline; rows 131 & 137 amongst BASDAI 50 responders, and rows 171 & 177 amongst BASDAI 50 non-responders

- Explanation for Columns O – P is as above for BASDAI changes from baseline. Conditional BASFI change from baseline data is presented in Table 45.

Table 45: Conditional BASFI Change from baseline from MEASURE 1 and MEASURE 2

BASFI Change from Baseline	Secukinumab 150mg			Placebo		
	n	Mean CFB	SD	n	Mean CFB	SD
BASDAI 50 responders at 12 weeks						
MEASURE 1	7	-3.15	2.411	3	-2.83	2.547
MEASURE 2	7	-4.43	3.243	2	-2.57	0.453
BASDAI 50 non-responders at 12 weeks						
MEASURE 1	25	-0.79	1.531	24	0.10	1.685
MEASURE 2	19	-0.64	1.534	24	0.02	1.597

Biologic naive population

Rows 22-28, 62-68, 102-108, 142-148, 182-188 relate to the biologic naïve population and use data from the naïve network meta-analyses.

Rows 22-28 relate to the BASDAI 50 response:

- Column O is the predicted absolute response rate calculated as:
    - EXP(Sum of Log Odds for active treatment + placebo)/((1+EXP(Sum of Log Odds for active treatment + placebo)))
- Column P is the Logs odds of BASDAI 50 response from the network meta-analyses

- Column Q is the standard error of the Logs odds of BASDAI 50 response from the network meta-analyses

Rows 62-68 and 102-108 relate to the BASDAI changes from baseline; rows 62-68 amongst BASDAI 50 responders, and rows 102-108 amongst BASDAI 50 non-responders.

- Column P is the co-efficient of BASDAI change from baseline treatment effect from the network meta-analyses
- Column Q is the standard error of the BASDAI change from baseline from the network meta-analyses

Estimation of conditional change from baseline in BASDAI and BASFI

- Calculations in row 45 are utilised in Column O, which represent the ratios of BASDAI change from baseline amongst responders versus non-responders.
- Conditional changes from baseline are only available for adalimumab and golimumab (from ATLAS and GO-RAISE respectively, in Table 78 of the assessment report for TA383), as well as for secukinumab (from both MEASURE 1 and MEASURE 2).
- For secukinumab a straight average of the MEASURE 1 and MEASURE 2 ratios was used.
- For comparators with no available conditional change from baseline data, the ratio of change from baseline amongst responders versus non-responders has been assumed to be a straight average of the four trials with available conditional data.
- The available conditional BASDAI change from baseline data, as well as the average ratios, are summarised in Table 46 below.

Table 46: Available ratios of conditional BASDAI changes from baseline

BASDAI Change from baseline	MEASURE 1	MEASURE 2	ATLAS	GO-RAISE	Overall average	MEASURE 1 & 2 average
Responders	-4.77	-4.51	-4.64	-4.74	4.37	4.27
Non-responders	-1.42	-0.99	-0.82	-1.22		
Ratio of responders to non-responders	3.96	4.57	5.66	3.89		

Rows 62-68:

- Column O is the predicted change from baseline amongst responders with a calculation based on the premise that:
    - Overall Δ = (Responder Δ x % responders) + (Non-responder Δ x % non-responders)
- Therefore; Responder Δ = Overall Δ x ((Ratio / (% responders x ratio) + (1 - % responders))

Rows 102-108:

- Column O is the predicted change from baseline amongst non-responders and utilises ratios in row 85 (which are a repeat of those in row 45):
    - Non-responder Δ = Overall Δ x (1 / (% responders x ratio) + (1 - % responders)))

Rows 142-148 and 182-188 relate to the BASFI changes from baseline; rows 142-148 amongst BASDAI 50 responders, and rows 182-188 amongst BASDAI 50 non-responders.

- Columns O, P & Q are as above for BASDAI changes from baseline
- Ratios of BASFI change from baseline amongst responders versus non-responders are at rows 125 and 165.
- The available conditional BASFI change from baseline data, as well as the average ratios, are summarised in Table 47 below.

Table 47: Available ratios of conditional BASFI changes from baseline

BASFI Change from baseline	MEASURE 1	MEASURE 2	ATLAS	GO-RAISE	Overall average	MEASURE 1 & 2 average
Responders	-3.76	-4.28	-2.92	-3.03	4.06	3.21
Non-responders	-1.15	-1.34	-0.72	-0.53		
Ratio of responders to non-responders	3.23	3.19	4.06	5.72		

Exploratory analysis of biologic experienced population

Rows 33-39, 73-79, 113-119, 153-159, 193-199 relate to the biologic experience population and are based on the naïve population network meta-analyses. The data in the Subgroup data sheet are identical to the blocks of cells directly above, relating to the biologic naïve population. When "Model sequential treatment" and "Model decline in efficacy" are set to "Yes" on the Settings sheet, efficacy reductions (as explained in response to B3), are applied with the Markov engines for second line treatments. The efficacy reductions are consistent across all comparators and are based on MEASURE 1 and MEASURE 2 data for biologic naïve vs. biologic experienced patients (see response to B3).

Other columns in the Subgroup data sheet

- Columns M:V relate to the base case NMA scenario which uses data from both MEASURE 1 and MEASURE 2, with data for each trial taken from the primary endpoint where this fell within the 12-16 week window (with the exception of the ASSERT study on infliximab where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab.
- Columns X:AG relate to the NMA scenario which uses data from both MEASURE 1 and MEASURE 2, with data for each trial taken at 12 weeks. This is presented as scenario 6b in the submission.

- Columns AI:AR relate to the NMA scenario which uses only data from MEASURE 2, with data for each trial taken from the primary endpoint where this fell within the 12-16 week window (with the exception of the ASSERT study on infliximab where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab. This is presented as scenario 6a in the submission.
- Columns AT:BC relate to the NMA scenario which uses only data from MEASURE 2, with data for each trial taken at 12 weeks. This is presented as scenario 6c in the submission.
- Columns BE:CU were placeholders for random effects network meta-analyses. Prior to the inclusion of ATLAS and Huang (see response to A16), it was not possible to solve for random-effects models in the biologic naïve networks since none of the comparisons were informed by more than a single trial, so in the original model the random effects columns were not utilised. With the inclusion of ATLAS and Huang in the biologic naïve networks, random effects models are possible, and base case random effects network meta-analysis results are included in columns BE:BN.
- In the latest version of the model, columns BP:CU include the analyses requested at B8;
    - Columns BP:BY reflect the assumption of identical effects across TNFα inhibitors and a fixed effects network meta-analysis (York Assessment Group approach A3)
    - Columns CA:CJ reflect the assumption of identical effects across TNFα inhibitors and a random effects network meta-analysis (York Assessment Group approach A4)
    - Columns CL:CU reflect the assumption of exchangeable effects across TNFα inhibitors (York Assessment Group approach A5)

In the above analyses, trial-specific ratios of responder change from baseline to non-responder change from baseline (at rows 45, 85, 125 and 165) are no longer used. Instead, the average ratio is used for all comparators, to reflect the assumed lack of differentiation between the TNFα inhibitors.

B7. **Priority request:** Baseline BASDAI, BASDAI 50 and absolute BASDAI change from baseline are correlated parameters. BASDAI 50 and absolute BASDAI change from baseline were modelled separately; the dependence of these 2 parameters was not reflected in the probabilistic sensitivity analysis. By contrast, the assessment group for TA383 (herein referred to as York) used joint modelling approaches for BASDAI and BASFI-related treatment outcomes (approaches B and C, see sections 6.1.4 and 6.1.5 as well as appendix 9 of the assessment report for TA383).

Please rerun the economic model using input data based on the results of the network meta-analysis models (including secukinumab), which incorporate dependencies between BASDAI, BASDAI 50 and BASFI. Please follow the approaches B1, B2, C1 and C2 (independent treatment effects) in the York assessment report for TA383.[26]

We have made best efforts at implementing this request. We identified some errors with the winBUGS code provided in Appendix 9 of the York Assessment Group report suggesting the included code may not have been the final version; further detail is provided in Appendix B: .

Although there are some similarities and trends in results excluding the secukinumab data, we were unable to replicate the York results exactly. The reasons for this could be:

- Number of chains, iterations, burn-in etc. MCMC conditions in winBUGS, which are not specified
- Initial values for the prior distribution, which are not specified.

Nonetheless we implemented both Models B and C using random effects and the following MCMC specifications; number of chains=1, Inits generated by winbugs, burn-in=10000, Total iterations =50000.

Please note that these analyses do not use conditional changes from baseline, as our approach to modelling conditional changes differs from the York evidence synthesis model (see Estimation of conditional change from baseline in BASDAI and BASFI

). The outputs from this model are provided in Table 48 to Table 51 below.

Table 48: Modelling approach B: results

	Estimated difference in change score from baseline	Assumed * probability of having a BASDAI50 response, placebo	Predicted probability of having a BASDAI50 response, anti-TNF	OR for BASDAI50 response, anti-TNF vs Placebo
Anti-TNFs	-1.867 (0.8684)	0.1412	0.4389 (0.1448)	6.057 (9.377)
D	-1.868 (0.3147)			
γ	0.7586 (0.2835)			
$\rho placebo$	0.6075 (0.2088)			
ρ**anti-tnf**	0.738 (0.2156)			
DIC	99.470			

Based on a BASDAI baseline score of 6.38 (sd=1.52) and a placebo change score of -0.97 (sd=1.94), which represent the average across trials (weighted by number of patients)

Table 49: Shrunken estimates of treatment effect from model B

	Change in BASDAI
ADA 40 mg	-1.663 (0.1288)
GOL 100 mg	-1.94 (0.2349)
GOL 50 mg	-2.009 (0.2363)
SEC 150 mg	-1.629 (0.1711)
CZP 200 mg	-1.683 (0.239)
CZP 400 mg	-1.61 (0.2283)
ETN 50 QW	-1.237 (0.3104)
INF 5 mg	-3.186 (0.441)

Table 50: Modelling approach C: results

	Estimated difference in change score from baseline	Assumed * probability of having a BASDAI50 response, placebo	Predicted probability of having a BASDAI50 response, anti-TNF	OR for BASDAI50 response, anti-TNF vs Placebo
Effect of anti-TNFs on BASDAI	-1.704 (0.419)	0.1415	0.406 (0.07447)	4.377 (1.745)
Effect of anti-TNFs on BASFI	-1.333 (0.3676)			
D(BASDAI)	-1.703 (0.2724)			
D(BASFI)	-1.332 (0.1952)			
$\gamma BASDAI$	0.4162 (0.1923)			
$\gamma BASFI$	0.2145 (0.1298)			
$\rho placebo$	0.6107 (0.2067)			
ρanti-tnf	0.7281 (0.2146)			
ρm	0.7049 (0.2624)			
σre	0.255 (0.1857)			
DIC	141.757			

Based on a BASDAI baseline score of 6.38 (sd=1.52) and a placebo change score of -0.97 (sd=1.94), which represent the average across trials (weighted by number of patients)

Table 51: Shrunken estimates of treatment effect from model C

	Change in BASDAI	Change in BASFI
ADA 40 mg	-1.682 (0.2684)	-1.271 (0.1853)
GOL 100 mg	-1.723 (0.3293)	-1.389 (0.2601)
GOL 50 mg	-1.744 (0.3338)	-1.409 (0.261)
SEC 150 mg	-1.638 (0.2885)	-1.387 (0.2111)
CZP 200 mg	-1.701 (0.3171)	-1.23 (0.2458)
CZP 400 mg	-1.672 (0.3174)	-1.266 (0.2502)
ETN 50 QW	-1.443 (0.3761)	-1.194 (0.2711)
INF 5 mg	-2.018 (0.5259)	-1.511 (0.3649)

Base case cost-effectiveness results using the above models are provided in Table 52 and Table 53.

Table 52: Based on Model B approach in York report: BASDAI 50 and BASDAI change from baseline correlations

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)

Secukinumab	£112,596	9.159				
Etanercept biosimilar	£116,068	8.647	£3,472	-0.512	Dominated	Dominated
Etanercept	£117,306	8.647	£4,710	-0.512	Dominated	Dominated
Certolizumab pegol – with PAS	£123,470	8.996	£10,874	-0.163	Dominated	Dominated
Adalimumab	£127,205	9.012	£14,609	-0.147	Dominated	Dominated
Golimumab	£129,438	9.260	£16,842	0.101	£167,423	£167,423
Infliximab biosimilar	£137,615	9.205	£25,019	0.045	£551,654	Dominated
Infliximab	£141,328	9.205	£28,732	0.045	£633,529	Dominated

Table 53: Based on Model C approach in York report: BASDAI and BASFI change from baseline correlations

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£116,433	8.868				
Etanercept biosimilar	£116,981	8.561	£547	-0.307	Dominated	Dominated
Etanercept	£118,152	8.561	£1,719	-0.307	Dominated	Dominated
Certolizumab pegol – with PAS	£125,761	8.755	£9,328	-0.113	Dominated	Dominated
Adalimumab	£129,254	8.786	£12,821	-0.082	Dominated	Dominated
Golimumab	£132,705	8.877	£16,272	0.009	£1,739,468	£1,739,468
Infliximab biosimilar	£139,509	8.782	£23,076	-0.086	Dominated	Dominated
Infliximab	£143,019	8.782	£26,586	-0.086	Dominated	Dominated

B8. In TA383, the appraisal committee concluded that TNF-alpha inhibitors were clinically effective compared with placebo and that they should be considered as a class with broadly similar, even if not completely identical, effects.[23] In the company submission for secukinumab there were no statistically significant differences between secukinumab and TNF-alpha inhibitors (except infliximab) for all trial outcomes in the network meta-analyses.

Please rerun the economic model using input data based on the results of the network meta-analysis models, which assume that all TNF-alpha inhibitors have the same treatment effect. Please follow the approaches A3, A4 and A5 in section 6.1.3 and appendix 9 of the York assessment report for TA383.[26]

The JAGS code for the exchangeable effects model is provided in Appendix C:

Cost-effectiveness results for the biologic naïve population based on the York assumptions are provided in Table 54 to Table 56 below. Please note that in these three scenarios a consistent

biologic withdrawal rate has been applied to all comparators; 11% per annum aligned to the York Assessment Group assumption. In both the scenarios in which TNFα inhibitors are assumed to have identical effects, secukinumab dominates the TNFα inhibitors as a class.

Table 54: Based on A3 approach in York report: Identical effects for TNFα inhibitors (fixed effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	[redacted]	9.383				
Etanercept biosimilar	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Etanercept	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Certolizumab pegol – with PAS	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Adalimumab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Golimumab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Infliximab biosimilar	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Infliximab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated

Table 55: Based on A4 approach in York report: Identical effects for TNFα inhibitors (random effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	[redacted]	9.501				
Etanercept biosimilar	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Etanercept	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Certolizumab pegol – with PAS	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Adalimumab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Golimumab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Infliximab biosimilar	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Infliximab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated

Table 56: Based on A5 approach in York report: Exchangeable effects for TNFα inhibitors (fixed effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£112,151	9.516				
Etanercept biosimilar	£123,503	9.204	-£11,352	0.312	Dominated	Dominated
Etanercept	£123,791	9.457	-£11,640	0.059	Dominated	Dominated
Certolizumab pegol – with PAS	£125,290	9.511	-£13,139	0.005	Dominated	Dominated
Adalimumab	£125,737	9.204	-£13,586	0.312	Dominated	Dominated
Golimumab	£126,511	9.382	-£14,360	0.134	Dominated	Dominated
Infliximab biosimilar	£139,226	9.653	-£27,074	-0.137	£197,687	£197,687
Infliximab	£143,140	9.653	-£30,989	-0.137	£226,269	Dominated

B9. Please provide all relevant input data for the model so that the other approaches described in the York assessment report for TA383 (A1-5, B3-5, C3-5) can be conducted.

The requested data and treatment / study codes are provided in Table 57 to Table 60 .

Table 57: Data table for Model B

s[]	t[]	n[]	r[]	b[]	prec[]	y[]	y.prec[]
1	2	208	94	6.3	1.7	-2.6	0.207
1	1	107	17	6.3	1.7	-0.8	0.206
2	3	140	56	6.9	1.5	-2.69	0.216
2	4	138	61	6.5	1.6	-2.83	0.216
2	1	78	12	6.6	1.5	-0.69	0.216
3	2	229	114	6	1.4	-2.8	0.127
3	1	115	19	6.2	1.4	-1.4	0.179
4	1	122	10	6.5	1.5	-0.59	0.18
4	5	125	47	6.4	1.6	-2.32	0.172
5	1	74	8	6.8	1.3	-0.85	0.252
5	5	72	22	6.6	1.5	-2.19	0.248
6	6	65	27	6.5	1.7	-2.6	0.224
6	7	56	23	6.2	1.3	-2.5	0.212
6	1	57	6	6.4	1.9	-1.1	0.174
7	8	39	18	6.4	1.2	-2.6	0.324
7	1	43	10	5.8	1.5	-1.4	0.32
8	8	25	NA	6.6	1.1	-1.16	0.216
8	9	25	NA	6.5	1.2	-3.39	0.216
9	2	26	NA	5.9	1.4	-3.6	0.216
9	1	20	NA	6.2	1.1	-2	0.216

Table 58: Data table for Model C

s[]	t[]	n[]	r[]	b[]	prec[]	y[]	y.prec[]	y.f[]	y.prec.f[]
1	2	208	94	6.3	1.7	-2.6	0.207	-1.86	0.156
1	1	107	17	6.3	1.7	-0.8	0.206	-0.45	0.225
2	3	140	56	6.9	1.5	-2.69	0.216	-1.55	0.208
2	4	138	61	6.5	1.6	-2.83	0.216	-1.63	0.208
2	1	78	12	6.6	1.5	-0.69	0.216	0.06	0.208
3	2	229	114	6	1.4	-2.8	0.127	-1.75	0.135
3	1	115	19	6.2	1.4	-1.4	0.179	-0.47	0.154
4	1	122	10	6.5	1.5	-0.59	0.18	-0.37	0.171
4	5	125	47	6.4	1.6	-2.32	0.172	-1.84	0.165
5	1	74	8	6.8	1.3	-0.85	0.252	-0.68	0.235
5	5	72	22	6.6	1.5	-2.19	0.248	-2.15	0.231
6	6	65	27	6.5	1.7	-2.6	0.224	-1.8	0.224
6	7	56	23	6.2	1.3	-2.5	0.212	-1.9	0.232
6	1	57	6	6.4	1.9	-1.1	0.174	-0.8	0.164
7	8	39	18	6.4	1.2	-2.6	0.324	-2.2	0.292
7	1	43	10	5.8	1.5	-1.4	0.32	-1	0.288
8	8	25	NA	6.6	1.1	-1.16	0.216	-1.49	0.208
8	9	25	NA	6.5	1.2	-3.39	0.216	-2.6	0.208
9	2	26	NA	5.9	1.4	-3.6	0.216	-1.9	0.208
9	1	20	NA	6.2	1.1	-2	0.216	-1	0.208

Table 59: Treatment codes

PBO	1
ADA 40 mg	2
GOL 100 mg	3
GOL 50 mg	4
SEC 150 mg	5
CZP 200 mg	6
CZP 400 mg	7
ETN 50 QW	8
INF 5 mg	9

Table 60: Study codes

ATLAS	1
GO-RAISE	2
Huang (2014)	3
MEASURE-1	4
MEASURE-2	5
RAPID-axSpA	6
SPINE	7
Giardina (2010)	8
Hu (2012)	9

B10. According to table 70, BASDAI 50 responses for biologic naïve patients are obtained from the network meta-analysis results (figure 26). However, results reported in table 70 differ from the results in figure 26. Please explain these differences and clarify how average values were calculated when corresponding outcomes for a comparator were lacking in the network meta-analysis.

An update to Table 70 was overlooked following identification of the mis-labelling issue mentioned at B6. The values in the original model (Clinical inputs sheet, cells F22:L22) were within 0.1% of the values in Figure 26. An updated version of Table 70, reflecting the updates to the NMA described at A16, is provided below in Table 61. For the included comparators, these figures align with the values in Figure 10 of this response to within 0.1%. The value for adalimumab differs very slightly due to rounding within the calculations.

Table 61. BASDAI 50 response applied in the model base case

Therapy	BASDAI 50 response for the modelled biologic naïve population	BASDAI 50 response for the modelled biologic experienced population
Secukinumab 150 mg	[redacted]	[redacted]
Adalimumab	[redacted]	
Etanercept	[redacted]	
Golimumab	[redacted]	
Infliximab	[redacted]	

Certolizumab pegol	[redacted]	
CC	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care.

For comparators missing from the network meta-analysis, the log odds of BASADI 50 response was assumed to be a straight average of log odds of BASADI 50 response for available TNFα inhibitors was assumed.

B11. The BASDAI 50 responses for TNF-alpha inhibitors (Table 70) appear to be inconsistent with the results in the York assessment report for TA383 (Table 7).[26] Please explain why they are different.

There are several potential sources of differences between the results using our model versus those generated by the York assessment group report:

- The NMA informing our cost-effectiveness model is based exclusively on studies reporting efficacy of biologic treatments amongst biologic naïve populations. The York assessment group did not differentiate between evidence for biologic naïve versus mixed populations (no evidence amongst biologic experienced populations was available to them since there is no published data on TNFα inhibitors in biologic experienced sub-groups).
- There are some differences in the studies which were included in the NMA, the results of which inform the model parameters (please see Table 48 of the submission and Table 2 of the York assessment report).[25] In the recent MTA in AS, 20 trials were eligible for inclusion in the NMA, 19 of which recruited an AS patient population, and one trial that recruited an AS and non-radiographic axial spondyloarthritis (nr-axSpA) population.[25] By comparison, the NMA presented in this submission included only 10 trials; studies such as Barkham et al. 2010; Calin et al. 2004 and Davis et al. 2003 were included in the MTA NMA but not included in the NMA presented in this submission. The reason for exclusion of these studies from our NMA is that it was unclear whether the populations included were intolerant or had inadequate response to conventional treatments. These differences are likely to be responsible for any differences seen in the NMA results.
- The York Assessment Group had access to additional conditional response data for etanercept and certolizumab, which was redacted in the report (Table 78) and addendum (Appendix page 10).[25, 27]
- Conditional baseline and changes from baseline in BASDAI and BASFI within the York model base case are derived from their synthesis model. Comparison of Tables 77 and 78 in the York Assessment Group report suggest that this model provides poor predictions for conditional baseline BASDAI scores.[25] In contrast conditional baseline scores within the submitted model are based on patient-level analyses of the secukinumab trial data.

B12. In TA383, recommendations were based on severe active ankylosing spondylitis. However, the inclusion criteria for MEASURE 1 and MEASURE 2 were not limited only to "severe" active ankylosing spondylitis. The scope for secukinumab is for adults with active ankylosing spondylitis.

Were any of the values used in the company model, which came from TA383[23] or the York assessment repor[t26] adjusted for the severity of the ankylosing spondylitis?

As discussed in response to Question A1, there is no agreed consensus on the terms used to classify the severity of AS. The scope, the licensed indication for secukinumab and clinical guidelines all refer to adults with active ankylosing spondylitis and as a result data were not adjusted according to severity.

B13. The text above table 71 suggests that the difference in baseline BASDAI and BASFI scores between responders and non-responders was based on response at week 12. However, the text following table 72 suggest that response was derived from pooled data from the MEASURE 1 and MEASURE 2 trials, which suggests that response at week 16 was used.

- Please specify the definition, including time point, of response used to differentiate between responders and non-responders when estimating baseline BASDAI and BASFI scores in table 72.

Within the model, response, defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the baseline total BASDAI score, is always assessed at week 12, based on NICE guidance and BSR guidelines.[5, 28] Different network meta-analyses inform the probability of patients on each treatment meeting this response criterion;

  - Network meta-analyses used for the base case and scenario 6a employ data for each trial taken at the primary endpoint where this fell within the 12-16 week window (the only exception being the infliximab ASSERT study where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab.
  - Network meta-analyses used for scenarios 6b and 6c, employed 12 week data for all comparators. Post hoc analyses of MEASURE 1 and MEASURE 2 informed these network meta-analyses.

However, regardless of the NMA data selected to model response probabilities, the model applies response assessment at 12 weeks.

- Please provide the number of patients (n) for each result in table 72.
- Please provide response-based BASDAI and BASFI figures not differentiated by treatment.

A revised version of Table 72 is provided below, including n numbers and conditional baseline BASDAI and BASFI scores for all responders and non-responders, regardless of treatment arm.

Table 62. Treatment-specific baseline BASDAI and BASFI conditional on BASDAI 50 response

Input	Biologic naïve						Biologic experienced					
	Biologics		CC		Pooled		Biologics		CC		Pooled	
	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score
Baseline BASDAI												
Responders	51	6.42	22	6.12	73	6.33	14	6.59	5	6.24	19	6.50
Non-responders	85	6.39	112	6.73	197	6.58	47	6.48	57	6.61	104	6.55
Baseline BASFI												
Responders	51	5.44	22	4.75	73	5.23	14	5.39	5	5.49	19	5.42
Non-responders	85	6.07	112	6.22	197	6.15	47	6.04	57	5.85	104	5.93

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care.

In the Excel model, the same baseline BASDAI and BASFI scores (given in table 72) are used even though different secukinumab trial data (week 12 and week 12-16) were chosen (sheet “Settings”, range “E60:F60”).

- Please provide BASDAI 50 response specific baseline BASDAI and BASFI scores based on different (week 12 or week 12-16) time point responses.

As discussed above, response was always defined at week 12 within the model. All conditional response analyses have defined responders at 12 weeks, not 16 weeks. There is no difference in baseline scores depending on choice of network meta-analysis scenario.

B14. Section 5.3.3.1 is difficult to follow. Please provide a step by step explanation showing all formulae used to calculate mean change in BASDAI and BASFI from the various sources (MEASURE 1 & 2 trials, network meta-analyses, York assessment report[26], TA383[23] and any other sources).

Please see explanation at B6 regarding the Subgroup data sheet, specifically the “Estimation of conditional change from baseline in BASDAI and BASFI

” onwards.

B15. By definition, the absolute BASDAI change from baseline at 3 months for the BASDAI 50 responders should be at least 50% of their baseline BASDAI. However, this does not appear to be the case for some of the model inputs (e.g. etanercept, adalimumab and conventional care; (tables 72 and 73).

Please explain this discrepancy for BASDAI 50 responders.

This question has led to the identification of an error in the way that NMA outputs were applied within the Subgroup Data sheet of the model. An original set of NMA results required placebo responses to be deducted from each comparator before entering the data into the model. In subsequent NMA results, this calculation had already been applied. However, a miscommunication resulted in placebo responses being once more deducted during data entry to

the model. Hence, placebo responses were effectively being deducted twice from comparator changes from baseline in the original version of the model. See response to B6 for updated versions of Tables 72 & 73. Updated results, which are now further in favour of secukinumab, are provided in Section E:.

B16. In the Excel model, differing baseline BASDAI and BASFI scores are used in subgroup (biologic experienced and biologic naïve) and scenario (only MEASURE 2 trial data as a data source for secukinumab) analyses.

Please justify why other baseline characteristics (age, weight and percentage males) are not varied in these subgroup/scenario analyses.

Amending patient baseline characteristics based on choice of NMA scenario was not prioritised as we did not anticipate these differences would have a material impact on results. A comparison of baseline characteristics pooled across MEASURE 1 and MEASURE 2 versus from MEASURE 2 alone is provided in Table 63 below.

Table 63: Baseline patient characteristics, pooled data vs MEASURE 2 only

	MEASURE 1 & 2 pooled (used in base case and Scenario 6b)	MEASURE 2 only (used in scenarios 6a and 6c)
% male	69.5%	69.9%
Mean age (years)	42.37	43.31
Mean weight (kg)	78.20	81.34
Weight SD (kg)	16.882	16.887

Comparison of results the MEASURE 2 scenario analyses (6a and 6c), utilising the MEASURE 2 specific baseline characteristics vs pooled baseline characteristics are provided in Table 64 and Table 65 below.

Table 64: Incremental costs, incremental QALYs and ICERs for Scenario 6a, with pooled baseline characteristics vs. MEASURE 2 baseline characteristics

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	-£17,762	0.095	SEC dominates	-£17,704	0.092	SEC dominates
Certolizumab pegol – with PAS	-£11,829	0.133	SEC dominates	-£11,779	0.129	SEC dominates
Etanercept	-£4,029	0.877	SEC dominates	-£3,978	0.870	SEC dominates
Etanercept biosimilar	-£2,948	0.877	SEC dominates	-£2,897	0.870	SEC dominates
Golimumab	-£19,009	-0.318	£59,771	-£18,925	-0.317	£59,737
Infliximab	-£30,252	0.072	SEC dominates	-£31,537	0.066	SEC dominates
Infliximab biosimilar	-£26,472	0.072	SEC dominates	-£27,628	0.066	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab **Abbreviations:** ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

Table 65: Incremental costs, incremental QALYs and ICERs for Scenario 6c, with pooled baseline characteristics vs. MEASURE 2 baseline characteristics

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	-£11,280	0.312	SEC dominates	-£11,207	0.307	SEC dominates
Certolizumab pegol – with PAS	-£4,768	0.367	SEC dominates	-£4,702	0.361	SEC dominates
Etanercept	£834	1.056	£790*	£903	1.046	£863*
Etanercept biosimilar	£1,796	1.056	£1,701*	£1,863	1.046	£1,781*
Golimumab	-£9,880	0.065	SEC dominates	-£9,788	0.063	SEC dominates
Infliximab	-£20,730	0.293	SEC dominates	-£21,823	0.286	SEC dominates
Infliximab biosimilar	-£17,450	0.293	SEC dominates	-£18,431	0.286	SEC dominates

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab. **Abbreviations:** ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

B17. BASDAI and BASFI change from baseline of TNF-alpha inhibitors in tables 73 and 74 appear to be inconsistent with the results reported in the York assessment report for TA383 (for example table 69 on page 167 of the York report).[26] Please explain these differences.

As discussed in response to Question B11, results would be expected to differ from those in the York assessment report due to the fact that different studies were included in the respective NMAs.

B18. Please provide details of the methods used to derive the values in table 73 of the company submission (especially for etanercept, certolizumab pegol and infliximab).

Please see explanation at B6 regarding application the Subgroup data sheet, specifically the "Estimation of conditional change from baseline in BASDAI and BASFI

" onwards.

B19. Please explain how the value of 0.15 for the annual BASFI progression rate for secukinumab (section 5.3.3.2, second paragraph on page 193) was derived from Ramiro et al. and MEASURE 1 week 104 rates.[29]

Haroon et al. report that the relative rate of mSASSS change with TNFα inhibitors is 0.42 i.e. the ratio of mSASSS change with TNFα inhibitors to mSASSS change with conventional care is 0.42.[30]

Over two years of treatment with secukinumab, mean mSASSS change of 0.3 units was observed (see Section 4.7.2.4 of submission). Assuming linear progression, which is supported by Ramiro et al., who found that "At the group level, a linear time course model fitted the data best", the estimated annual rate of mSASSS change with secukinumab is 0.3 / 2 = 0.15 units.[31]

Ramiro et al. provide an estimate for the background annual rate of mSASSS change, across the total cohort studied, of 0.98 mSASSS units.[31]

The relative rate of mSASSS change with secukinumab was therefore calculated as 0.15 / 0.98 = 0.15.

It should be noted that the York Assessment Group selected a higher background mSASSS progression rate, from a sub-group of patients within the Ramiro et al. study;[31] those with a baseline mSASSS≥10, who had an annual rate of mSASSS change of 1.44 units. Had this higher background rate been assumed, the relative rate of mSASSS change with secukinumab would have been even lower (0.15 / 1.44 = 0.10), and cost-effectiveness results more strongly in favour of secukinumab.

Adverse events

B20. Please justify why switching to a second TNF-alpha inhibitor was not allowed following an adverse event.

Within the model exploratory analysis in which biologic sequencing was incorporated, patients experiencing a serious adverse event on their first biologic were modelled to discontinue this biologic in line with BSR guidelines that biologic therapy should be withdrawn upon evidence of

severe adverse events or evidence of inefficacy.[5] However, patients experiencing an adverse event *were* permitted to switch to a second biologic therapy. Page 181 explains that second line TNFα inhibitors were only included in the exploratory sequencing analyses; "In the base case analysis of the biologic naïve population, transition to conventional care occurred on biologic discontinuation as it was assumed that patients could not receive a second-line biologic therapy". In the exploratory sequencing analyses all discontinuations switched to the "basket" therapy. Page 188 mentions that the included discontinuations could be for any reason: "Within the model, this [withdrawal of TNFα inhibitors upon development of severe adverse events or evidence of inefficacy] is captured by discontinuation of biologic therapy, which could be for any reason including adverse events or loss of efficacy". We acknowledge that this was not may not have been made sufficiently explicit in the write-up of the economic model, but clarify here that patient movement to a second-line biologic was permitted following discontinuation of a first biologic due to an adverse event.

Utilities

B21. Priority request: Please provide the details of the methods used to generate the utility regression equation (section 5.4.5.4, page 198) used for mapping to EQ-5D.

- Please provide details of the regression models considered, the explanatory variables assessed, and the variable selection method used to obtain the final model.

A linear mixed model was used to fit EQ-5D utility score as a response variable with BASDAI, BASFI, age and sex as predictors. The choice of predictive variables was aligned to the MacLeod 2007 and Wailoo 2015 utility analyses in ankylosing spondylitis.[32, 33] The effect of correlation within the data was explored using subject as a random effect to account for the within-subject correlation between assessments.

- Please provide all related regression outputs, e.g. coefficients, test scores and goodness of fit.

The requested data is provided in Table 66 and
Table 67 below.

Table 66: EQ-5D Utility Model Outputs: MEASURE 1 & MEASURE 2, Full Analysis Set

		Estimate (SE)	95% CI	p value
Intercept		0.9610 (0.02503)	0.9118, 1.0101	<.0001
BASDAI score		-0.0442 (0.00312)	-0.0503, -0.0380	<.0001
BASFI score		-0.0330 (0.00316)	-0.0391, -0.0268	<.0001
Sex	**Male**	-0.0111 (0.01335)	-0.0374, 0.0151	0.4049
	Female	reference		
Age (years)		-0.0005 (0.00049)	-0.0015, 0.0005	0.2939

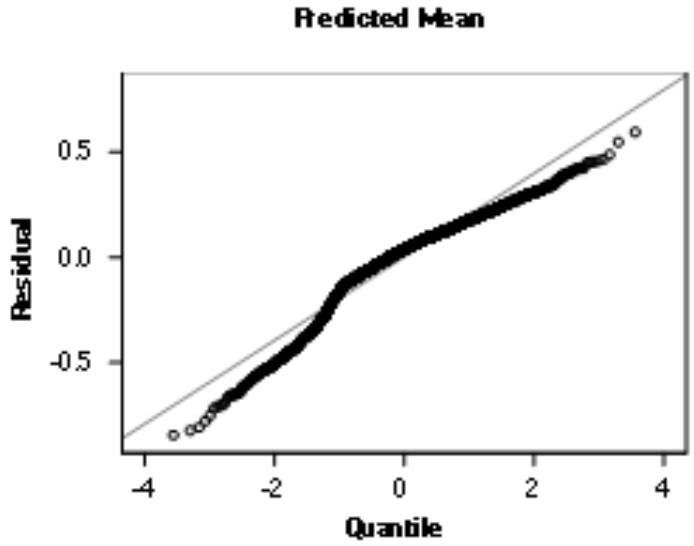
Table 67: EQ-5D Utility Model Fit Statistics: MEASURE 1 & MEASURE 2, Full Analysis Set

Objective / Log likelihood	-2098.6
AIC	-2094.6

- Please provide a Q-Q plot for all 3 utility regression methods (MEASURE 1-2 model, Wailoo et al. 2015 method and McLeod et al. 2007 method) to compare the 3 utility mapping models.[34, 35]

The Q-Q plot for the utility model generated from the MEASURE 1 and MEASURE 2 trial data is provided in Figure 2.

Figure 2: Q-Q plot for the utility model generated from MEASURE 1 and MEASURE 2 trial data



Wailoo et al. 2015 and McLeod et al. 2007 are published algorithms.[32, 33] Since the patient level data from which these algorithms were generated is not available, it is not possible to provide Q-Q plots for them. However, the Wailoo et al. paper include some similar information regarding observed versus predicted EQ-5D utility scores, which is provide in Table 68 below.[33]

Table 68: Observed versus predicted EQ-5D utility scores for the Wailoo et al. linear algorithm.

Percentiles	Observed	Linear Model
1%	-0.184	-0.160
5%	-0.016	0.054
10%	-0.003	0.170
25%	0.516	0.363
50%	0.689	0.570
75%	0.796	0.765
90%	0.883	0.935
95%	1.000	1.033
99%	1.000	1.213

Costs

B22. Please update the cost regression (section 5.5.5, page 157) used for active disease health state according to 2016 NHS prices.

Please check the study on which this regression method is based and whether the assumptions of the regression model are still relevant for the UK clinical setting.[36]

The value of £1,284.19 applied in the cost regression was taken directly from the York assessment report, for consistency with TA383. The cost year for this value is not determinable from the assessment report, with this value being referenced to the Abbvie submission.

We would highlight that the results of the deterministic sensitivity analysis (Figure 43 in our original submission), in which the intercept value of the cost regression equation (£1,284.19) was varied, did not find this model parameter to be a key cost driver. Further detail on the results of one-way sensitivity analyses of both the regression intercept and BASFI co-efficient are provided in Table 69 below. In these analyses the cost equation intercept was varied between a lower bound of £929.35 and an upper bound of £1774.50, whilst the BASFI co-efficient was varied between a lower bound of 0.139 and an upper bound of 0.287. Therefore, a small update to this figure based on inflation would not be anticipated to influence the overall conclusions of the cost-effectiveness analyses.

Table 69: OWSA of both cost regression parameters

	Total cost with upper bound	Total cost with upper bound	Total QALYs	ICER vs baseline with upper bound	ICER vs baseline with lower bound
Cost equation intercept					
Secukinumab	£148,501	£87,680	9.805		
Adalimumab	£165,141	£102,011	9.446	SEC dominates	SEC dominates
Certolizumab pegol – with PAS	£159,371	£95,675	9.447	SEC dominates	SEC dominates
Etanercept	£154,287	£86,997	8.759	SEC dominates	£653*
Etanercept biosimilar	£153,272	£85,982	8.759	SEC dominates	£1,623*
Golimumab	£165,437	£104,215	9.830	£684,332	£668,098
Infliximab	£176,149	£112,873	9.590	SEC dominates	SEC dominates
Infliximab biosimilar	£172,574	£109,299	9.590	SEC dominates	SEC dominates
BASFI co-efficient					
Secukinumab	£170,627	£78,601	9.805		
Adalimumab	£189,179	£92,017	9.446	SEC dominates	SEC dominates
Certolizumab pegol – with	£184,278	£85,352	9.447	SEC dominates	SEC dominates

PAS					
Etanercept	£182,268	£75,232	8.759	SEC dominates	£3,220*
Etanercept biosimilar	£181,253	£74,217	8.759	SEC dominates	£4,190*
Golimumab	£188,289	£94,870	9.830	£713,655	£657,355
Infliximab	£201,222	£102,566	9.590	SEC dominates	SEC dominates
Infliximab biosimilar	£197,648	£98,991	9.590	SEC dominates	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab.

B23. The drug acquisition costs are the same as those in the York assessment report for TA383, from 2014.[26] Please verify that these drug prices have not changed since 2014.

All drug acquisition costs have been verified against the BNF 2016 [online] and no changes to the drug prices for certolizumab pegol, etanercept, adalimumab, infliximab or golimumab have been made since 2014.[37] Since our submission was sent to NICE on February 5th 2016, a list price for biosimilar etanercept has become available – Benepali is priced at 1 x 1 ml = £164.00; 4 x 1ml = £656.00. Therefore we have now updated the acquisition costs to include this information (Table 70). As mentioned at B5, cost-effectiveness analyses are now provided versus biosimilar etanercept (see Section E:). Secukinumab dominates biosimilar etanercept in the base case and all scenarios except one; in which biosimilar etanercept falls in the south-west quadrant, with only a £1,701 saving per QALY lost.

Table 70: Unit costs associated with drug acquisition – etanercept biosimilar added

Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
Acquisition costs						
List price: £1,218.78 per pack of two 150 mg pre-filled syringes/ SensoReady® pens **PAS price:** [redacted] per pack of two 150 mg pre-filled syringes/ SensoReady® pens	£357.50 per 200 mg pre-filled syringe The NICE MTA in AS also indicates that there is an agreed PAS with the department of health for certolizumab pegol, such that the first 12 weeks of treatment are provided free. This PAS is taken	**Originator Etanercept:** £178.75 per 50 mg pre-filled syringe **Biosimilar Etanercept:** Benepali: £164.00 per 50mg/ml solution for injection in pre-filled syringe or	£352.14 per 40 mg pre-filled syringe	**Originator infliximab:** Remicade®: £419.62 per 100 mg vial Average cost per dose calculated as £1,850.59 – see "Infliximab cost calculations"	£762.97 per pre-filled syringe Although the 100 mg pre-filled syringe of golimumab has a higher list price than that of golimumab 50 mg, a PAS has been agreed with the department	BNF 2016 and MIMS

	into account in the cost-effectiveness analysis.	pre-filled pen, 1 x 1ml=£164.00		**Biosimilar infliximab:** Remsima: £377.66 per 100 mg vial Inflectra: £377.66 per 100 mg vial Average cost per dose calculated as £1,665.54 – see "Infliximab cost calculations"	of health that provides the 100 mg dose of golimumab at the same price as the 50 mg dose.	

Abbreviations: AS, ankylosing spondylitis; BNF, British National Formulary; PAS, patient access scheme; MIMS, Monthly Index of Medical Specialties; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; QW, once a week.

B24. Please explain the calculation methods for the number of doses for all interventions (especially for certolizumab pegol) (Excel Model Sheet "Resource Use Inputs", Range G15:I20).

See Table 68 of the submission for details of the posology secukinumab and biologic comparators.

Secukinumab and golimumab are dosed monthly so the number of doses reflects the number of months per 3 month period (with an increased number of secukinumab doses in the first 3 months reflecting the loading doses).

For certolizumab pegol and adalimumab adjustments were applied to account for fortnightly dosing, given that model cycles reflect periods of 3 calendar months.

The calculation of the number of fortnights per 3 month model cycle is:

- Number of weeks per year = 365.25 / 7 = 52.18
- Number of fortnights per year = 52.18 / 2 = 26.09
- Number of fortnights per 3 month model cycle = 26.09 / 4 = 6.52

For certolizumab pegol, the double doses required at loading were accounted for by multiplying the number of fortnights in the first 3 months by 150%. This does over-estimate the certolizumab doses during the first 3 months since loading is only required for the first 3 doses. However, these dose assumptions do not account for the patient access scheme in place for certolizumab pegol. In the revised analyses (see Section E:) the number of doses for certolizumab pegol in the

first 3 months has been reduced to zero, to reflect that the NHS does not incur drug acquisition costs for these doses. Simultaneously, the oversight of not applying the adjustment to the subsequent 3 month periods for certolizumab pegol has been corrected. These changes do not impact the overall conclusions of the cost-effectiveness analysis, as secukinumab continues to dominate certolizumab pegol,

The same adjustment was applied for etanercept and infliximab in subsequent 3 month periods, based on 4-weekly dosing and 8-weekly dosing, respectively. Whilst the adjustment could also be applied to the first 6 month periods for etanercept and infliximab (and would favour secukinumab), the impact on results will be negligible since these small adjustments only relate to a small proportion of the total model time horizon.

B25. According to the NHS choices website, surgery is part of the treatment pathway. The model does not include costs related to surgeries. Please justify the assumption of excluding surgery costs.

Surgery costs were not explicitly included in the model based on the fact that the York assessment report for TA383 did not include the cost of surgery.[25] In addition, the disease-related costs derived from the Boonen et al. study reflect hospital admissions and therefore include surgery costs.[38]

Validation

B26. Please provide a table similar to table 110 for the comparison of total QALYs in the company model for secukinumab and the York model for TA383. Please provide a comparison for disaggregated costs in table 110.

A comparison with QALYs reported for TA383 is provided in Table 71.

Table 71: Comparison of total QALYs by intervention in submission model and York model in AS

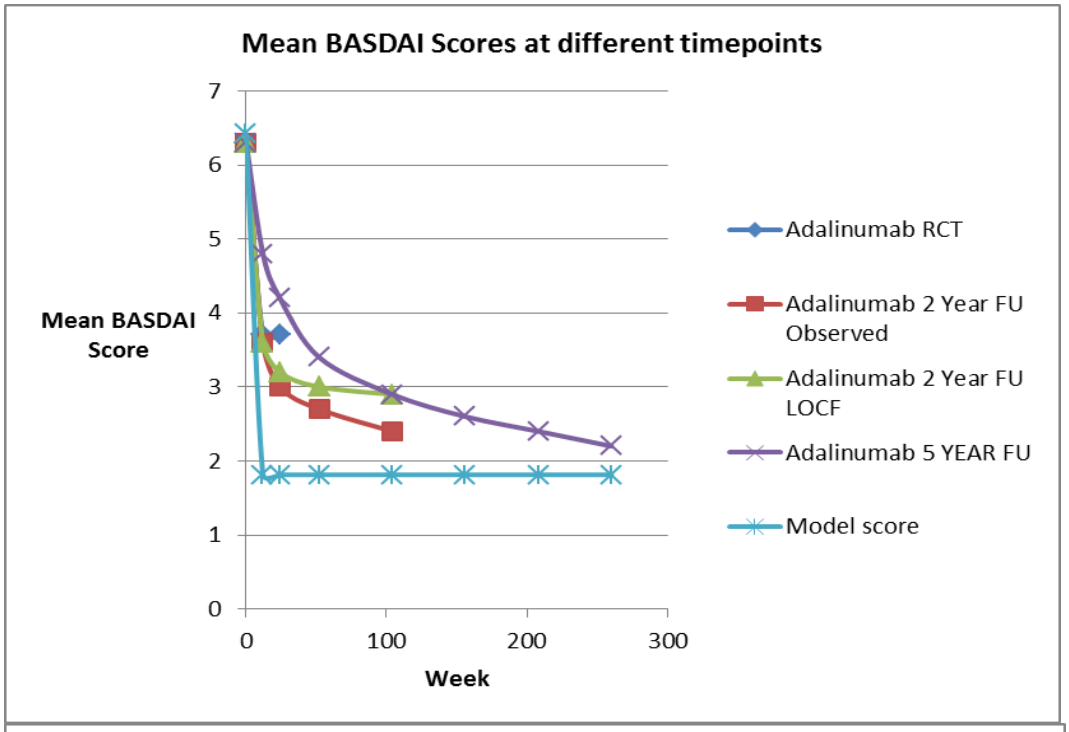
	Total QALYs – model presented in this submission	Total QALYs – York model in AS (base case)
Conventional care	8.537	7.245
Etanercept	8.759	8.163
Certolizumab pegol – with PAS	9.447	8.163
Adalimumab	9.446	8.163
Golimumab	9.830	8.163
Infliximab	9.590	8.163

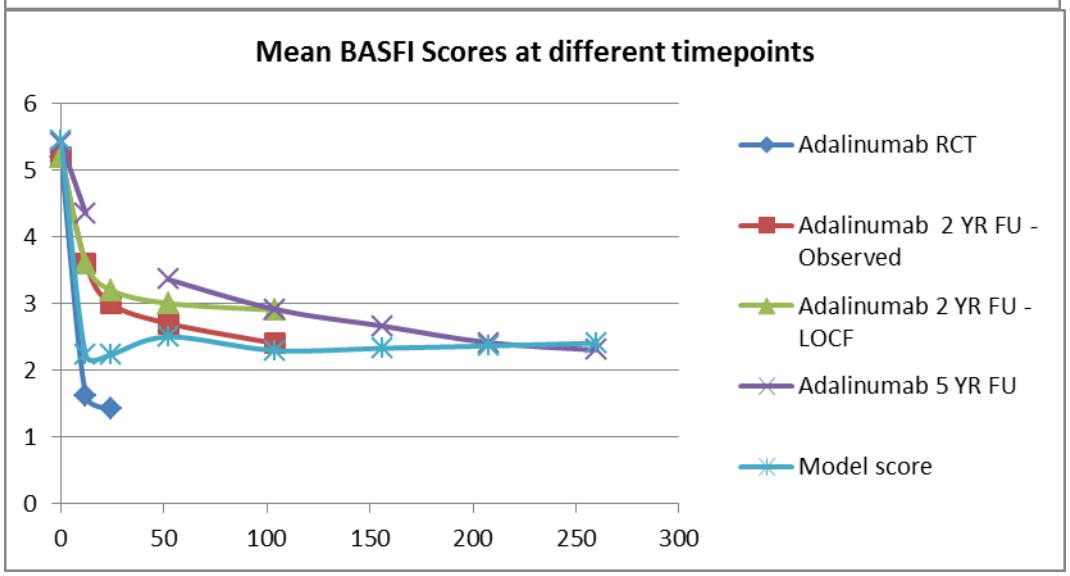
No comparison with disaggregated costs is possible, since these are not reported in the assessment report for TA383.

B27. Please provide a figure that compares the average BASDAI and BASFI scores at different time points from the model with average BASDAI and BASFI scores at different time points from relevant clinical trials.

Please find below figures comparing the average BASDAI and BASFI scores over time from relevant clinical trials versus the cost-effectiveness model. The general trend is that the model is predicting lower BASDAI and BASFI scores than have been observed in clinical trials, due to the model assumption that non-responders discontinue biologic treatment, whilst within clinical trials both responders and non-responders continue treatment.

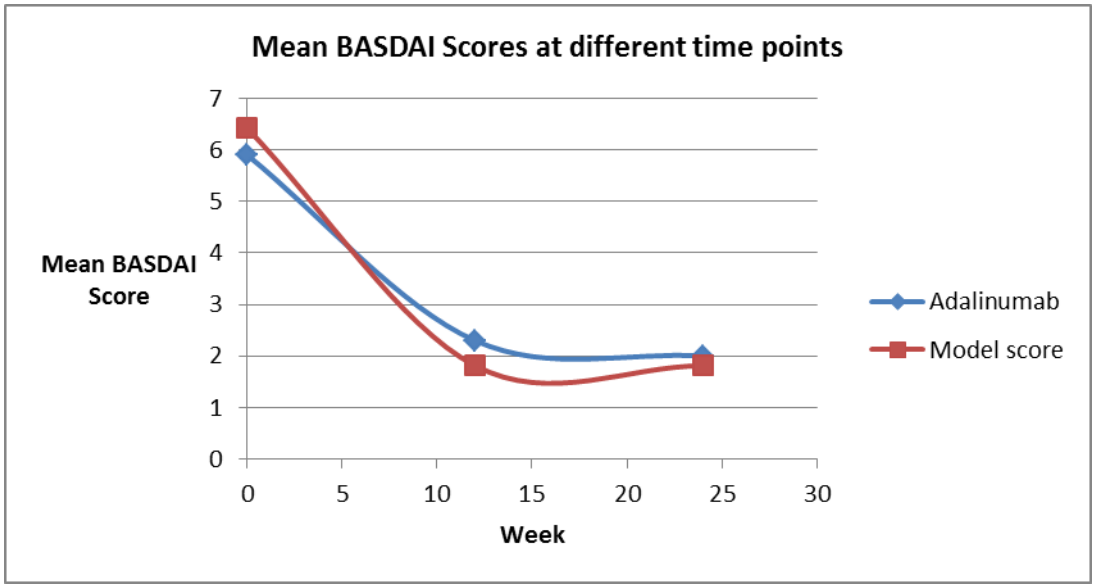
ATLAS

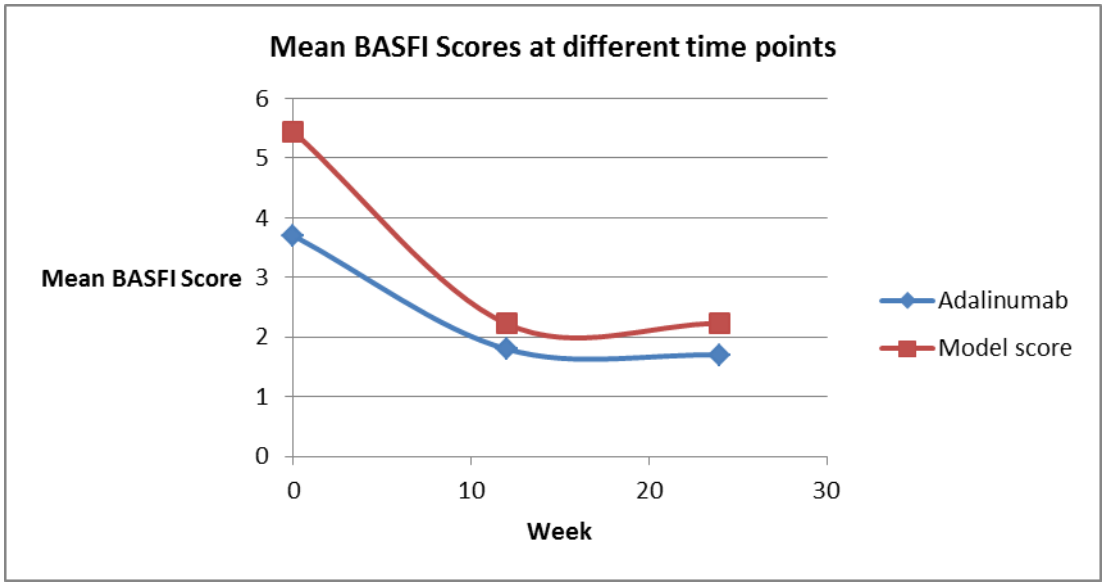




References: van der Heijde 2006,[7] van der Heijde 2009,[39] van der Heijde 2015[40]

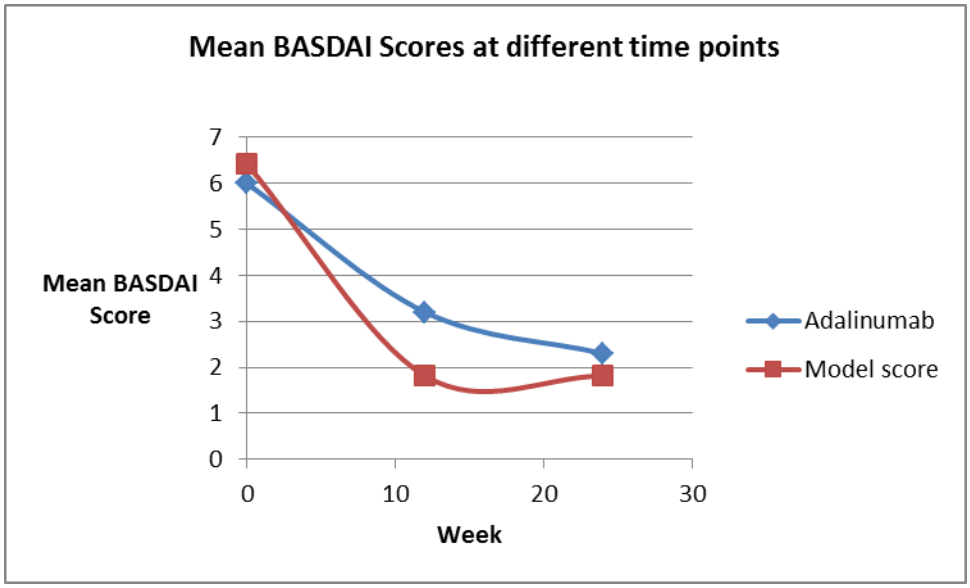
HU

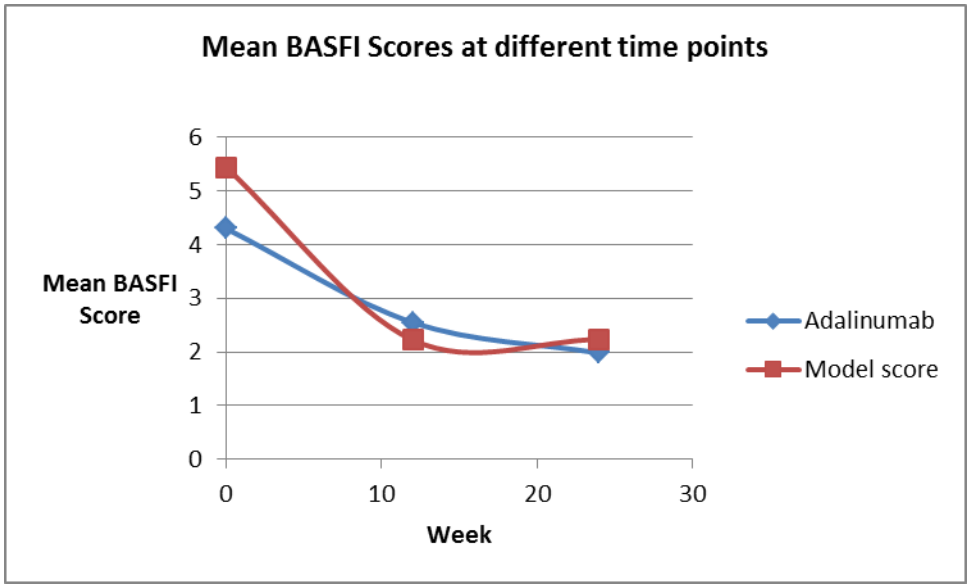




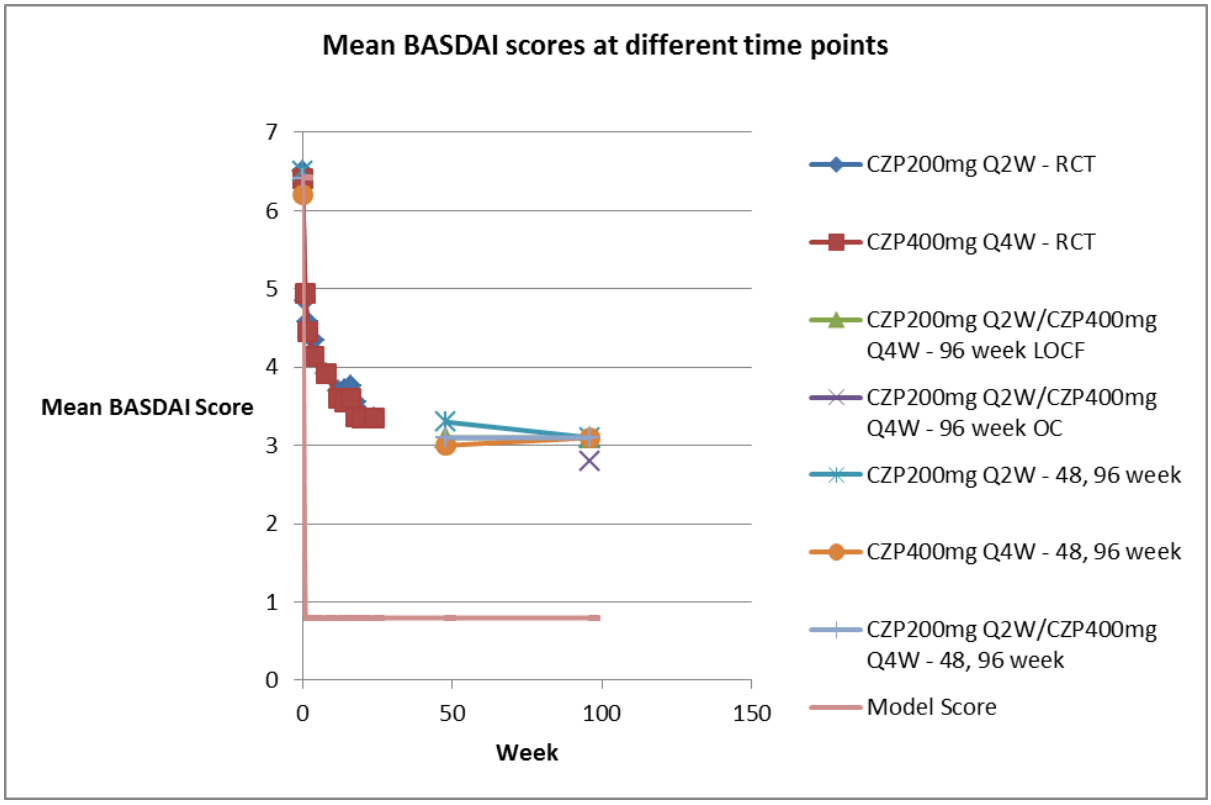
Reference: Hu 2012[41]

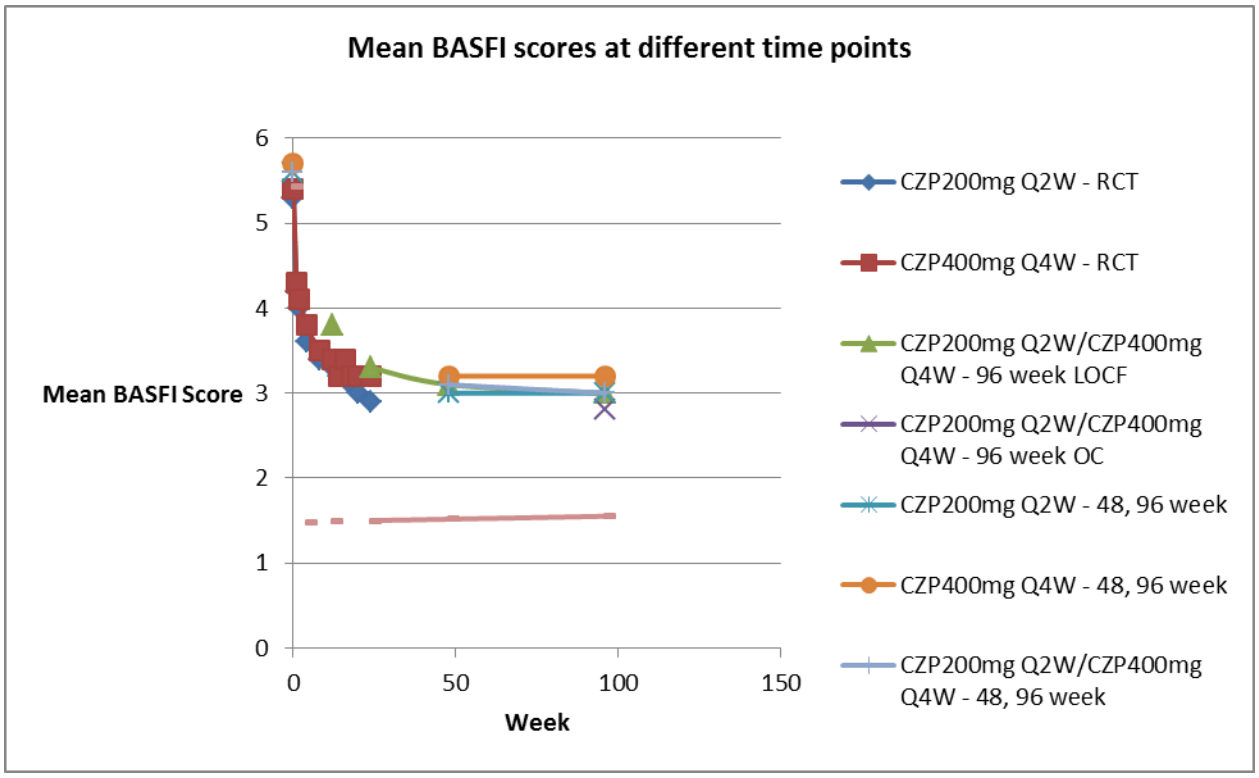
HUANG





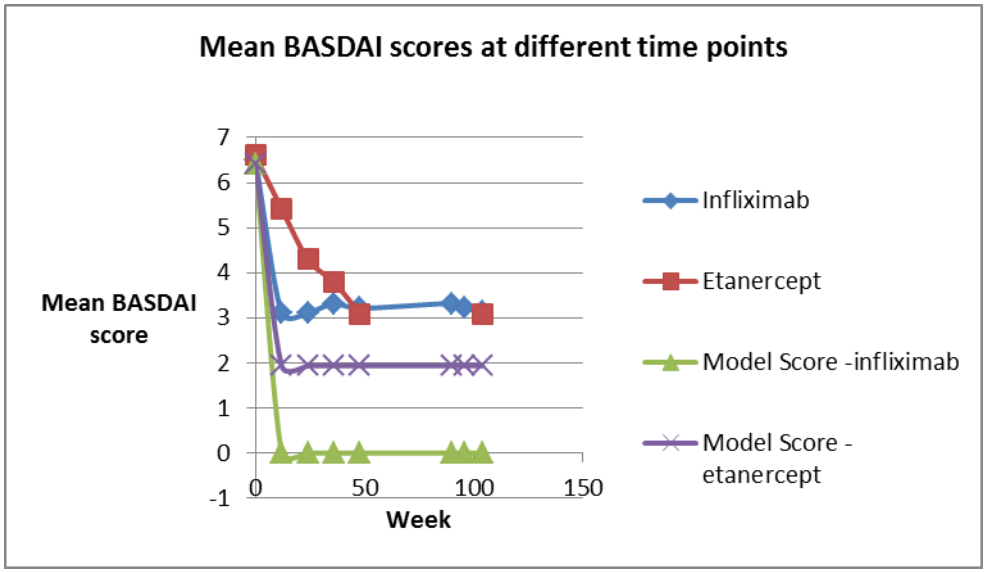
Reference: Huang 2014[42]

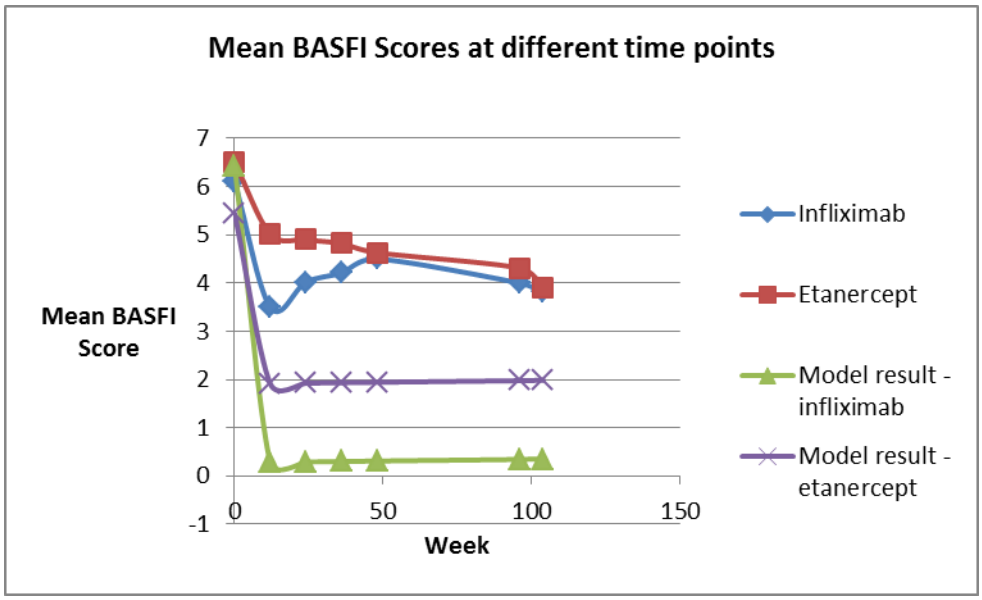




References: Landewe 2013,[43] Landewe 2013 Supplementary information,[44] Sieper 2015[45]

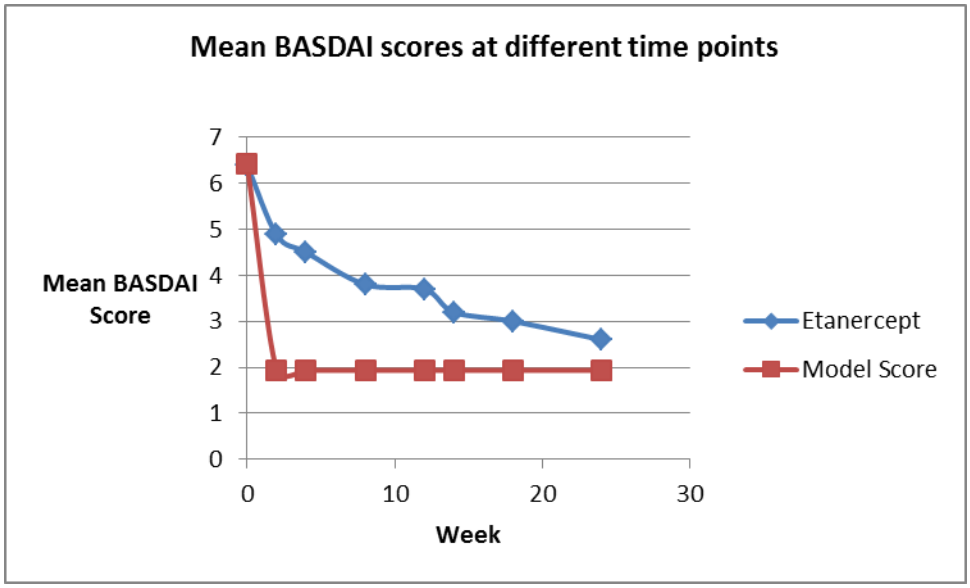
GIARDINA

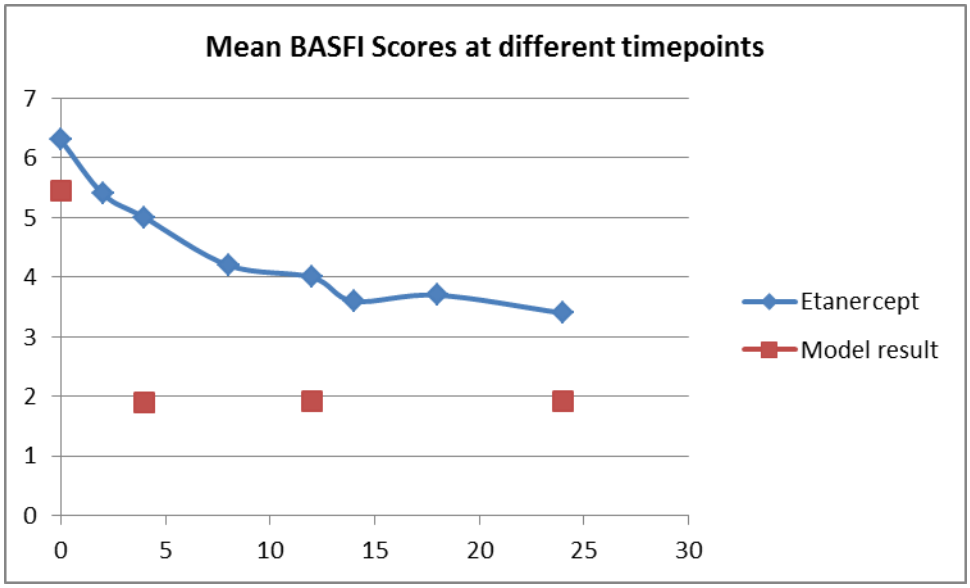




Reference: Giardina et al 2010[46]

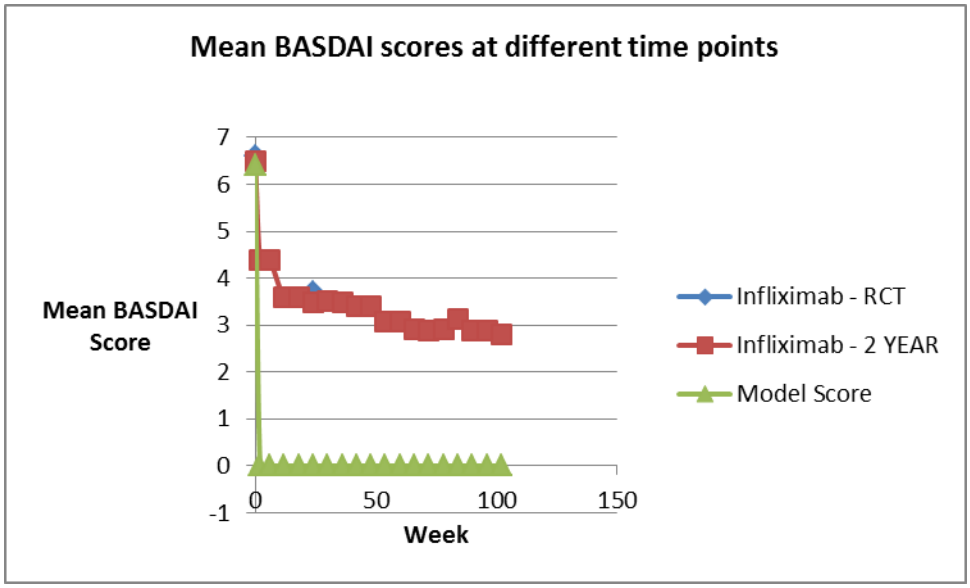
SPINE

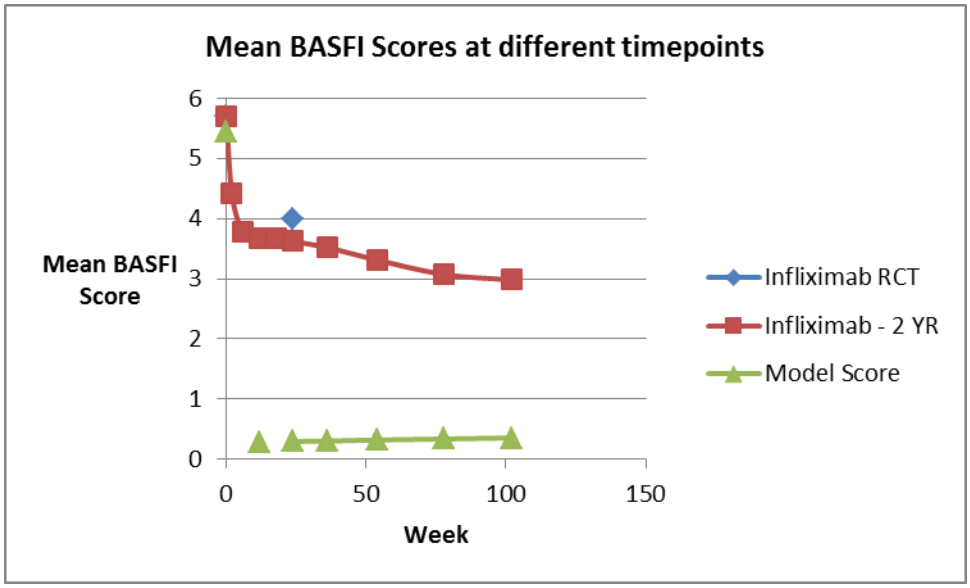




References: Dougados 2011[47], Dougados 2012[48]

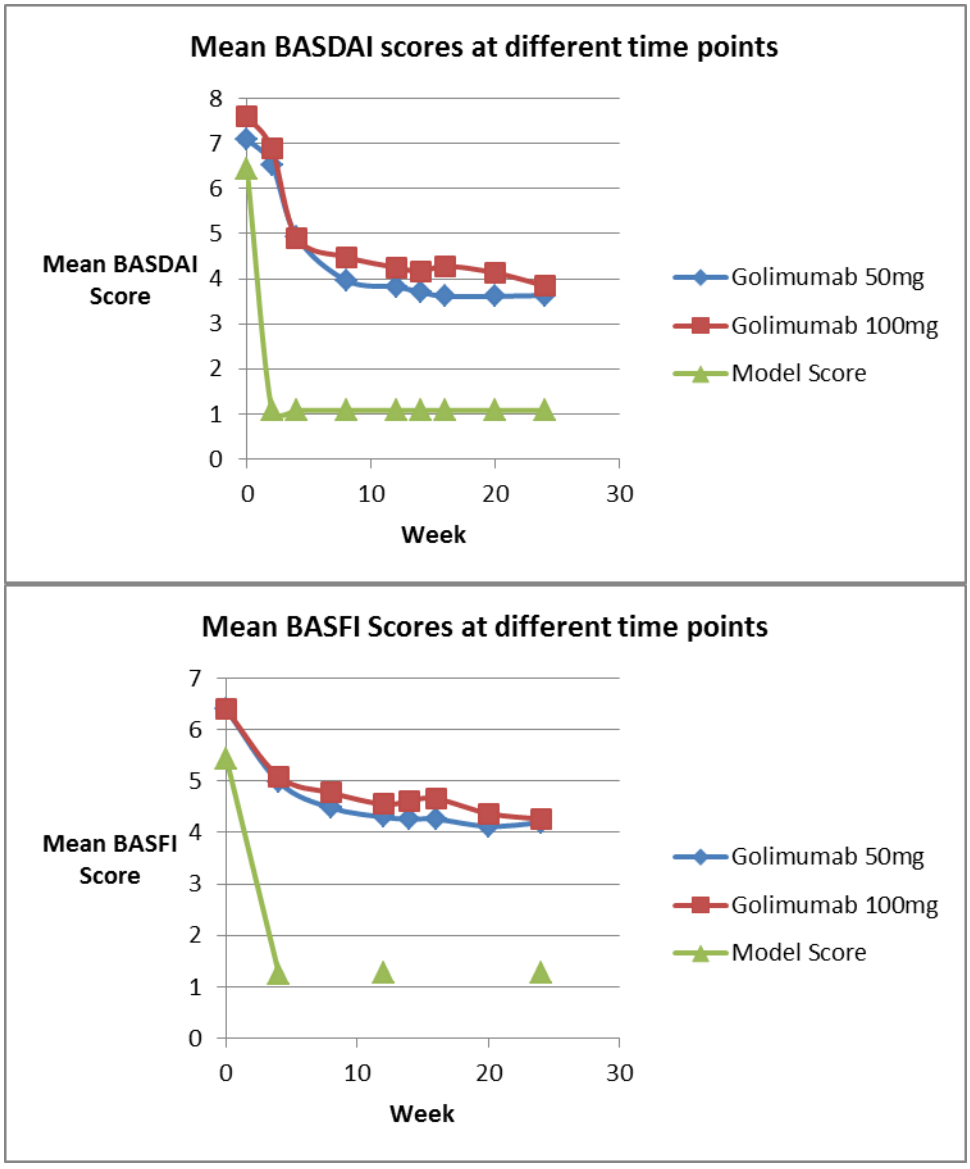
ASSERT





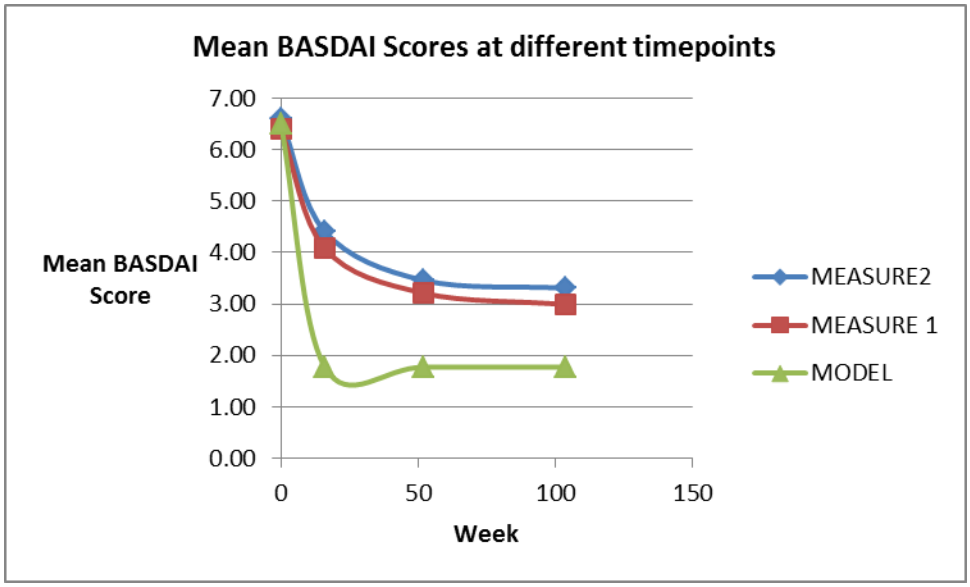
References: van der Heijde 2005,[49] Braun 2008[50]

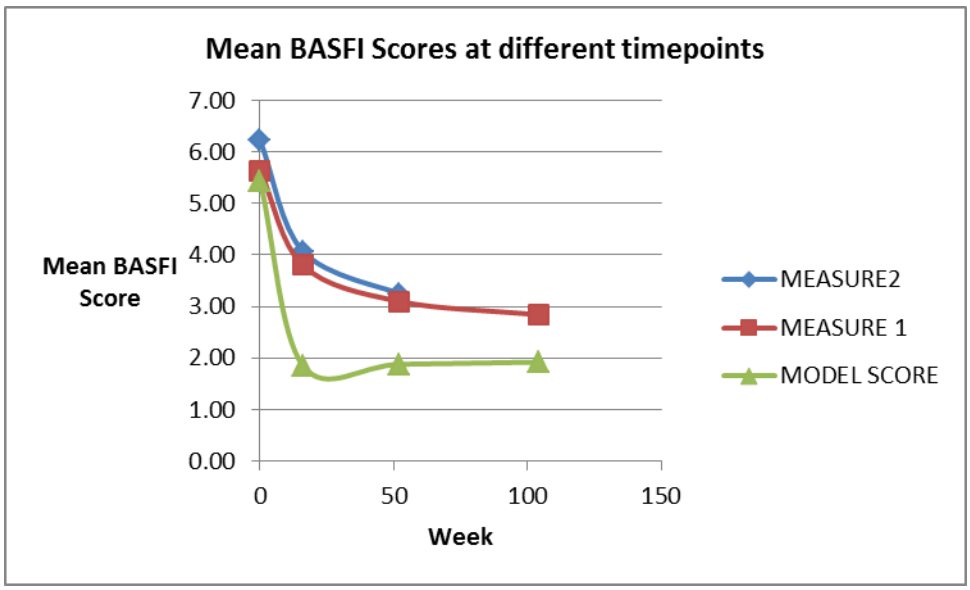
GO-RAISE



Reference: Inman 2008[13]

MEASURE1 and MEASURE 2





B28. In the excel model, it seems that the model estimates are not the same for total QALYs and LYs, even though a utility of 1 is used for each alive state (and no disutilities for adverse events were considered). Please confirm if this is a programming error. If this is the case, please provide a corrected version.

Due to the application of half-cycle correction, some patients are counted in the initial treatment health state in the second cycle of the model. This was not taken into account in the calculation of QALYs but has now been corrected.

B29. In the excel model it appears that the discount rate for costs was used when discounting both costs and health outcomes. Please confirm if this is a programming error and if so, provide a corrected version.

This has been corrected in the revised version of the model.

B30. In the excel model it seems that variations in non-responder BASFI baseline value, and in non-responder change in BASDAI and BASFI, have no effect at all on costs and QALYs. Please confirm if this is meant to be the case and provide an explanation.

Baseline BASDAI for non-responders does have a slight impact on QALYs. This is because patients who discontinue biologic therapy are assumed to immediately revert to baseline BASDAI, in line with the York Assessment Group assumptions.

Baseline BASFI for non-responders has a small impact on QALYs when the BASFI rebound assumption is Natural History, but not with the base case setting of rebound to Initial Gain i.e. baseline.

With base case settings the model does not include non-responder baseline BASFI or change in BASDAI / BASFI for non-responders within the calculations. This is a minor limitation of the latest model version. However, since these parameters would only affect the first cycle for non-responders, the impact on QALYs of implementing a correction would be extremely small.

B31. In the excel model, there is a big difference between the averages from probabilistic sensitivity analyses (PSA) and base case deterministic results, especially in QALYs. Please explain the underlying reasons for this.

BASDAI and BASFI changes from baseline are calculated based on the coefficient of the respective treatment added to the coefficient for conventional care. This is done on the Subgroup data sheet and then feeds into the SA inputs sheet. The probabilistic changes from baseline in BASDAI and BASFI were calculated on the SA inputs sheet using treatment specific changes from baseline, and then adding conventional care changes from baseline. This resulted in BASDAI and BASFI changes from baseline for conventional care being double counted in the probabilistic values, and hence sampled values that were on average much higher than the mean change for the respective treatment.

To prevent this from happening, the probabilistic values are now calculated on the subgroup data sheet. They use coefficients and SEs only, and not calculated change values. Probabilistic values are now calculated using the same method as is used for calculating the lower and upper bounds.

B32. In the excel model, some of the model input parameters were not included in the PSA (e.g. relative risk of BASDAI 50 response for biologic experienced patients). Please justify the inclusion criteria that were applied to the input parameters for PSA.

Three parameters relating to analysis of secukinumab versus conventional care in the biologic experienced population, based on the results of the MEASURE 1 and MEASURE 2 studies, were omitted from the PSA in error; relative risk of BASDAI 50 response, relative risk of BASDAI change from baseline and relative risk of BASFI change from baseline. This has been corrected in the revised version of the model. See Section E: for updated PSA results.

B33. Please provide the BASDAI and BASFI changes from baseline used in Scenario 3 described in section 5.8.3 (page 232).

Scenario 3 was executed in a simplistic manner, by setting the ratio data in rows 45 and 85 of the Subgroup data sheet to 1. As previously run, the scenario did not consider the implication of

assuming no difference between change scores for responders and non-responders, on baseline scores. The scenario has now been re-run, using overall pooled baseline scores (in F40:F45 of the Clinical Inputs sheet) calculated as weighted averages of MEASURE 1 and MEASURE 2 baseline scores, which can be found in Table 15 of the submission , with pooled data provided in Table 72. A comparison of revised results with and without this adjustment to baseline scores is provided in Table 73.

Table 72: Baseline BASDAI and BASFI scores pooled across MEASURE 1 & MEASURE 2

	Secukinumab 150mg	Placebo
BASDAI	5.85	5.92
BASFI	6.47	6.61

Table 73: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population – Scenario 3 with and without non-conditional baseline BASDAI and BASFI scores

	Scenario 3 – with conditional baseline scores			Scenario 3 – without conditional baseline scores		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Adalimumab	£14,979	-0.290	SEC dominates	£15,273	-0.291	SEC dominates
Certolizumab pegol – with PAS	£8,847	-0.311	SEC dominates	£9,216	-0.313	SEC dominates
Etanercept	£467	-0.726	SEC dominates	£1,227	-0.730	SEC dominates
Etanercept biosimilar	-£547	-0.726	£754	£212	-0.730	SEC dominates
Golimumab	£17,426	-0.063	SEC dominates	£17,549	-0.063	SEC dominates
Infliximab	£25,904	-0.132	SEC dominates	£26,218	-0.134	SEC dominates
Infliximab biosimilar	£22,330	-0.132	SEC dominates	£22,643	-0.134	SEC dominates

Section C: Textual clarifications and additional points

C1. Table 6: The inclusion criteria list patients with intolerance or inadequate response. However, the exclusion criteria list “treatment-naïve patients”. Please explain this discrepancy.

We do not consider there to be a discrepancy here. To clarify, studies that considered patients who had received conventional treatments, regardless of response (i.e. including those who were intolerant or had inadequate response to those prior conventional treatments) were included. In contrast, studies of patients who were treatment-naïve (ie. had not received any prior therapy) were excluded. No distinction between intolerance and inadequate response as the reason for failure of prior therapy was made in applying the eligibility criteria.

C2. Details of how many patients remain in MEASURE 2 at different time points were provided. However, outcomes reported in tables and appendices do not always reflect these numbers. For example, table 139 reports on 68 patients at 16 weeks in the secukinumab arm yet there were only 66 patients in study at this point. Please add reasons for any differences in the patient numbers to each table.

At the end of week 16 there were 66 patients who remained in the study on the secukinumab 150 mg arm of MEASURE 2, these patients were assessed for all of the study endpoints. In addition to these 66 patients there were 5 patients who withdrew from the study due to adverse events, of these 5 patients data were available for 2 of these patients for some of the secondary and exploratory endpoints. As the data were available for some of the endpoints it was included for completeness.

To confirm the actual patient numbers at week 16 for secukinumab 150 mg for these endpoints:

- hsCRP change from baseline - Full analysis set: **68 patients**
- Patient's global assessment of disease activity (VAS) change from baseline - Full analysis set: **67 patients**
- ASDAS-CRP change from - Full analysis set: **67 patients**

C3. Cross-references are missing on page 58 and 213 (the text says “please see section 0”). Please confirm the correct section numbers that should be referenced here.

The cross-references on page 58 and page 213 should read Section 4.7.1 and Section 5.3.7, respectively.

Additional textual clarifications

On page 193 there is a statement “However, this may be a conservative assumption as secukinumab has demonstrated efficacy upon radiographic outcomes (Section 4.8.3) that may be better than that of TNFα inhibitors”. The cross-reference here is incorrect – it should refer to Section 4.7.2.4.

Table 190 (Appendix J): The title is misleading as it indicates that response is relative to placebo, however this is not the case for the week 24 and week 52 results since no placebo data at these time points is available. The week 12 and week 16 results are the risk differences relative to placebo. The week 24 and week 52 results are absolute probabilities of response.

Section D: Revised NMA Results

Since our original submission was made, Novartis has identified two genuine errors in the analyses run as part of the NMA:

- The ATLAS study should have been included in the networks relating to the BASFI outcome but was omitted in error from the analyses performed.
- The Huang et al. study should have been included in all networks for the biologic naïve population but was omitted in error from the analyses performed.

Therefore, Novartis has revised the analyses to correct for these errors. The updated network diagrams and results of the base case and sensitivity analysis NMAs are provided below.

Revised network diagrams

Figure 3: Network Diagram of Evidence for BASFI Change from Baseline – whole population *[correction of Figure 59 in submission appendices]*

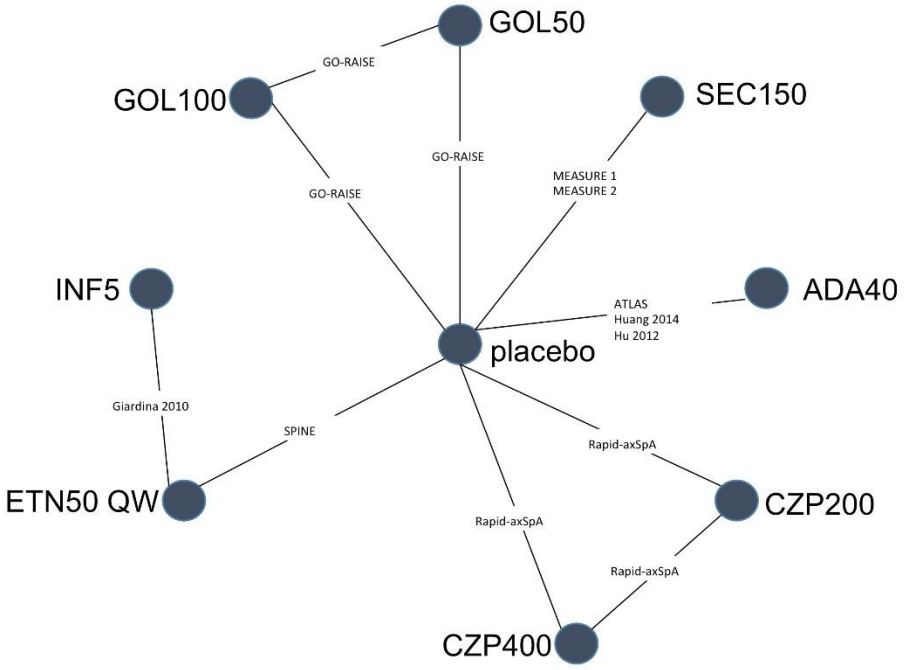


Figure 4: Network Diagram of Evidence for ASAS20 Response – biologic naïve population *[correction of Figure 52 in submission appendices]*

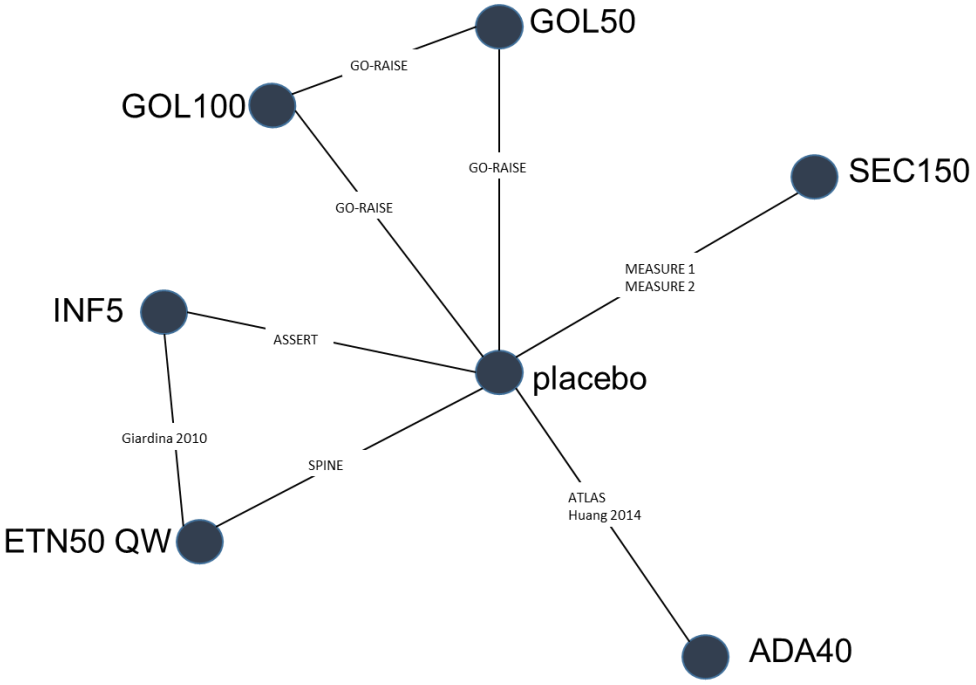


Figure 5: Network Diagram of Evidence for ASAS40 – biologic naïve population *[correction of Figure 54 in submission appendices]*

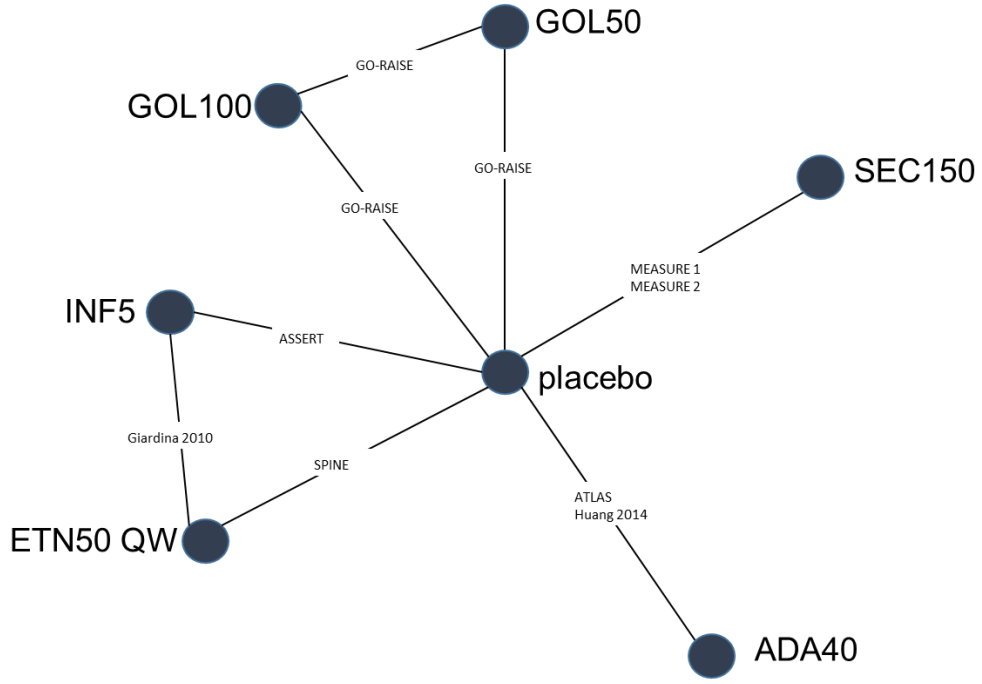


Figure 6: Network Diagram of Evidence for BASDAI 50 – biologic naïve population ***[correction of Figure 56 in submission appendices]***

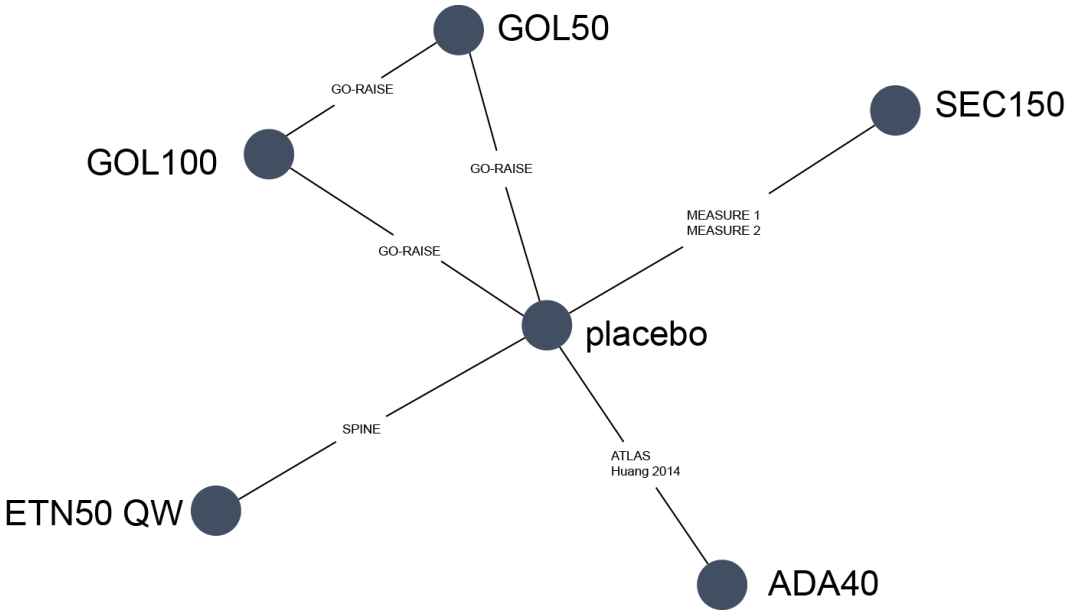


Figure 7: Network Diagram of Evidence for BASDAI Change from Baseline – biologic naïve population ***[correction of Figure 58 in submission appendices]***

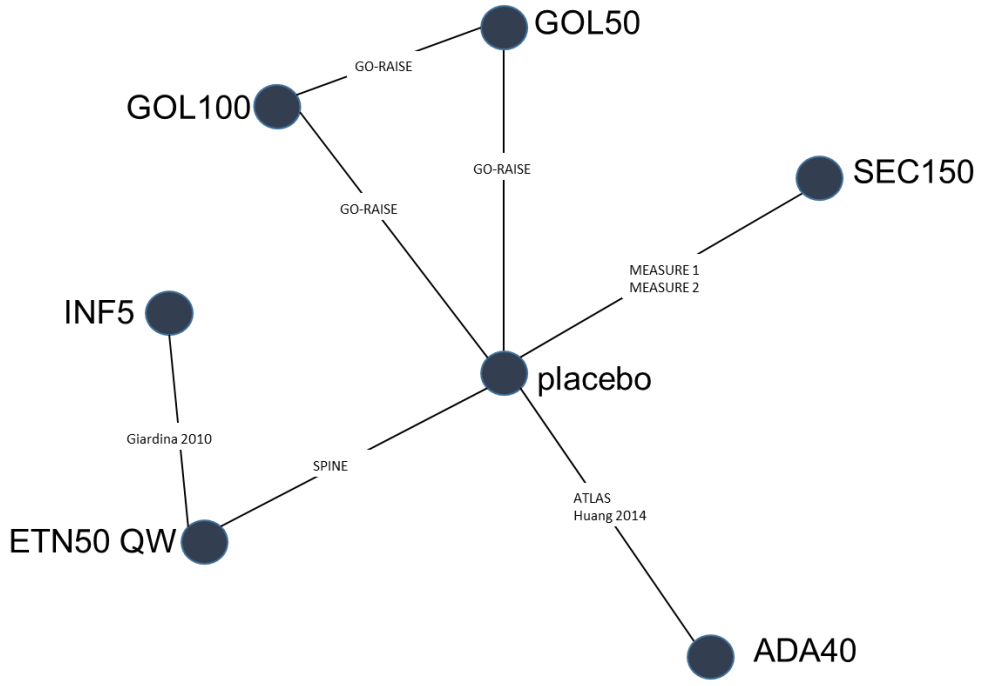
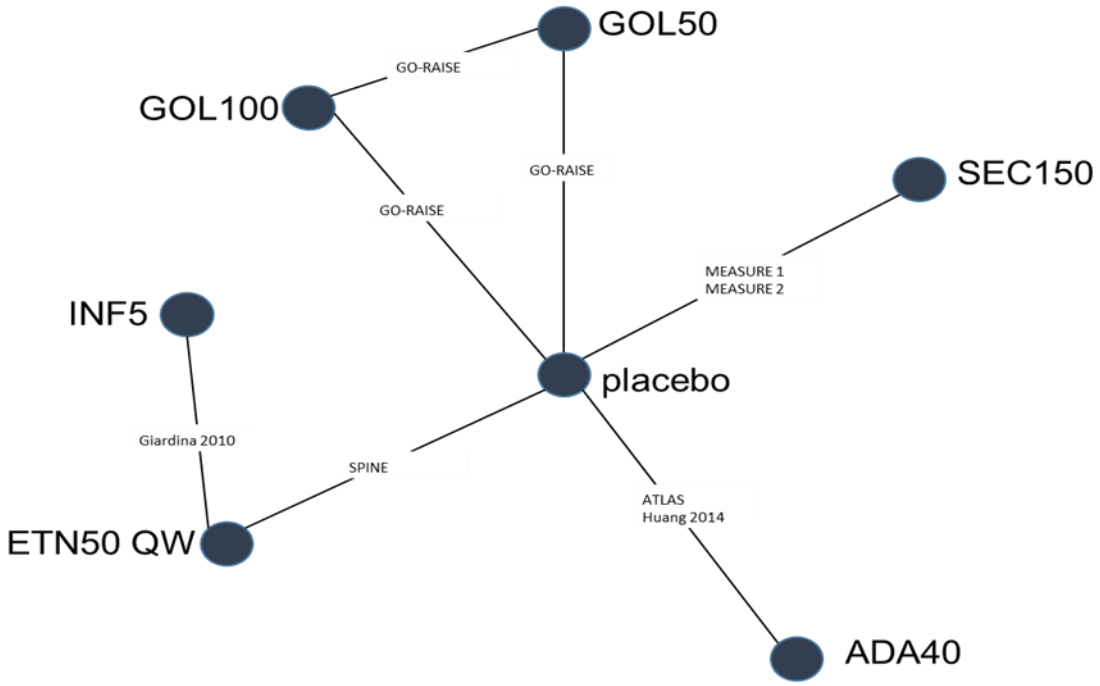


Figure 8: Network Diagram of Evidence for BASFI Change from Baseline – biologic naïve population *[correction of Figure 60 in submission appendices]*



Revised results – base case analysis

Results tables and figures for the base case analysis from the original submission are replicated below, with results updated taking into account the corrections required to the NMA. Where results have not changed, this is indicated in the following tables.

Revised summary of statistical significance of relative treatment comparisons

Table 74: Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – whole population *[correction of Table 51 in submission main body]*

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

Table 75: Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – biologic naive population *[correction of Table 52 in submission main body]*

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	-	-	-	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

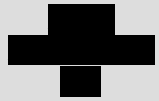
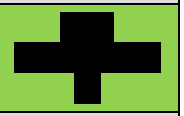
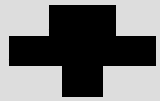
Revised results of comparisons of relative treatment effects

Table 76: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints *[correction of Table 52 in submission main body]*

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20	*No changes to any of these results versus the original submission Table 52*							
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BN, biological naïve; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Table 77: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints *[correction of Table 54 in submission main body]*

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline	*No changes to any of these results versus the original submission Table 54*							
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BN, biological naïve; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Revised predicted absolute responses for each treatment

Whole population:

- ASAS20, ASAS40, BASDAI 50 and BASDAI change from baseline – no change versus figures 21, 23, 25 and 27, respectively, in the original submission
- BASFI change from baseline – see Figure 9 for corrected results

Figure 9: Modelled mean change from baseline BASFI response according to the fixed-effects NMA at 12 to 16 weeks in the mixed population with MEASURE-1 included ***[correction of Figure 29 in submission main body]***

Biologic naïve population:

- All absolute results in the biologic naïve population have altered. Corrected versions of figures 22, 24, 26, 28 and 30 from the original submission are provided below.

Figure 10: Absolute ASAS20 response – biologic naïve population *[correction of Figure 22 in submission main body]*

Figure 11: Absolute ASAS40 response – biologic naïve population *[correction of Figure 24 in submission main body]*

Figure 12: Absolute BASDAI 50 response – biologic naïve population *[correction of Figure 26 in submission main body]*

Figure 13: Absolute BASDAI change from baseline – biologic naïve population *[correction of Figure 28 in submission main body]*

Figure 14: Absolute BASFI change from baseline – biologic naïve population *[correction of Figure 30 in submission main body]*

Revised results – sensitivity analysis

Results tables for the sensitivity analyses from the original submission are replicated below, with results updated taking into account the corrections required to the NMA. Where results have not changed, this is indicated in the following tables.

Revised results of comparisons of relative treatment effects

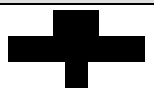
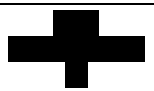
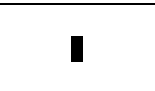
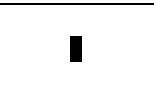
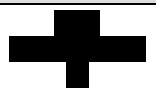
Table 78: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints – sensitivity analyses *[correction of Table 55 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	ASAS20	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
	ASAS40	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
	BASDAI 50	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
Biologic naïve population	ASAS20	1								
		2								
		3								
	ASAS40	1								
		2								
		3								
	BASDAI 50	1								
		2								
		3								

Green cells represent a statistically significantly meaningful result. -=not analysed (i.e. could not be included in network)

Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 79: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints – sensitivity analyses ***[correction of Table 56 in submission main body]***

Population	Continuous endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	BASDAI change from baseline	1	*No changes to any of these results versus the original submission Table 56*							
		2	*No changes to any of these results versus the original submission Table 56*							
		3	*No changes to any of these results versus the original submission Table 56*							
	BASFI change from baseline	1								
		2								
		3								
Biologic naïve population	BASDAI change from baseline	1								
		2								
		3								
	BASFI change from baseline	1								
		2								

		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Revised predicted absolute responses for each treatment

Table 80: Absolute results for binomial endpoints – sensitivity analyses *[correction of Table 57 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	ASAS20	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
	ASAS40	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
	BASDAI 50	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
Biologic naïve population	ASAS20	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	BASDAI 50	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

-=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 81: Absolute results for continuous outcomes – sensitivity analyses *[correction of Table 58 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	BASDAI change from baseline	1	*No changes to any of these results versus the original submission Table 58*								
		2	*No changes to any of these results versus the original submission Table 58*								
		3	*No changes to any of these results versus the original submission Table 58*								
	BASFI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	BASDAI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

-=not analysed (i.e. could not be included in network)

Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Section E: Revised Cost-effectiveness Results

Base-case incremental cost effectiveness analysis results

The summary results of the base case analysis are presented in Table 82 for the biologic naïve population and Table 83 for the biologic experienced population.

Table 82. Revised Summary base case results – biologic naïve population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£113,216	9.805				
Etanercept	£114,234	8.759	£1,018	-1.046	Dominated	Dominated
Etanercept biosimilar	£115,249	8.759	£2,033	-1.046	Dominated	Dominated
Certolizumab pegol – with PAS	£122,418	9.447	£9,202	-0.359	Dominated	Dominated
Adalimumab	£128,516	9.446	£15,300	-0.359	Dominated	Dominated
Golimumab	£129,919	9.830	£16,703	0.025	£674,914	£674,914
Infliximab biosimilar	£135,865	9.590	£22,649	-0.216	Dominated	Dominated
Infliximab	£139,439	9.590	£26,223	-0.216	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 83. Revised Summary base case results – biologic experienced population population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£107,417	8.161			
Secukinumab	£109,164	8.939	£1,747	0.778	£2,245

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Exploratory cost-effectiveness analyses in biologic naïve and biologic experienced populations

The summary results for the exploratory analysis of the biologic naïve population, including sequencing, are provided in Table 84 below.

Table 84. Summary results – exploratory sequencing analyses on biologic naïve population

Treatment pathway	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Secukinumab -> Mixed Tx	£121,209	9.987			
Etanercept -> Mixed Tx	£124,499	9.047	-£3,684	0.940	Dominated
Etanercept biosimilar-> Mixed Tx	£125,886	9.047	-£4,677	0.940	Dominated
Certolizumab pegol -> Mixed Tx	£131,066	9.655	-£9,857	0.332	Dominated
Adalimumab -> Mixed Tx	£136,401	9.648	-£15,192	0.339	Dominated
Golimumab -> Mixed Tx	£137,515	10.017	-£16,305	-0.030	£545,767*
Infliximab biosimilar -> Mixed Tx	£142,884	9.791	-£22,069	0.196	Dominated
Infliximab -> Mixed Tx	£146,628	9.791	-£25,419	0.196	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The summary results for the exploratory analysis of the biologic experienced population, comparing secukinumab to the other biologic therapies, are provided in Table 85.

Table 85. Summary results – exploratory comparison with TNFα inhibitors in biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,379	8.166			
Etanercept	£110,928	8.463	£3,549	0.297	Extendedly Dominated
Etanercept biosimilar	£111,571	8.463	£4,192	0.297	Extendedly Dominated
Secukinumab	£112,125	8.791	£4,746	0.625	£7,597
Certolizumab pegol – with PAS	£115,344	8.678	£7,965	0.512	Dominated
Adalimumab	£119,876	8.680	£12,497	0.514	Dominated
Golimumab	£121,114	8.796	£13,736	0.630	£1,614,375
Infliximab biosimilar	£125,438	8.778	£18,059	0.612	Dominated
Infliximab	£127,650	8.778	£20,271	0.612	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Probabilistic sensitivity analysis

Probabilistic mean costs, QALYs and resultant ICERs for the analysis of the biologic naïve population are presented in Table 86, followed by the scatterplots for the comparison of secukinumab to each comparator (Figure 15 to Figure 20) and the CEAC (Figure 22) in this population. The ICERs for the probabilistic analysis in the biologic experienced population are presented in Table 87, followed by the scatterplot (Figure 23) and CEAC (Figure 24).

Table 86. Summary probabilistic base case results – biologic naïve population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Secukinumab	£116,011	£29,355	10.494	0.959			
Etanercept	£120,471	£35,462	9.500	0.959	£4,459	-0.994	Dominated
Etanercept biosimilar	£120,614	£34,936	9.456	0.953	£4,602	-1.038	Dominated
Certolizumab pegol – with PAS	£127,032	£32,659	10.124	0.989	£11,020	-0.370	Dominated
Adalimumab	£131,609	£31,241	10.152	0.952	£15,598	-0.342	Dominated
Golimumab	£134,921	£31,933	10.465	1.008	£18,910	-0.029	Dominated
Infliximab biosimilar*	£156,555	£42,181	9.945	1.052	£40,544	-0.549	Dominated
Infliximab	£160,533	£47,027	9.865	1.070	£44,522	-0.629	Dominated

Abbreviations: SD, standard deviation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SEC, secukinumab.
*Please note results for infliximab and etanercept biosimilars require separate PSA runs in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 15. Scatterplot for secukinumab vs etanercept – biologic naïve population

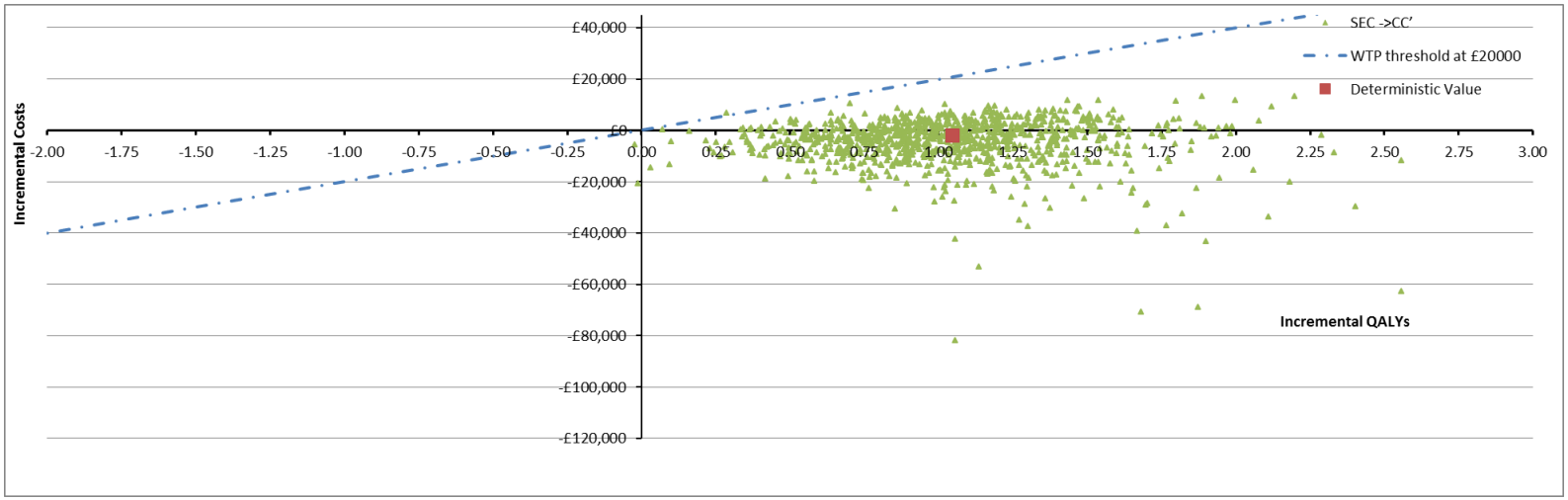


Figure 16. Scatterplot for secukinumab vs etanercept biosimilar – biologic naïve population

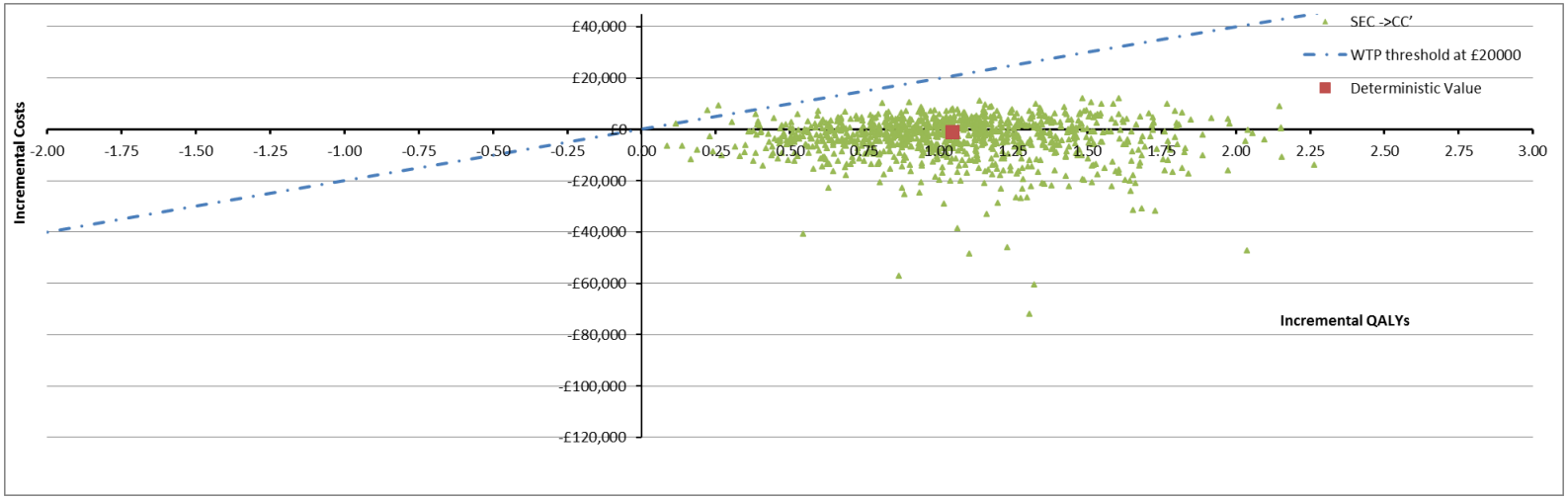


Figure 17. Scatterplot for secukinumab vs certolizumab pegol – biologic naïve population

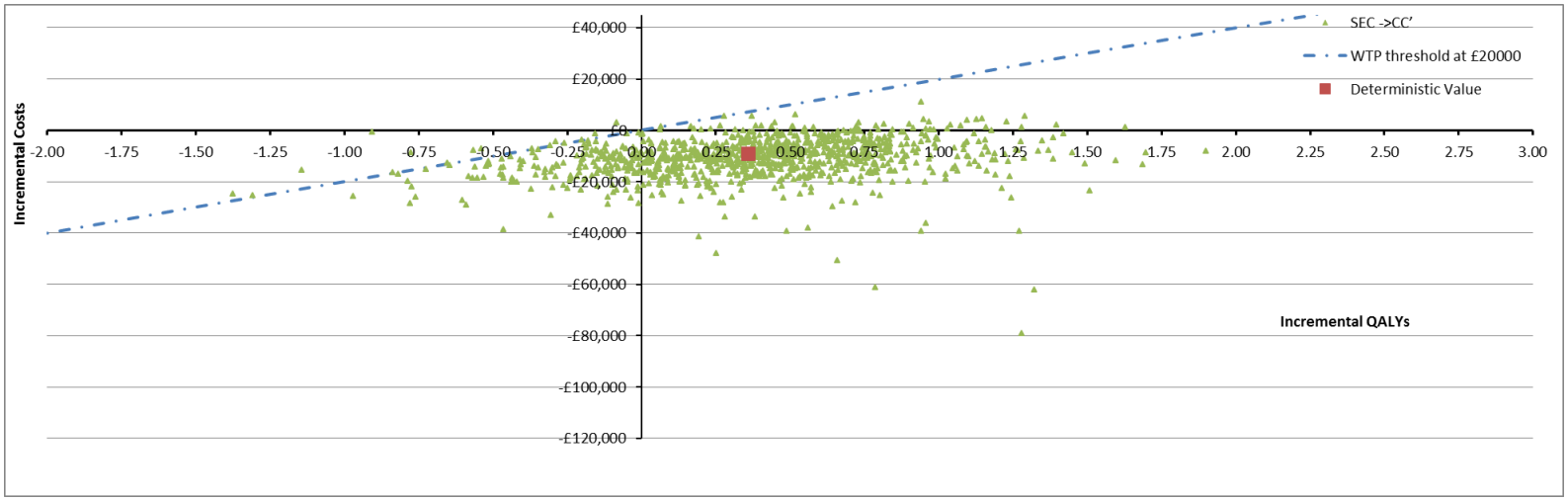


Figure 18. Scatterplot for secukinumab vs adalimumab – biologic naïve population

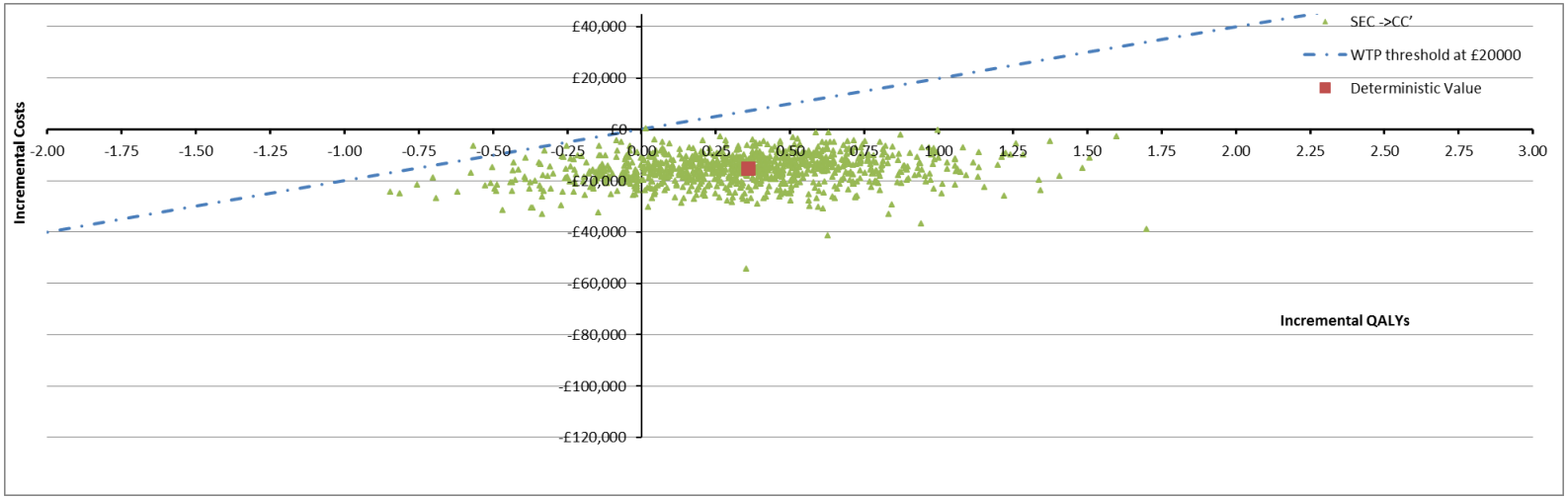


Figure 19. Scatterplot for secukinumab vs golimumab – biologic naïve population

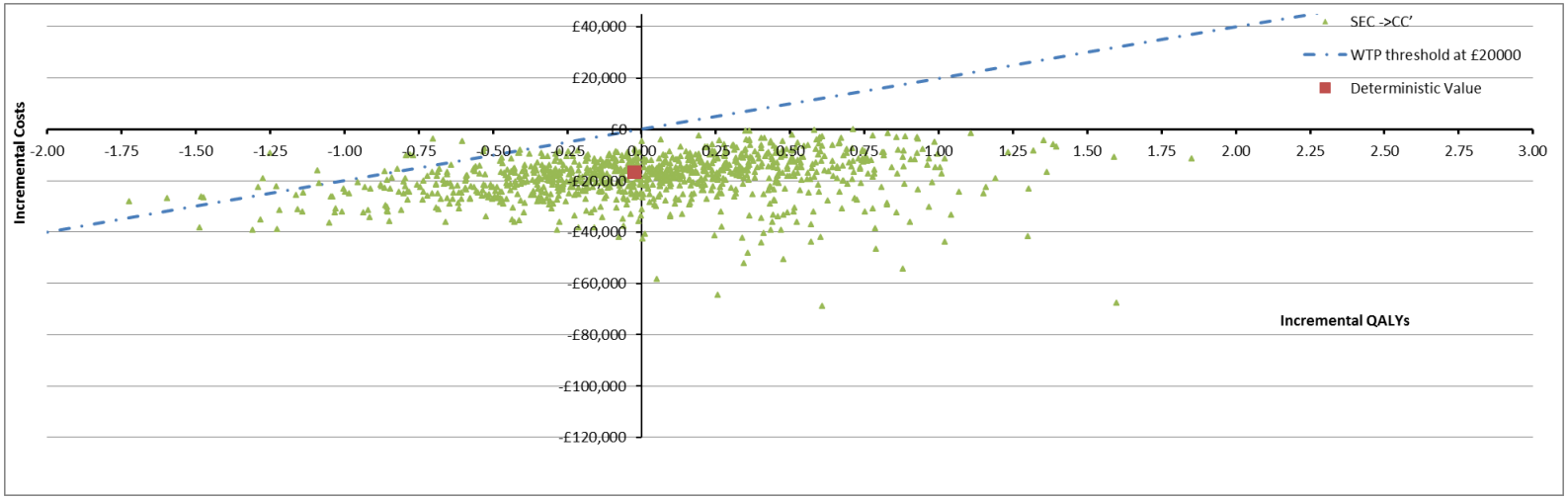


Figure 20. Scatterplot for secukinumab vs infliximab – biologic naïve population

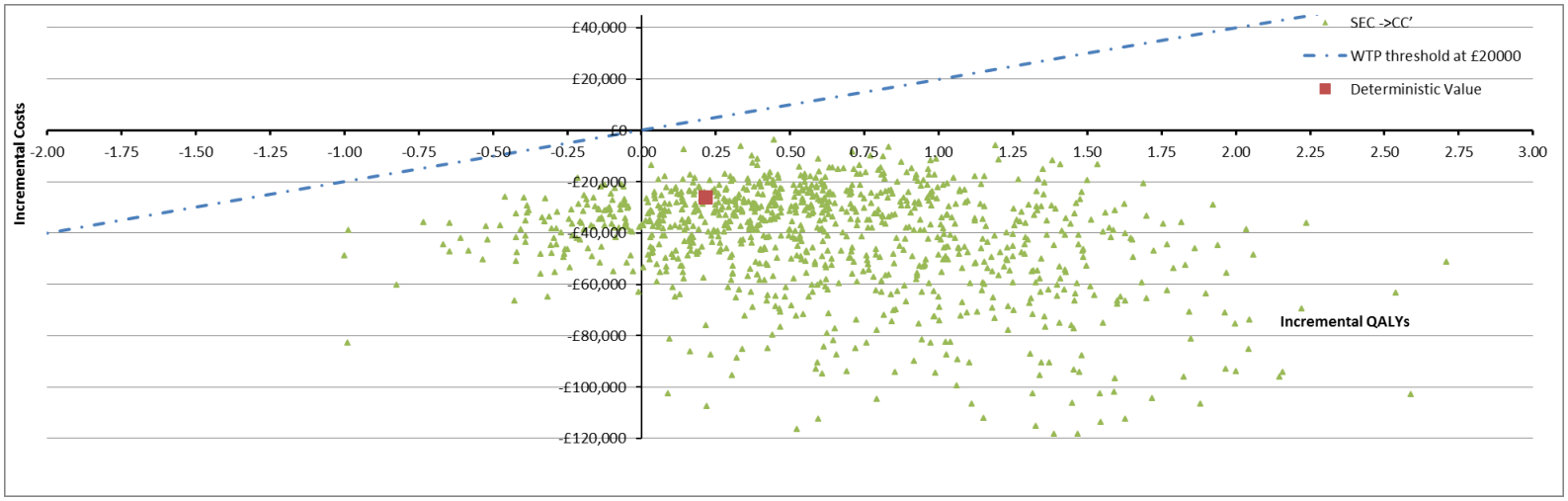
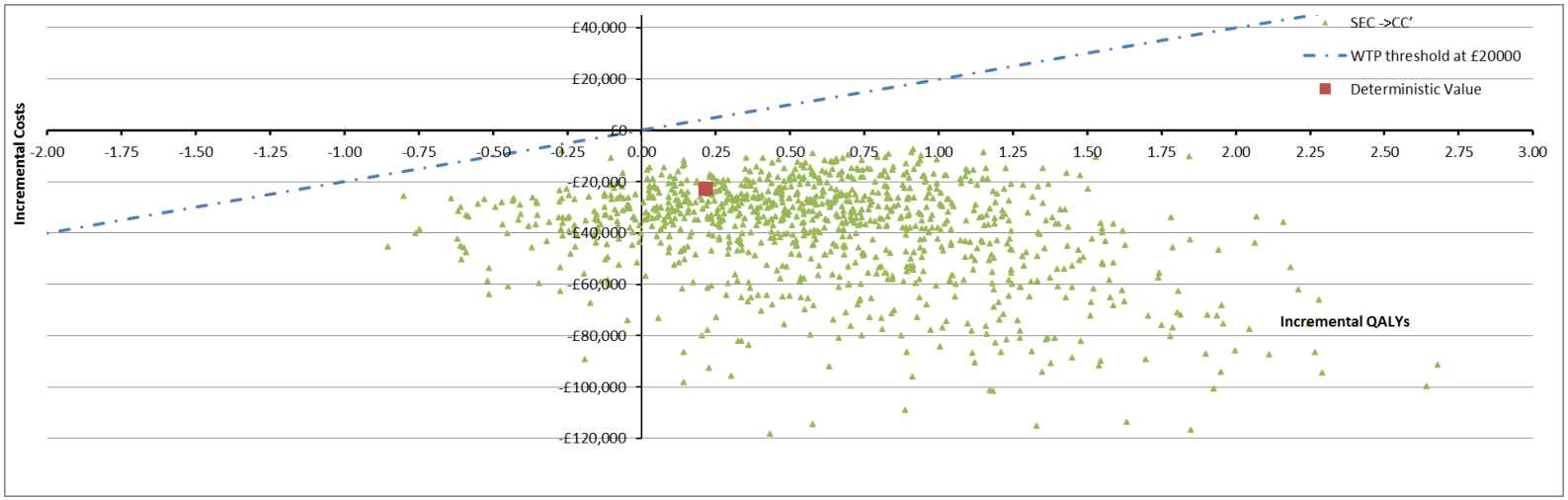
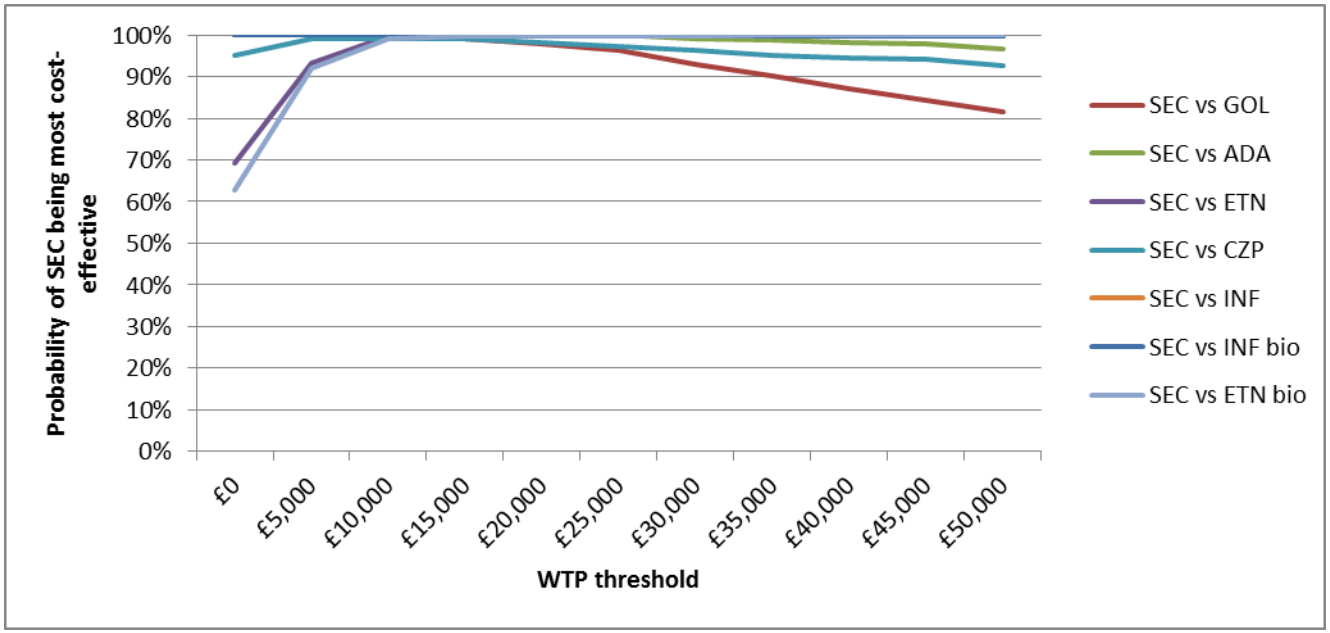


Figure 21. Scatterplot for secukinumab vs infliximab biosimilar – biologic naïve population*



*Please note results for infliximab biosimilar require a separate PSA run in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 22. CEAC for secukinumab versus comparators in the biologic naïve population*



*The above chart combines results of two comparator CEAC results for secukinumab versus each comparator.

Table 87. Summary probabilistic base case results – biologic experienced population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Conventional care	£111,974	£36,811	8.858	0.972			

Secukinumab	£113,433	£32,639	9.662	1.016	£1,458	£1	£1,815

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SEC, secukinumab.

Figure 23. Scatterplot for secukinumab vs conventional care – biologic experienced population

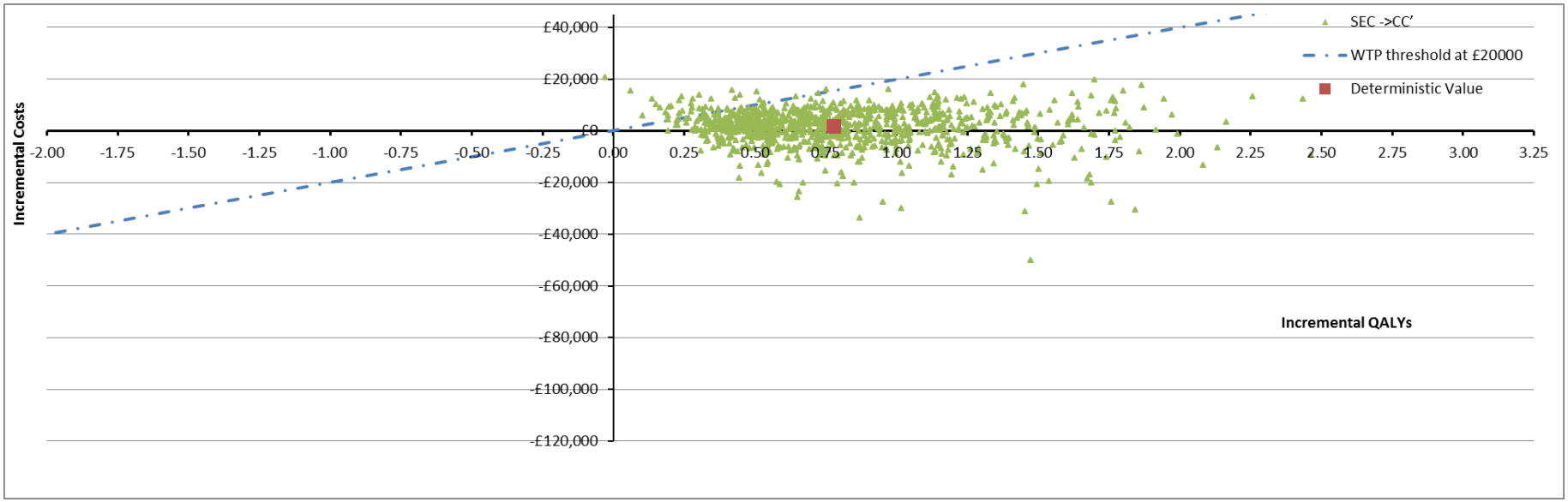
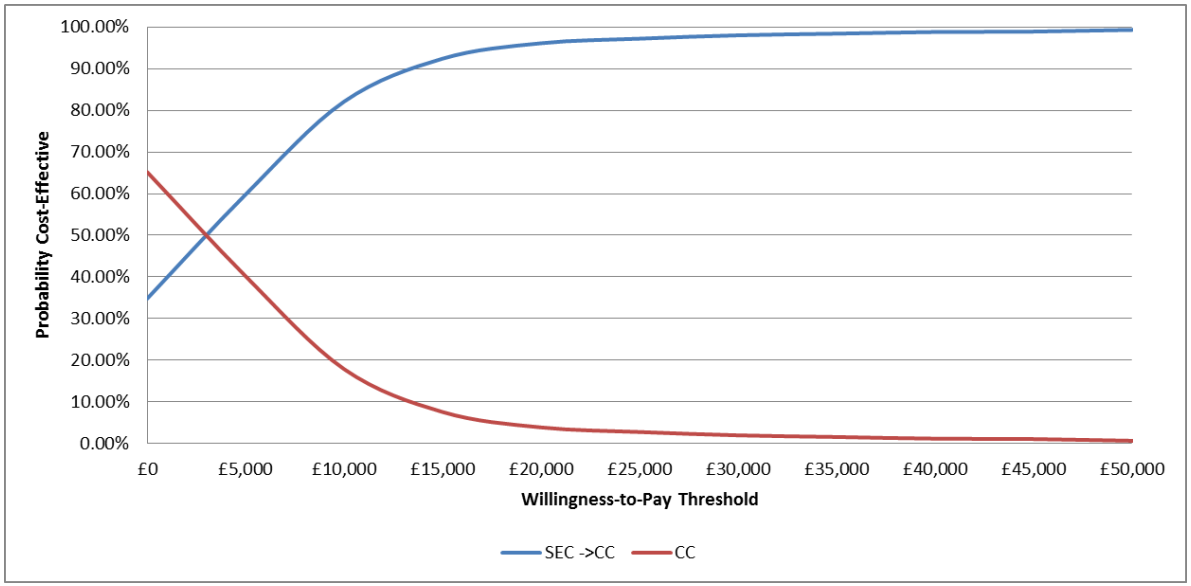


Figure 24. CEAC for secukinumab vs. conventional care – biologic experienced population



Deterministic sensitivity analysis

The tornado diagrams below present the variation in base case model results from OWSA in terms of net monetary benefits (valuing one QALY at £20,000). Net monentary benefits are presented instead of ICERs due to incremental costs of secukinumab being negative versus all comparators i.e. in the southern quadrants of the cost-effectiveness plane, where ICERs are not informative. Tornado diagrams for the biologic naïve population are provided in Figure 25 to Figure 31. The tornado diagram for the analysis in the biologic experienced population is provided in Figure 32.

Figure 25. OWSA results for secukinumab vs etanercept – biologic naïve population

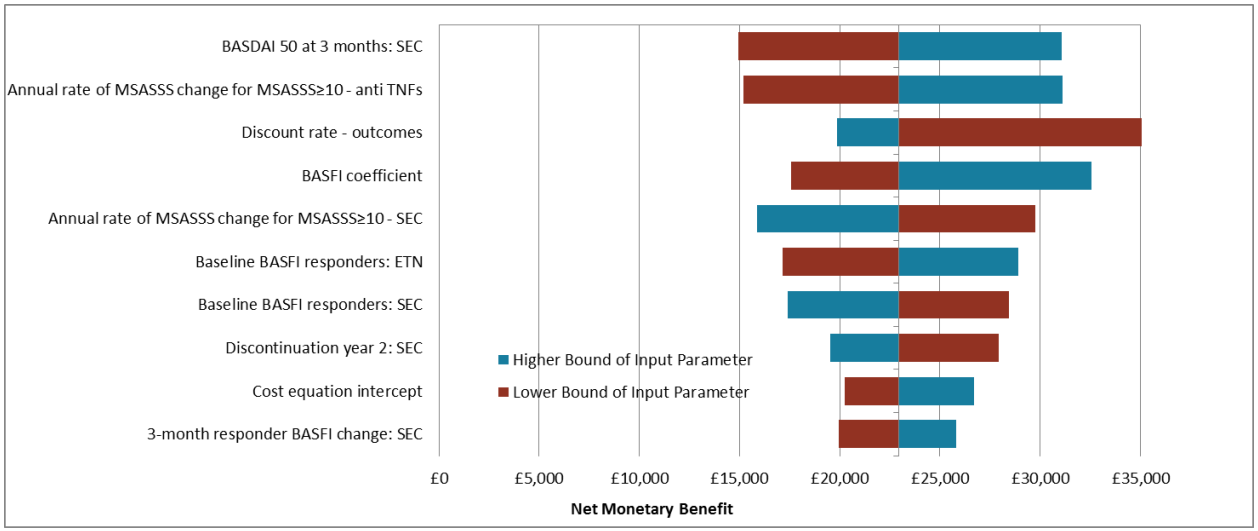


Figure 26: OWSA results for secukinumab vs biosimilar etanercept – biologic naïve population

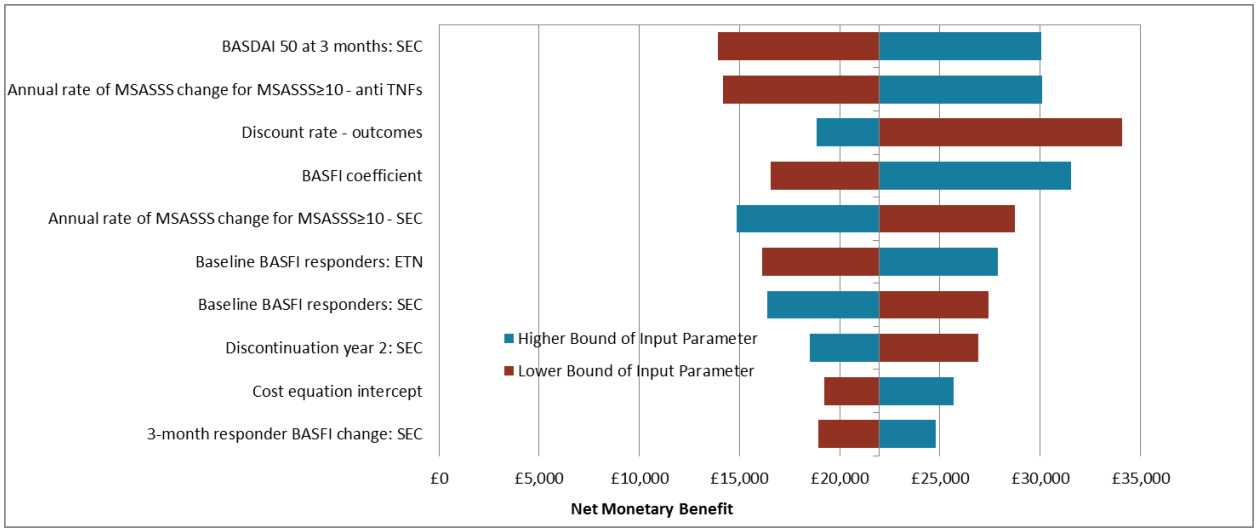


Figure 27. OWSA results for secukinumab vs certolizumab – biologic naïve population

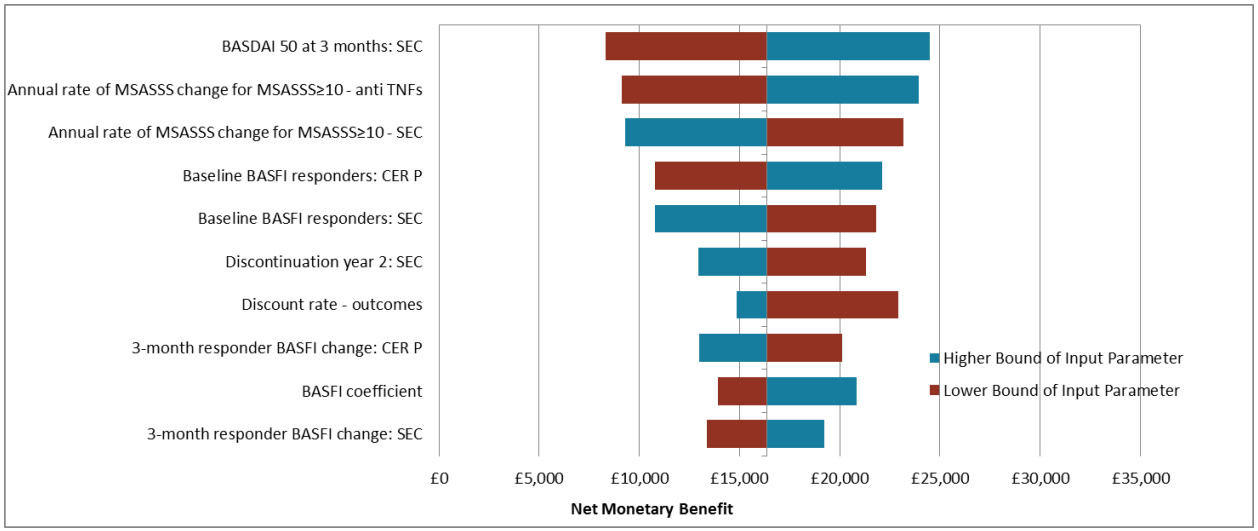


Figure 28. OWSA results for secukinumab vs adalimumab – biologic naïve population

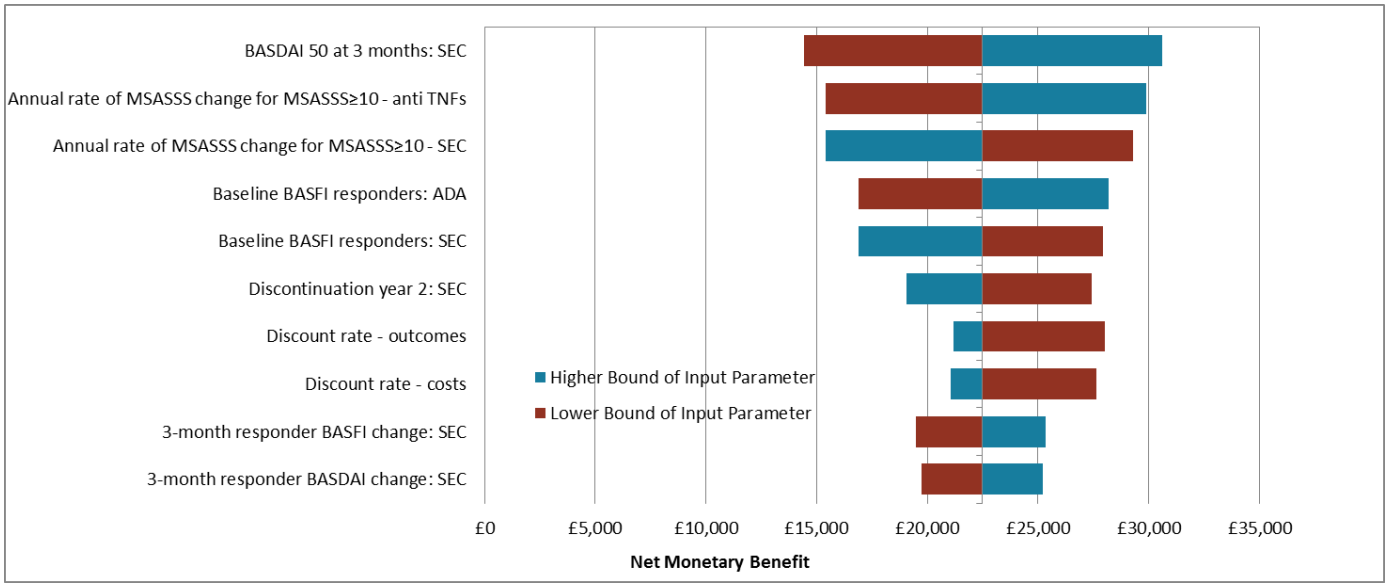


Figure 29. OWSA results for secukinumab vs golimumab – biologic naïve population

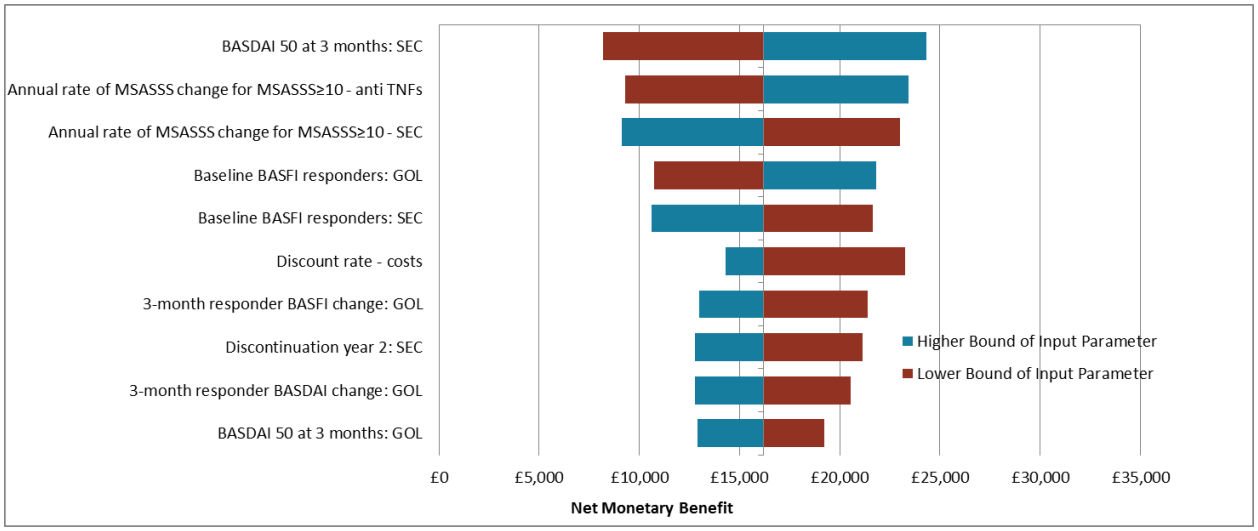


Figure 30. OWSA results for secukinumab vs infliximab – biologic naïve population

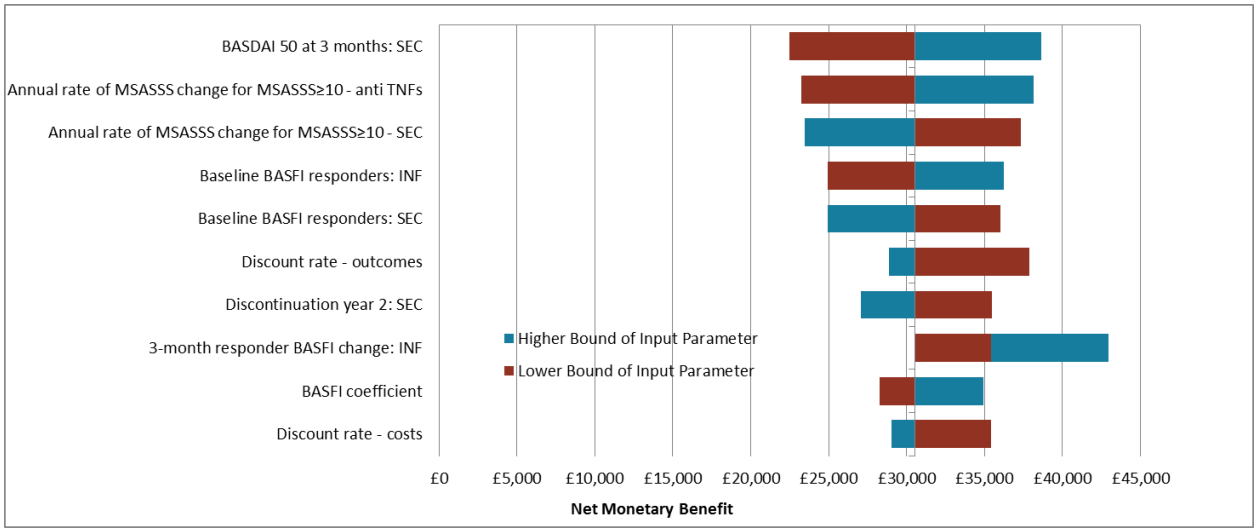


Figure 31. OWSA results for secukinumab vs infliximab biosimilar – biologic naïve population

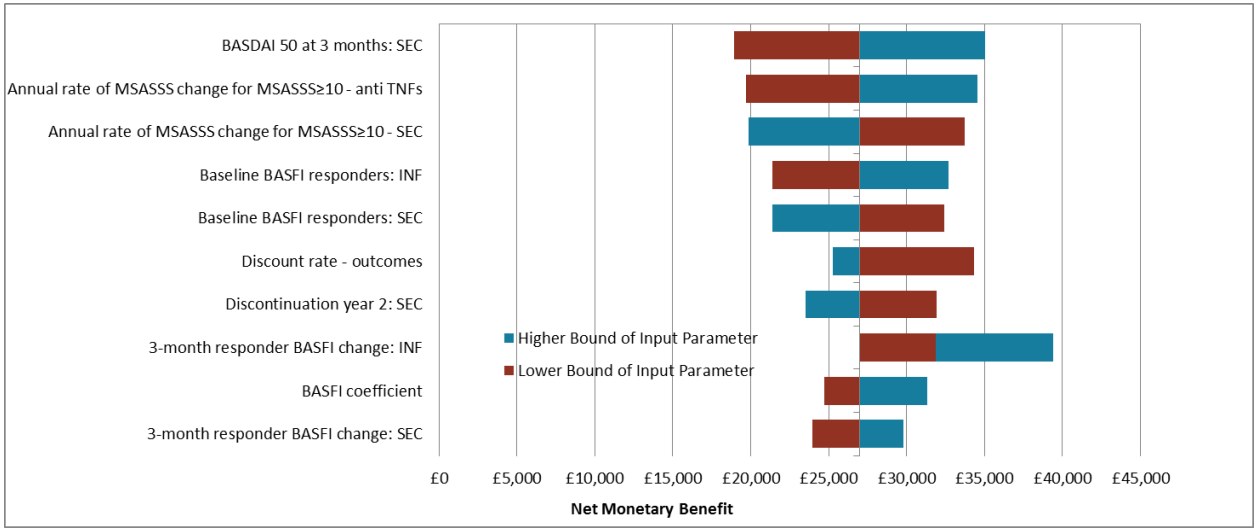
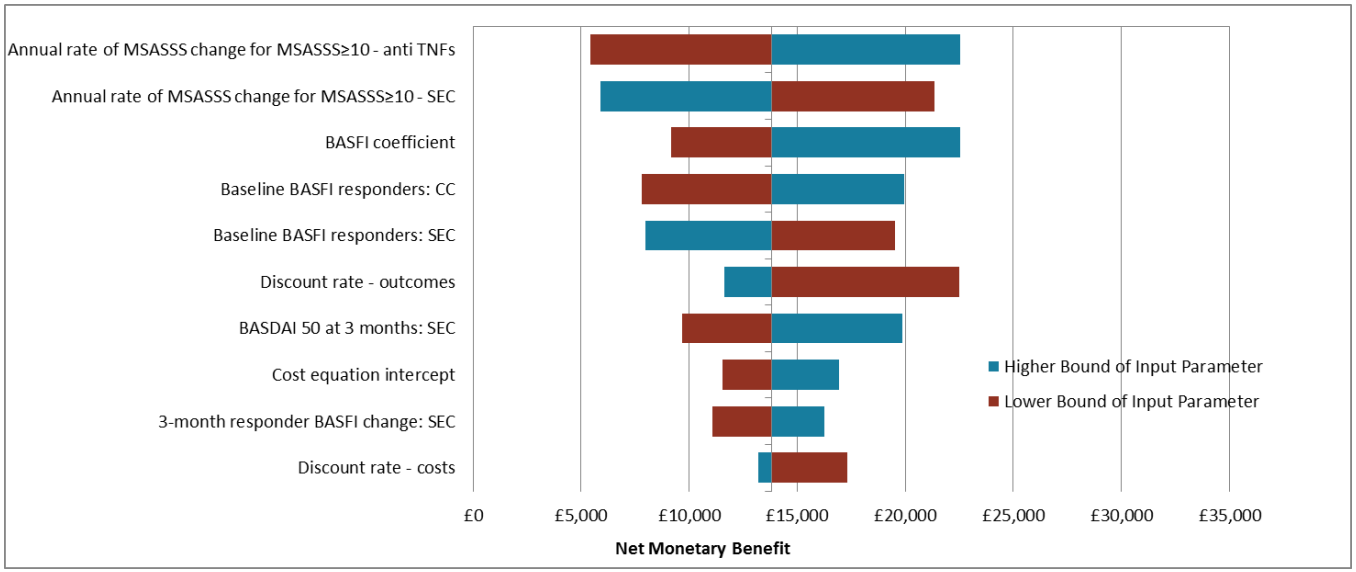


Figure 32. OWSA results for secukinumab vs conventional care – biologic experienced population



Scenario analysis

Table 88 and Table 89 below shows the results of the scenario analyses for each biologic comparator versus secukinumab in the biologic naïve population. Results are presented in this way since secukinumab is the lowest cost option in all but two scenarios (scenarios 3 and 6c, where etanercept is in the least expensive option). Table 90 presents the results of the scenario analyses in the biologic experienced population. In this case, results are expressed as ICERs for secukinumab versus conventional care.

Table 88: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part a]

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£15,300	-0.359	SEC dominates	£9,202	-0.359	SEC dominates	£16,703	0.025	£674,914

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Scenario 1a	£15,217	-0.354	SEC dominates	£9,092	-0.352	SEC dominates	£16,623	0.026	£632,894
Scenario 1b	£14,296	-0.260	SEC dominates	£8,441	-0.238	SEC dominates	£14,949	0.041	£361,558
Scenario 2	£16,025	-0.380	SEC dominates	£10,113	-0.386	SEC dominates	£16,923	0.018	£941,421
Scenario 3≠	£15,273	-0.291	SEC dominates	£9,216	-0.313	SEC dominates	£17,549	-0.063	SEC dominates
Scenario 4	£15,203	-0.120	SEC dominates	£10,671	-0.033	SEC dominates	£13,402	0.036	£374,910
Scenario 5	£23,265	-0.471	SEC dominates	£14,903	-0.474	SEC dominates	£25,783	0.029	£874,073
Scenario 6a	£17,762	-0.095	SEC dominates	£11,829	-0.133	SEC dominates	£19,009	0.318	£59,771
Scenario 6b	£17,318	0.086	£200,791	£10,361	0.062	£166,570	£16,205	0.358	£45,225
Scenario 6c	£11,280	-0.312	SEC dominates	£4,768	-0.367	SEC dominates	£9,880	-0.065	SEC dominates
Scenario 7a	£15,300	-0.369	SEC dominates	£9,202	-0.465	SEC dominates	£16,703	-0.065	SEC dominates
Scenario 7b	£15,300	-0.330	SEC dominates	£9,202	-0.331	SEC dominates	£16,703	0.022	£755,800
Scenario 8	£15,300	-0.359	SEC dominates	£9,202	-0.359	SEC dominates	£16,703	0.025	£674,914
Scenario 9	£16,581	-0.410	SEC dominates	£10,482	-0.409	SEC dominates	£17,984	-0.025	SEC dominates
Scenario 10	£15,344	-0.357	SEC dominates	£9,137	-0.353	SEC dominates	£16,606	0.028	£591,477

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.
≠Analysis has changed versus original approach – see response to B33

Table 89: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part b]

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,033	-1.046	SEC dominates	£1,018	-1.046	SEC dominates	£26,223	-0.216	SEC dominates	£22,649	-0.216	SEC dominates
Scenario 1a	£1,828	-1.037	SEC dominates	£813	-1.037	SEC dominates	£26,104	-0.208	SEC dominates	£22,529	-0.208	SEC dominates
Scenario 1b	£1,171	-0.867	SEC dominates	£157	-0.867	SEC dominates	£25,658	-0.069	SEC dominates	£22,129	-0.069	SEC dominates
Scenario 2	£3,185	-1.086	SEC dominates	£2,171	-1.086	SEC dominates	£27,402	-0.250	SEC dominates	£23,827	-0.250	SEC dominates
Scenario 3≠	£1,227	-0.730	SEC dominates	£212	-0.730	SEC dominates	£22,643	-0.134	SEC dominates	£26,218	-0.134	SEC dominates
Scenario 4	£10,228	-0.367	SEC dominates	£8,344	-0.367	SEC dominates	£29,192	0.167	£174,456	£25,394	0.167	£151,759
Scenario 5	£1,792	-1.378	SEC dominates	£325	-1.378	SEC dominates	£37,686	-0.122	SEC dominates	£32,454	-0.122	SEC dominates
Scenario 6a	£4,029	-0.877	SEC dominates	£2,948	-0.877	SEC dominates	£30,252	-0.072	SEC dominates	£26,472	-0.072	SEC dominates
Scenario 6b	£3,265	-0.618	SEC dominates	£2,186	-0.618	SEC dominates	£27,711	0.231	£119,703	£24,046	0.231	£103,872

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Scenario 6c	-£834	-1.056	£790*	-£1,796	-1.056	£1,701*	£20,730	-0.293	SEC dominates	£17,450	-0.293	SEC dominates
Scenario 7a	£2,033	-1.084	SEC dominates	£1,018	-1.084	SEC dominates	£26,223	-0.421	SEC dominates	£22,649	-0.421	SEC dominates
Scenario 7b	£2,033	-0.956	SEC dominates	£1,018	-0.956	SEC dominates	£22,649	-0.197	SEC dominates	£26,223	-0.197	SEC dominates
Scenario 8	£2,033	-1.046	SEC dominates	£1,018	-1.046	SEC dominates	£47,993	-0.216	SEC dominates	£44,419	-0.216	SEC dominates
Scenario 9	£3,313	-1.097	SEC dominates	£2,299	-1.097	SEC dominates	£27,504	-0.266	SEC dominates	£23,930	-0.266	SEC dominates
Scenario 10	£1,701	-1.028	SEC dominates	£686	-1.028	SEC dominates	£26,303	-0.214	SEC dominates	£22,729	-0.214	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.
≠Analysis has changed versus original approach – see response to B33

Table 90. Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population

	Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
Base case	£1,747	0.778	£2,245
Scenario 1a	£3,358	0.643	£5,223
Scenario 1b	£1,979	0.769	£2,574
Scenario 2	£8,556	0.601	£14,248
Scenario 3*	N/A	N/A	N/A
Scenario 4	£1,363	0.654	£2,083
Scenario 5	£3,704	1.036	£3,574
Scenario 6a	N/A	N/A	N/A
Scenario 6b	N/A	N/A	N/A
Scenario 6c	N/A	N/A	N/A
Scenario 7a	£1,747	0.882	£1,979
Scenario 7b	£1,747	0.711	£2,455
Scenario 8	N/A	N/A	N/A
Scenario 9	£1,238	0.798	£1,551
Scenario 10	£2,173	0.762	£2,853

Note: Scenarios 3, 6a, 6b & 6c are not relevant to comparison versus conventional care since the ratio of BASDAI / BASFI change from baseline amongst responders versus non-responders and the network meta-analysis results only affect comparisons versus the TNFα inhibitors. Scenario 8 is not relevant to comparison versus conventional care since it only affects comparison with infliximab and infliximab biosimilar.

REFERENCES

1. Braun J, Sieper J. Building consensus on nomenclature and disease classification for ankylosing spondylitis: results and discussion of a questionnaire prepared for the International Workshop on New Treatment Strategies in Ankylosing Spondylitis, Berlin, Germany, 18-19 January 2002. Ann Rheum Dis 2002;61 Suppl 3:iii61-7.

2. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 2014;48-49:128-33.

3. Novartis Data on File: MEASURE 2 Clinical Study Report – Week 52 Analysis.

4. Novartis Data on File: MEASURE 1 Clinical Study Report – Week 52 Analysis.

5. Keat A, Barkham N, Bhalla A, et al. BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. Rheumatology (Oxford) 2004;44:939-47.

6. Committee for Medicinal Products for Human Use. Draft Guideline on CLinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. June 2005.

7. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136-46.

8. Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.

9. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 2014;73:587-94.

10. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39-47.

11. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 2010;30:1437-40.

12. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.

13. Inman RD, Davis JC, Jr., Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008b;58:3402-12.

14. Department of Health. The Musculoskeletal Services Framework. 2006.

15. Office of National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland. Mid-2006. Available at http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland. Last accessed 08/03/2016.

16. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford) 2014;53:650-7.

17. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. New England Journal of Medicine 2015;373:2534-2548.

18. Ciurea A *et al.* The Reason of Discontinuation of a First TNF Inhibitor Affects Drug Retention of a Second Anti-TNF Agent in Axial Spondyloarthritis. 2015 ACR/ARHP Annual Meeting. 29th September 2015. Abstract No. 976

19. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64:1568-75.

20. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Medical Decision Making 2013;33:618-640.

21. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model [Internet]. Sheffield: 2011 [accessed 24.2.16].

22. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials [Internet]. Sheffield: 2014 [accessed 24.2.16].

23. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance TA383 [Internet], 2016 [accessed 24.2.16]:70.

24. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. Available at https://www.nice.org.uk/article/pmg9/chapter/Foreword. Last accessed 10.3.16. 2013.

25. National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233): Assessment Report. 2014. Available at https://www.nice.org.uk/guidance/gid-tag355/documents/ankylosing-spondylitis-and-

axial-spondyloarthritis-nonradiographic-adalimumab-etanercept-infliximab-and-golimumab-inc-rev-ta143-and-ta233-assessment-report-2. Last accessed 13th January 2016.

26. Corbett M, Soares M, Jhuti G, et al. TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233. York: CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, 2014:371.

27. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA383]. Multiple Technology Appraisal (MTA): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis - Addendum. 2016. Available at https://www.nice.org.uk/guidance/TA383/documents/ankylosing-spondylitis-and-axial-spondyloarthritis-nonradiographic-adalimumab-etanercept-infliximab-and-golimumab-inc-rev-ta143-and-ta233-id694-committee-papers4. Last accessed 2nd February 2016.

28. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA383]. Multiple Technology Appraisal (MTA): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. 2016. Available at https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077. Last accessed 2nd February 2016.

29. Ramiro S, van Tubergen A, van der Heijde D, et al. How to deal with missing items in BASDAI and BASFI. "RHEUMATOLOGY (OXFORD, ENGLAND)" 2014;53:374-6.

30. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.

31. Ramiro S, Stolwijk C, van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. Annals of the Rheumatic Diseases 2013.

32. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-158, iii-iv.

33. Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. Value Health 2015;18:425-31.

34. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. HEALTH TECHNOLOGY ASSESSMENT 2007;11:1-158, iii-iv.

35. Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. VALUE IN HEALTH 2015;18:425-31.

36. Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. ANNALS OF THE RHEUMATIC DISEASES 2003;62:732-40.

37. BMJ Group and Pharmaceutical Press. British National Formulary (BNF). Available at: https://www.medicinescomplete.com/mc/bnf/current/. Last accessed 08/03/2016.

38. Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. Ann Rheum Dis 2003;62:732-40.

39. van der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 2009;68:922-9.

40. van der Heijde D, Breban M, Halter D, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. Rheumatology (Oxford) 2015;54:1210-9.

41. Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.

42. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 2014;73:587-94.

43. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Annals of the Rheumatic Diseases 2013.

44. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Supplementary Data. Annals of the Rheumatic Diseases 2013.

45. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. Arthritis Rheumatol 2015;67:668-77.

46. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 2010;30:1437-40.

47. Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 2011;70:799-804.

48. Dougados M, Braun J, Szanto S, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. Rheumatology (Oxford) 2012;51:1687-96.

49. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.

50. Braun J, Deodhar A, Dijkmans B, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. Arthritis Rheum 2008;59:1270-8.

Appendices

Appendix A: A21 diagrams

Figure 33: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case)

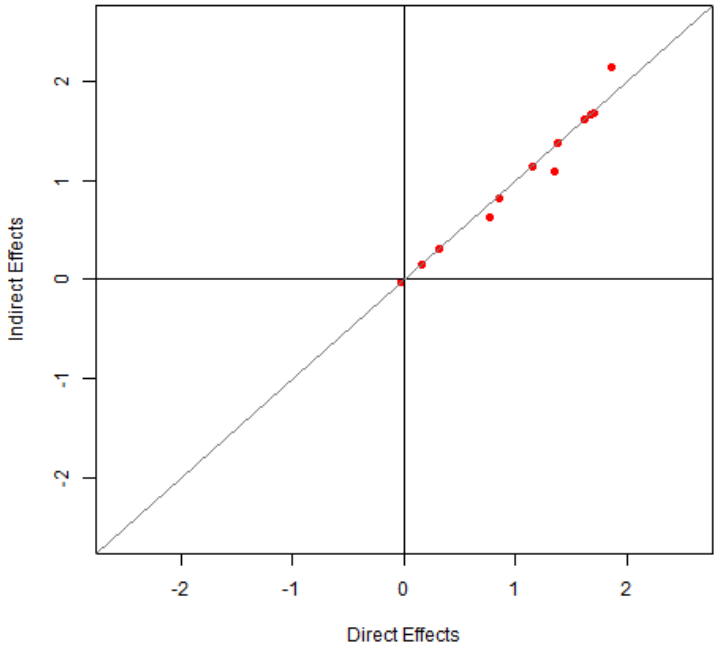


Figure 34: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case)

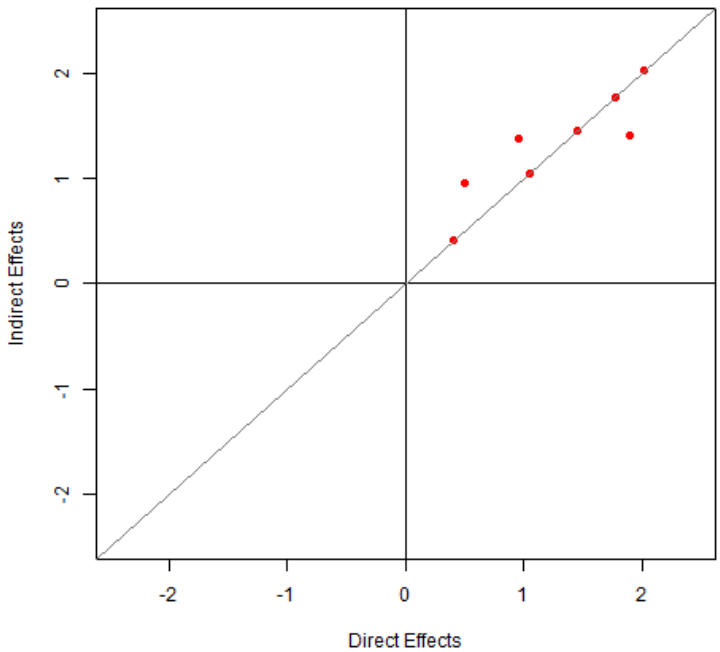


Figure 35: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 excluded (Sensitivity analysis 1)

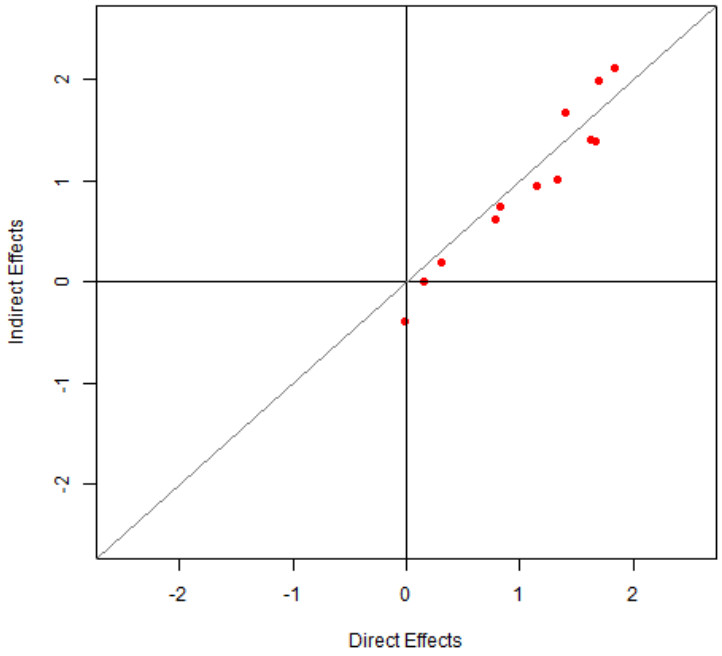


Figure 36: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 excluded (Sensitivity analysis 1)

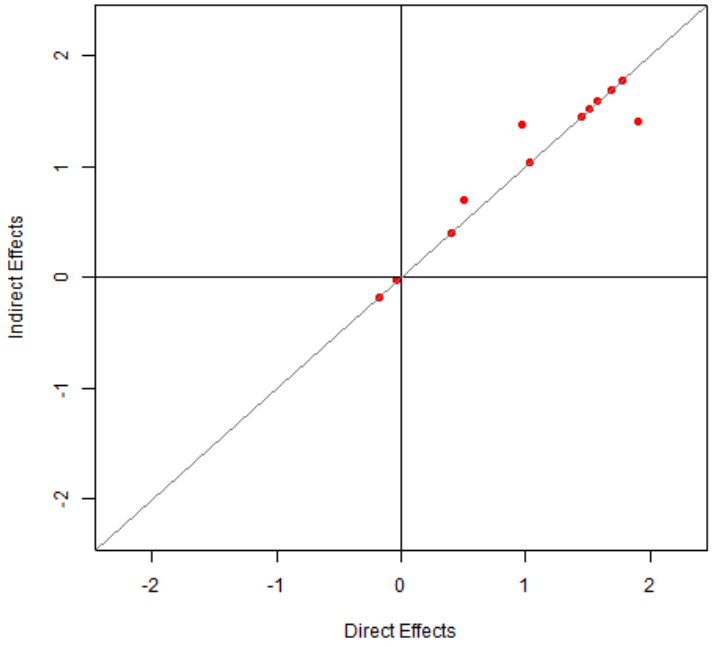


Figure 37: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2)

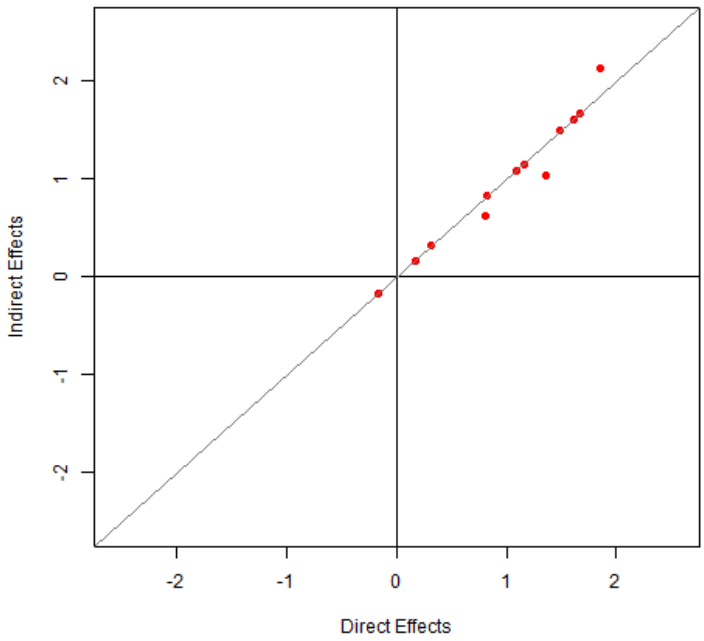


Figure 38: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2)

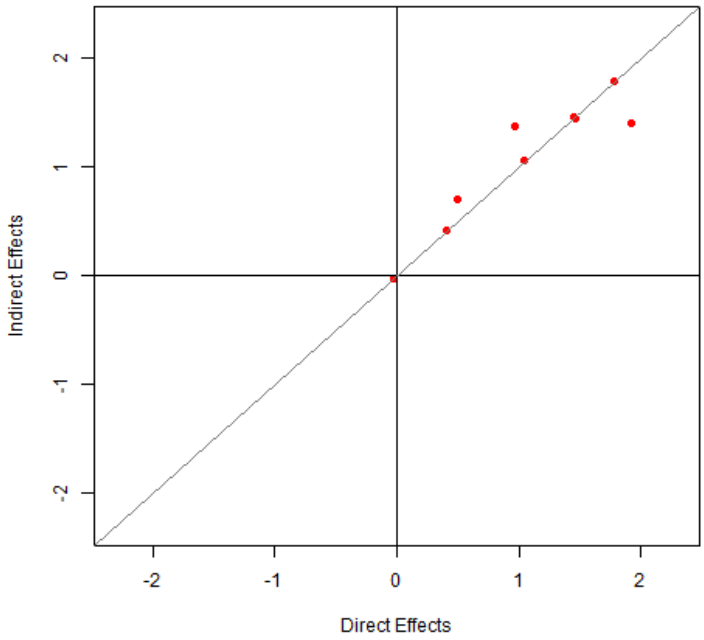


Figure 39: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3)

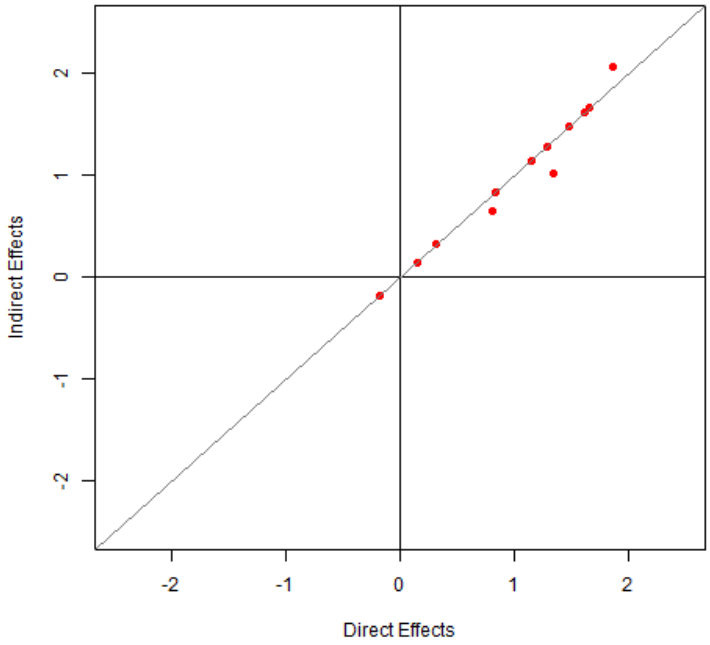


Figure 40: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3)

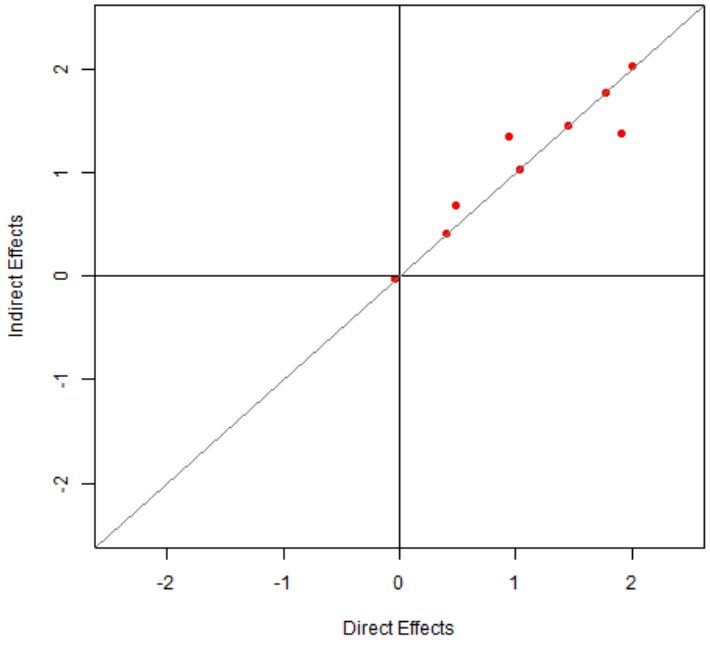


Figure 41: Comparison of estimated relative risk in ASAS20 response from fixed- NMA at 12 to 16 weeks with Measure 1 and 2 (Base case) among biologics-naïve

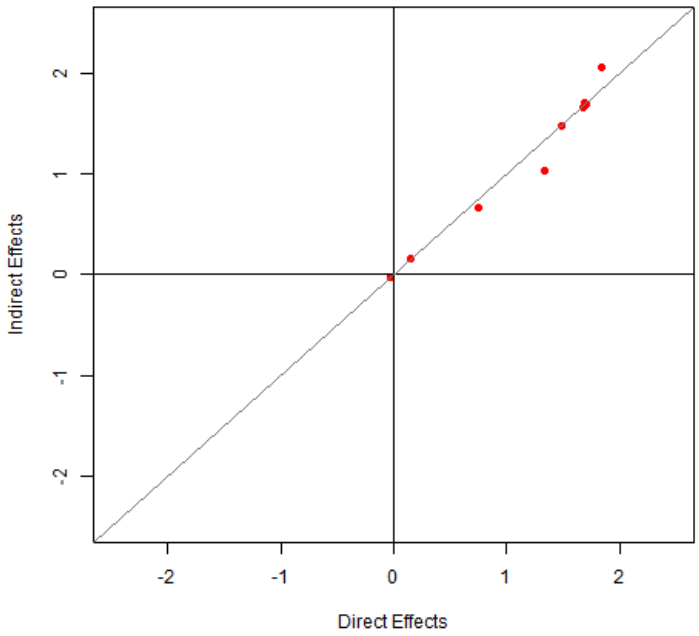


Figure 42: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case) among biologics-naïve

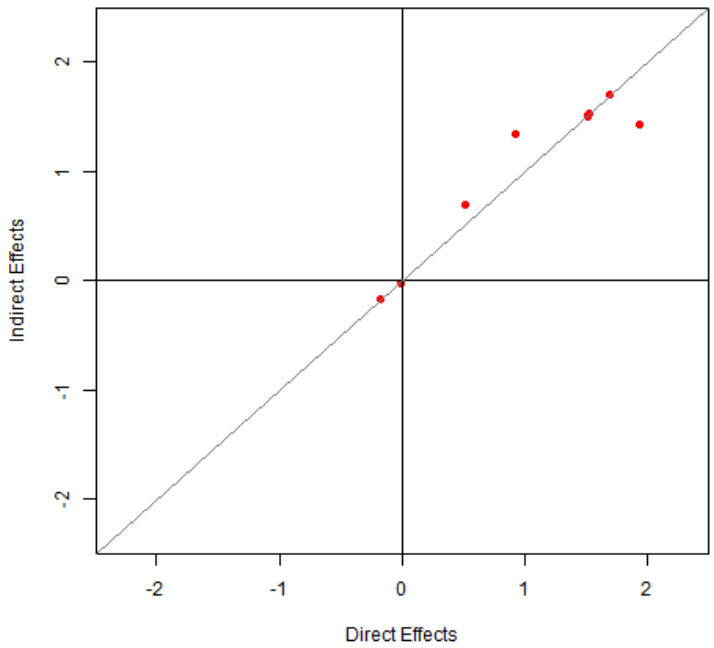


Figure 43: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 removed (Sensitivity analysis 1) among biologics-naïve

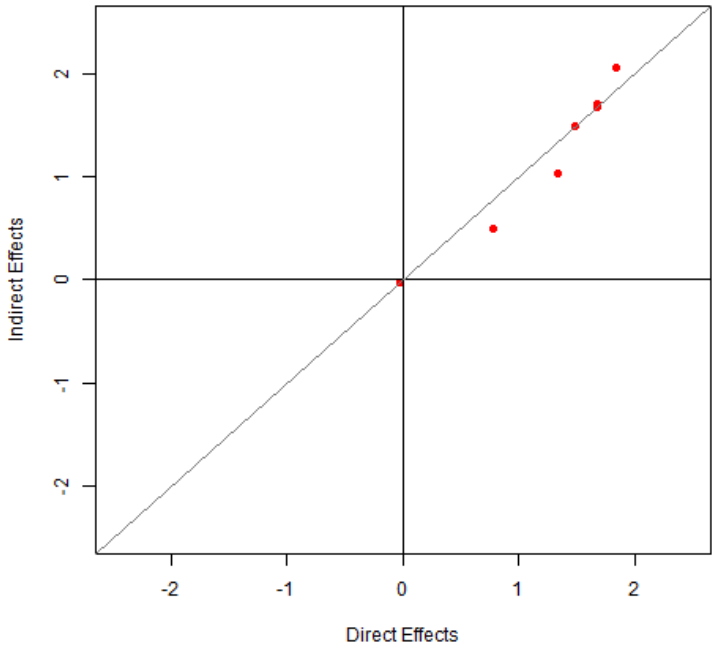


Figure 44: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 removed (Sensitivity analysis 1) among biologics-naïve

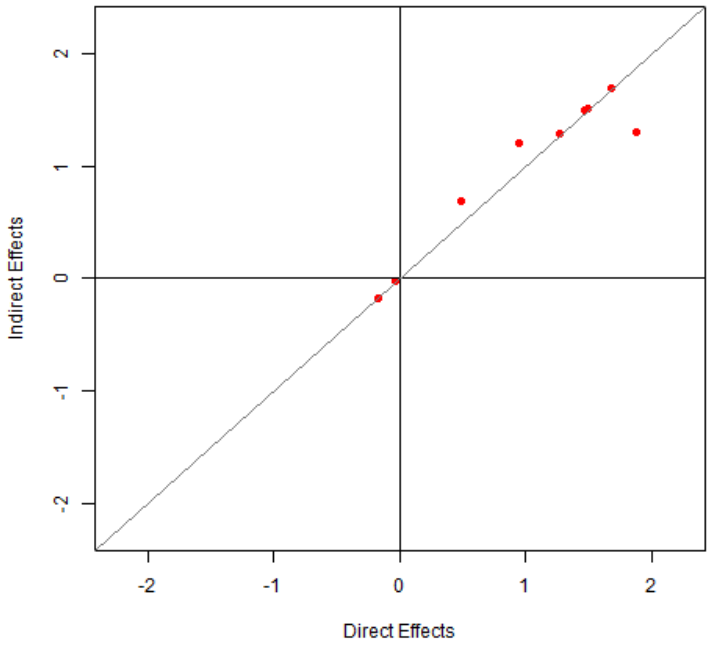


Figure 45: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2) among biologics-naïve

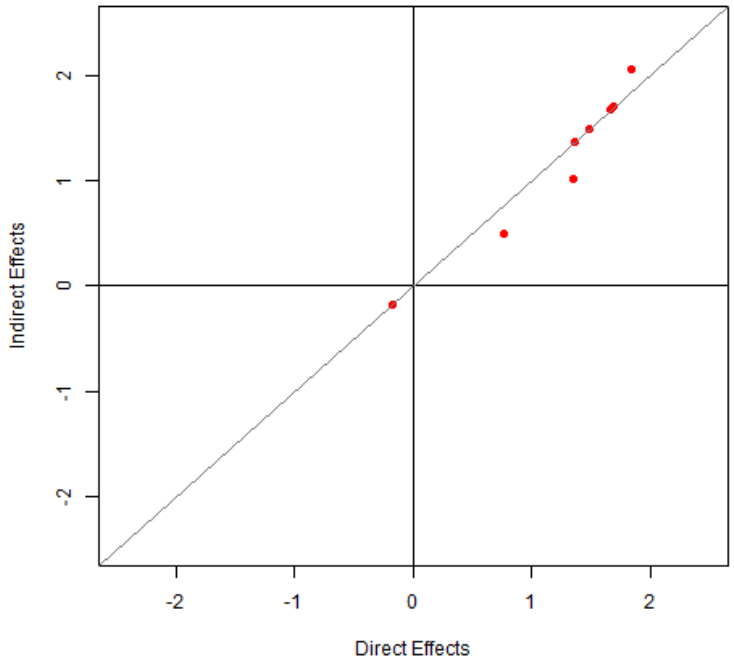


Figure 46: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2) among biologics-naïve

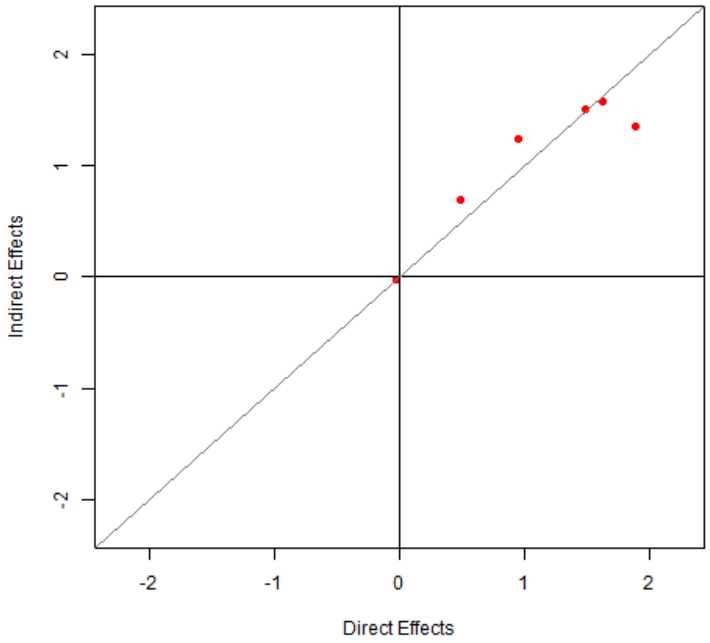


Figure 47: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3) among biologics-naïve

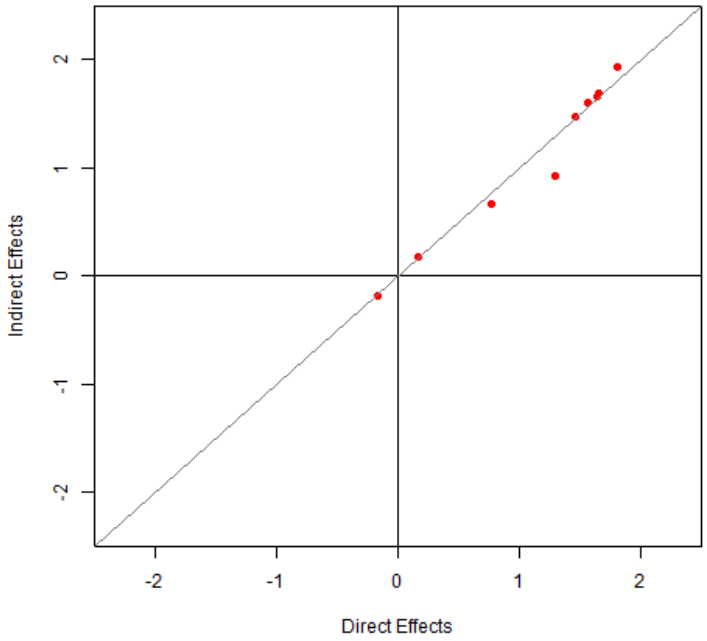
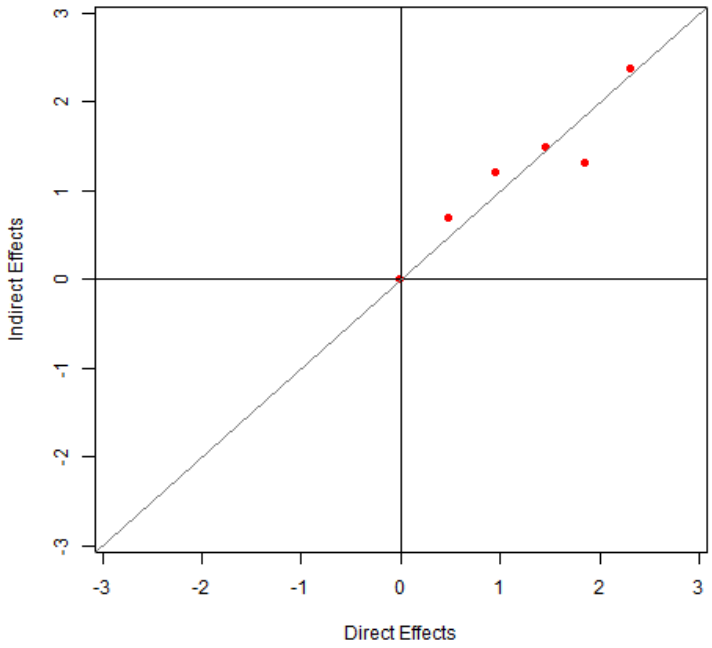


Figure 48: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3) among biologics-naïve



Appendix B: B7 WinBugs code

Model B: Code from Assessment Group Report Appendix 9 which did not run

```
model{
for (i in 1:10) {
y[i] ~ dnorm(theta[i], y.prec[i]) #change in score
theta[i] <- mu[s[i]] + d[t[i]]
}
for (i in 11:18) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
theta[i] <- mu[s[i]] + d[t[i]]
}
for (i in 19:28) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
theta[i] <- mu[s[i]] + d[t[i]]
}
for (j in 1:14) {
mu[j] ~ dnorm(0,0.001)
}
d[1] <- 0
for (k in 2:6) {
d[k] ~ dnorm(re,intau)
}
re ~ dnorm(0, 0.01)
intau <- 1/tau
tau <- pow(sd,2)
sd ~ dunif(0,2)
re.pred ~ dnorm(re,intau)
rho[1] ~ dunif(-1,1)
rho[2] ~ dunif(-1,1)
}
```

Comment [GS1]: Incorrect specification of standard deviation. Changed this to incorporate correct specification as per winBUGS

Comment [GS2]: Probit function in winBUGS caused error. This has also been noticed in other situations. Used the standard normal function which is the same as using probit(p[i]).

Comment [GS3]: The reciprocal of the square root of standard deviation was used, where just the standard deviation needs to be given as per statistical model B

Comment [GS4]: Similar comment on sd as per comment 1

Comment [GS5]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i].

Comment [GS6]: Same as comment 2.

Model B: Modified code used to generate results:

```
model{
  for (i in 1:10) {
    y[i] ~ dnorm(theta[i], y.prec.n[i])
    y.prec.n[i]<-1/pow(y.prec[i],2)#change in score
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (i in 11:18) {
    r[i] ~ dbin(p[i], n[i])
    aux[i] <- equals(t[i],1)+1
    p[i] <- phi(-(b[i]*0.5 + theta[i])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (i in 19:28) {
    r[i] ~ dbin(p[i], n[i])
    y[i] ~ dnorm(theta[i], y.prec.n[i]) #change in score
    y.prec.n[i]<-1/pow(y.prec[i],2)
    aux[i] <- equals(t[i],1)+1
    p[i] <- phi(-(b[i]*0.5 + theta[i])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (j in 1:14) {
    mu[j] ~ dnorm(0,0.001)
  }
```

```
  d[1] <- 0
  for (k in 2:6) {
    d[k] ~ dnorm(re,intau)
  }
  re ~ dnorm(0, 0.01)
  intau <- 1/tau
  tau <- pow(sd,2)
  sd ~ dunif(0,2)
  re.pred ~ dnorm(re,intau)
  rho[1] ~ dunif(-1,1)
  rho[2] ~ dunif(-1,1)
}
```

Model C: Code from Assessment Group Report Appendix 9 which did not run:

```
model{
for (i in 1:10) {
y[i] ~ dnorm(theta[i,1], y.prec[i]) #change in score
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 11:14) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 15:16) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
}
for (i in 17:26) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i,1], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 27:28) {
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 29:30) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i,1], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
}
for (i in 1:30) {
theta[i,1:2] ~ dmnorm(delta[i,1:2],B[1:2,1:2])
delta[i,1] <- mu1[s[i]] + d1[t[i]]
delta[i,2] <- mu2[s[i]] + d2[t[i]]
}
d1[1] <- 0
d2[1] <- 0
for (k in 2:6) {
d1[k] ~ dnorm(re1,intau)
d2[k] ~ dnorm(re2,intau)
}
B[1,1]<- 1/(pow(sd[1],2)*(1-pow(cor,2)))
B[2,2]<- 1/(pow(sd[2],2)*(1-pow(cor,2)))
B[1,2]<- -cor/(sd[1]*sd[2]*(1-pow(cor,2)))
B[2,1]<- B[1,2]
sd[1] ~ dunif(0,5)
sd[2] ~ dunif(0,5)
cor~dunif(0,1)
for (i in 1:15) {
mu1[i] ~ dnorm(0,0.01)I(-5,5)
mu2[i] ~ dnorm(0,0.01)I(-5,5)
}
re1 ~ dnorm(0, 0.01)I(-10,10)
re.pred1 ~ dnorm(re1,intau)
re2 ~ dnorm(0, 0.01)I(-10,10)
re.pred2 ~ dnorm(re2,intau)
intau <- 1/tau
tau <- pow(sd.re,2)
sd.re ~ dunif(0,2)
rho[1] ~ dunif(0,1)
rho[2] ~ dunif(0,1)
for (k in 2:6) {
d1.pred[k] ~ dnorm(re1,intau)
}
}
```

Comment [GS1]: Correct standard deviation specification, refer to comment 1.

Comment [GS2]: Correct standard deviation specification, refer to comment 1.

Comment [GS3]: Refer to comments 2 & 3

Comment [GS4]: Correct standard deviation specification, refer to comment 1.

Comment [GS5]: Refer to comments 2 & 3

Comment [GS6]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i] (same as comment 5)

Comment [GS7]: Refer to comments 2 & 3

Comment [GS8]: Refer to comments 2 & 3

Comment [GS9]: Refer to comments 2 & 3

Comment [GS10]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i] (same as comment 5)

Comment [GS11]: Refer to comments 2 & 3

Model C: Modified code used to generate results:

```
model{
  for (i in 1:10) {
```

```
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 11:14) {
  r[i] ~ dbin(p[i], n[i])
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 15:16) {
  r[i] ~ dbin(p[i], n[i])
  aux[i] <- equals(t[i],1)+1
  probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5))
}
for (i in 17:26) {
  r[i] ~ dbin(p[i], n[i])
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 27:28) {
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 29:30) {
  r[i] ~ dbin(p[i], n[i])
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
}
for (i in 1:30) {
  theta[i,1:2] ~ dmnorm(delta[i,1:2],B[1:2,1:2])
  delta[i,1] <- mu1[s[i]] + d1[t[i]]
  delta[i,2] <- mu2[s[i]] + d2[t[i]]
}
d1[1] <- 0
d2[1] <- 0
for (k in 2:6) {
  d1[k] ~ dnorm(re1,intau)
  d2[k] ~ dnorm(re2,intau)
}
B[1     ,1]<- 1/(pow(sd[1],2)*(1-pow(cor,2)))
B[2,2]<- 1/(pow(sd[2],2)*(1-pow(cor,2)))
B[1,2]<- -cor/(sd[1]*sd[2]*(1-pow(cor,2)))
B[2,1]<- B[1,2]
sd[1] ~ dunif(0,5)
```

```
  sd[2] ~ dunif(0,5)
  cor~dunif(0,1)
  for (j in 1:15) {
    mu1[j] ~ dnorm(0,0.01)I(-5,5)
    mu2[j] ~ dnorm(0,0.01)I(-5,5)
  }
  re1 ~ dnorm(0, 0.01)I(-10,10)
  re.pred1 ~ dnorm(re1,intau)
  re2 ~ dnorm(0, 0.01)I(-10,10)
  re.pred2 ~ dnorm(re2,intau)
  intau <- 1/tau
  tau <- pow(sd.re,2)
  sd.re ~ dunif(0,2)
  rho[1] ~ dunif(0,1)
  rho[2] ~ dunif(0,1)
  for (k in 2:6) {
    d1.pred[k] ~ dnorm(re1,intau)
  }
}
```

Appendix C: B8 JAGS Code

```
# Binomial likelihood, logit link
model{                                          # *** PROGRAM STARTS

for(i in 1:ns){
mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i])  {
        r[i,k] ~ dbin(p[i,k],n[i,k])
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
        rhat[i,k] <- p[i,k] * n[i,k]
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
           +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

       }
    resdev[i] <- sum(dev[i,1:na[i]])
    }

totresdev <- sum(resdev[])
d[1]<-0
d[2] ~ dnorm(0,.0001)
for (k in 3:nt){  d[k] ~ dnorm(classmu,.0001) }
classmu ~ dnorm(0,.0001) }

for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
```

```
        RR[c,k] <-T[k]/T[c]
        RD[c,k] <-T[k]-T[c]
        }
    }
for (c in 1:(nt)) {
     for (k in 1:(c)) {
          OR[c,k] <- 0
           lor[c,k] <- 0
           RR[c,k] <-0
          RD[c,k] <-0
          }
    }

for (i in 1: ns){
                    mu1[i] <- mu[i]*equals(t[i,1],1)}
                    A<- sum(mu1[])/nt1
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

}                                                   # *** PROGRAM ENDS

# Continuous outcomes, identity link
model{                                              # *** PROGRAM STARTS
for(i in 1:ns){
   mu[i] ~ dnorm(0,.0001)

   for (k in 1:na[i]) {
      vr[i,k] <- pow(se[i,k],2)

          prec[i,k] <- 1/vr[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k
     }
   resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])
for(i in 1:ns){
    for (k in (na[i]):(maxn + 1)){
        dev[i,k+1] <- 0
            theta[i,k+1] <- 0
      }
    }

d[1]<-0
d[2] ~ dnorm(0,.0001)
```

```
for (k in 3:nt){   d[k] ~ dnorm(classmu, classtau) }  # class specific priors for antiTNF treatment effects
classmu ~ dnorm(0,0.001)              # hyperprior for antiTNF class mean
classtau <- 1/(clsd*clsd)
clsd~dunif(0,5)              # hyperprior for antiTNF class sd

for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        D[c,k] <- (d[k]-d[c])
       }
  }

for (c in 1:(nt)) {
     for (k in 1:(c)) {
        D[c,k] <- 0
                  }
    }

for (i in 1: ns){
                  mu1[i] <- mu[i]*equals(t[i,1],1)}
                  A<- sum(mu1[])/nt1

for (k in 1:nt) { T[k] <- A + d[k]  }

}                                                  # *** PROGRAM ENDS
```

Appendix D: Update to Appendix J in the original submission (matching-adjusted indirect comparison of secukinumab and adalimumab)

With MEASURE 2

A matching-adjusted indirect comparison (MAIC) was conducted between secukinumab and adalimumab by matching the pooled secukinumab dose arms in MEASURE 2 to the adalimumab arm in the ATLAS trial, and the placebo arm from MEASURE 2 to the placebo arm in the ATLAS trial.

The base case scenario matched patients from both trials according to age, gender, CRP, prior TNFα inhibitor treatment and baseline BASFI score (see Table 93) Two further scenarios were performed, which matched patients according to the same characteristics, with the exception that in the second scenario baseline BASDAI score was matched instead of baseline BASFI score, and in the third scenario, both BASDAI and BASFI baseline scores were matched (see Table 96 and Table 99).

Results for ASAS20 and ASAS40 for secukinumab 150 mg and adalimumab in the base case scenario at Week 12, Week 16, Week 24 and Week 52 are shown in Table 91 and Table 92, respectively. At Week 24, the MAIC demonstrated that secukinumab 150 mg was associated with statistically significantly better results than adalimumab 40 mg with regards to ASAS20 and ASAS40 response relative to placebo. This was also the case at Week 52 for the ASAS20 response, demonstrating the significant sustained effects of secukinumab 150 mg in comparison to an active biologic comparator (adalimumab).

Statistically significantly better results for secukinumab 150 mg compared to adalimumab at Week 24 for both ASAS20 and ASAS40 relative to placebo were seen consistently across both alternative scenarios. At Week 52, ASAS20 and ASAS40 results for secukinumab 150 mg were numerically higher than adalimumab relative to placebo across all both alternative scenarios, though the results were not statistically significant. However this lack of statistical significance should be interpreted taking into account the fact that the adalimumab data at Week 52 used LOCF analysis and did include placebo switchers, thus not following the intention-to-treat principle. Results for secukinumab 150 mg were based on the more conservative non-responder imputation and also followed the intention-to-treat principle.

MEASURE 2 Base Case (Scenario 1):

Table 91: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 92. ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 93: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in the base case scenario

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=34)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	42.0 (12.48)	42.4 (9.1)

Female, n (%)	51 (24.5%)	26 (36.1%)	28.8%
Disease characteristics			
BASFI, mean (SD)	5.2 (2.2)	6.2 (2.1)	5.5 (1.7)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.3 (2.9)
TNF-naïve, n (%)	100%	44 (61.6%)	100.0%

ESS: Effective Sample Size

MEASURE 2 Scenario 2:

Table 94. ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]							
Adalimumab 40 mg								

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 95: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]							
Adalimumab 40 mg								

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 96: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in scenario 2

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=39)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	41.9 (12.5)	41.7 (9.5)
Female, n (%)	51 (24.5%)	26 (36.1%)	29.5%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.6 (1.5)	6.4 (1.0)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.2 (3.1)
TNF-naïve, n (%)	100%	43 (60.6%)	100.0%

ESS: Effective Sample Size

MEASURE 2 Scenario 3:

Table 97: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 98: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; Abbreviations: NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 99: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in scenario 3

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=34)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	41.9 (12.5)	42.7 (8.9)
Female, n (%)	51 (24.5%)	26 (36.1%)	28.5%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.6 (1.5)	6.3 (1.0)
BASFI, mean (SD)	5.2 (2.2)	6.2 (2.1)	5.6 (1.6)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.4 (2.9)
TNF-naïve, n (%)	100%	43 (61.1%)	100.0%

ESS: Effective Sample Size

With MEASURE 1

In addition to the matching-adjusted indirect comparison (MAIC) using MEASURE 2, another MAIC was conducted between secukinumab and adalimumab by matching secukinumab arms of MEASURE 2 to the adalimumab arm in the ATLAS trial.

The base case scenario matched patients from both trials according to age, gender, CRP, prior TNFα inhibitor treatment and baseline BASFI score (see Table 102) Two further scenarios were performed, which matched patients according to the same covariates, with the exception that in the second scenario baseline BASDAI score was matched instead of baseline BASFI score, and in the third scenario, both BASDAI and BASFI baseline scores were matched (see Table 105 and Table 108).

Results for ASAS20 and ASAS40 response relative to placebo for secukinumab 150 mg and adalimumab in the base case scenario at Week 12, Week 16, Week 24 and Week 52 are shown in Table 10 and Table 11, respectively. At Week 16 the MACI demonstrated that secukinumab 150mg was associated with statistically significantly better results than adalimumab with regards to ASAS20. ASAS40 was not reported for adalimumab at week 16. At week 24, secukinumab 150 mg was associated with statistically significantly better results than adalimumab 40 mg with regards to ASAS20 and ASAS40 responses.

Statistically significantly better results for secukinumab 150 mg compared to adalimumab at Week 24 for both ASAS20 and ASAS40 were seen consistently across both alternative scenarios. In some of the comparisons, statistically significant results were also observed at week 16 and week 52.

At Week 52, ASAS20 and ASAS40 results for secukinumab 150 mg were numerically higher than adalimumab across all scenarios, though the results were not statistically significant. However this lack of statistical significance should be interpreted taking into account the fact that the adalimumab data at Week 52 used LOCF analysis and did include placebo switchers, thus not following the intention-to-treat principle. Results for secukinumab 150 mg were based on the more conservative non-responder imputation and also followed the intention-to-treat principle.

MEASURE 1 Base Case (scenario 1):

Table 100: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (base case scenario)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 101: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (base case scenario)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 102: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in the base case scenario

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=88)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.1 (10.0)
Female, n (%)	51 (24.5%)	41 (32.8%)	25.4%
Disease characteristics			
BASFI, mean (SD)	5.2 (2.2)	5.6 (2.2)	5.3 (1.8)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (2.1)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

MEASURE 1 Scenario 2:

Table 103: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]		[redacted]		[redacted]		[redacted]	
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 104: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]		[redacted]		[redacted]		[redacted]	
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 105: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in Scenario 2

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=88)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.8 (9.9)
Female, n (%)	51 (24.5%)	41 (32.8%)	27.1%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.3 (1.6)	6.4 (1.3)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (2.1)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

MEASURE 1 Scenario 3:

Table 106: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 107: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 108: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in Scenario 3

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=83)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.8 (9.8)
Female, n (%)	51 (24.5%)	41 (32.8%)	26.4%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.3 (1.6)	6.4 (1.2)
BASFI, mean (SD)	5.2 (2.2)	5.6 (2.2)	5.3 (1.8)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (1.9)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

Novartis Clarification Questions Response Addendum:

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors [ID719]

Textual clarification on response to A11:

"In addition, as described in the submission dossier, pooled subgroup analyses based on ethnicity and weight revealed no clinically meaningful differences in efficacy or safety results based on these subgroups."

Should have read:

"In addition, as described in the ***regulatory*** submission dossier, pooled subgroup analyses based on ethnicity and weight revealed no clinically meaningful differences in efficacy or safety results based on these subgroups."

Further data in response to A14:

Table 1 to Table 10 present the results of the requested interaction tests between treatment and subgroup for the additional outcomes of particular clinical relevance from both MEASURE 1 and MEASURE 2; ASAS40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline and ASQoL change from baseline. Please note that the MEASURE 1 and MEASURE 2 studies were not powered to detect a difference between the TNFα inhibitor-naïve subgroup and the TNFα inhibitor-inadequate responder subgroup, and hence these analyses were not included in the pre-specified analysis plan. Relatively small patient numbers in the TNFα inhibitor-inadequate responder subgroup mean that these results should not be relied upon. Whilst the tests for interaction do not reach statistical significance, we consider them to be clinically meaningful. In addition, switching to an alternative TNFα inhibitor in axial spondyloarthropathies has been shown to be associated with lower response rates (Ciurea A *et al.*2015).Please note that these analyses were carried out at a trial level, and thus included the unlicensed 75mg dose of secukinumab.

Table 1 MEASURE 1 ASAS40 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	45/92 (48.9)	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	14/89 (15.7)	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	7/33 (21.2)	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	2/33 (6.1)	NA	NA	NA	NA	

M=Number of patients in each treatment group; n=Number of ASAS40 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 2 MEASURE 2 ASAS40 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	19/44 (43.2)	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	8/45 (17.8)	NA	NA	NA	NA	
TNFα inhibitor-	Secukinumab 75 mg	[redacted]	Placebo	NA*	NA*	NA*	

inadequate responder	Secukinumab 150mg	7/28 (25.0)	Placebo	NA*	NA*	NA*	
	Placebo	0/29 (0.0)	NA	NA	NA	NA	

M=Number of patients in each treatment group; n=Number of ASAS40 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.
* Cannot be calculated due to zero response in the placebo arm

Table 3 MEASURE 1 BASDAI50 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	

M=Number of patients in each treatment group; n=Number of BASDAI50 responders in each treatment group (missing BASDAI responses were considered non-responders);
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 4 MEASURE 2 BASDAI50 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	

naïve		[redacted]					[redacted]
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	

M=Number of patients in each treatment group; n=Number of BASDAI50 responders in each treatment group (missing BASDAI responses were considered non-responders);
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 5 MEASURE 1 BASDAI change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	89, -2.72 (0.19)	Placebo	[redacted]	[redacted]	<0.0001	
	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	32, -1.72 (0.33)	Placebo	[redacted]	[redacted]	0.0287	
	Placebo	[redacted]	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 6 MEASURE 2 BASDAI change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	43, -2.56 (0.32)	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	42, −1.15 (0.32)	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	24, -1.60 (0.41)	Placebo	[redacted]	[redacted]	0.0928	
	Placebo	22, −0.59 (0.43)	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;
Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 7 MEASURE 1 BASFI change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	

	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 8 MEASURE 2 BASFI change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;
Abbreviations: BASFI, Bath Ankylosing Spondylitis Functional Index; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 9 MEASURE 1 ASQoL change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 10 MEASURE 1 ASQoL change from baseline by subgroup at Week 16 using MMRM (full analysis set)

Subgroup	Treatment Group	n, mean change (SE)	Comparator	Treatment contrast mean (SE)	95% confidence interval	p-value	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	43, -5.02 (0.68)	Placebo	[redacted]	[redacted]	[redacted]	
	Placebo	43, -1.94	NA	NA	NA	NA	

		(0.68)					
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	Placebo	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	23, -2.39 (0.84)	Placebo	[redacted]	[redacted]	0.1184	
	Placebo	23, -0.49 (0.85)	NA	NA	NA	NA	

n=Number of subjects with measurements at both baseline and week 16;
Abbreviations: ASQoL, Ankylosing Spondylitis Quality of Life; NA, not applicable; TNFα, tumour necrosis factor alpha.

Textual clarification on response to A22 – A24:

An additional file was provided with the response, which was not referred to in the response document "ID719 Secukinumab AS MAIC Description of Methods AIC A24". This document is provided in support of the responses to clarification questions A22 – A24.

Further data in response to B3:

We omitted to include the baseline BASDAI / BASFI scores and changes from baseline employed in the model for second-line treatments. Please find these in Table 11 andTable 12 below for the biologic naïve and biologic experienced populations, respectively.

Please note that the values in Table 11 refer to the setting "Model decline in efficacy = No"; if "Yes" is selected in this field then the change from baseline values would be multiplied by the values in cells F58: F59 on the Clinical inputs sheet.

Table 11 BASDAI and BASFI baseline and change from baseline for second-line treatment within the biologic naïve population

	BASDAI		BASFI	
	2nd line baseline	2nd line change from baseline	2nd line baseline	2nd line change from baseline
Secukinumab	Responders: 6.42 Non-responders: 6.39	Responders: -5.63 Non-responders: -1.27	Responders: 5.44 Non-responders: 6.07	Responders: -4.01 Non-responders: -0.93
Certolizumab	Responders: 6.42 Non-responders: 6.39	Responders: -5.44 Non-responders: -1.23	Responders: 5.44 Non-responders: 6.07	Responders: -3.94 Non-responders: -0.96
Etanercept	Responders: 6.42	Responders: -5.66	Responders: 5.44	Responders: -4.02

	Non-responders: 6.39	Non-responders: -1.28	Non-responders: 6.07	Non-responders: -0.98
Adalimumab	Responders: 6.42 Non-responders: 6.39	Responders: -5.64 Non-responders: -1.33	Responders: 5.44 Non-responders: 6.07	Responders: -4.08 Non-responders: -0.99
Infliximab	Responders: 6.42 Non-responders: 6.39	Responders: -4.95 Non-responders: -1.12	Responders: 5.44 Non-responders: 6.07	Responders: -3.70 Non-responders: -0.90
Golimumab	Responders: 6.42 Non-responders: 6.39	Responders: -5.49 Non-responders: -1.21	Responders: 5.44 Non-responders: 6.07	Responders: -3.89 Non-responders: -1.01
Source	Estimated as average of all biologic treatments. Average of cells F40:K40 in clinical inputs sheet.	This value is taken as average of all biologics except the first line treatment.	Estimated as average of all biologic treatments. Average of cells F44:K44 in clinical inputs sheet. This is also adjusted based on the median cycle of discontinuation*	For the mixed Tx, this value is taken as average of all biologics except the first line treatment.

*Model identifies the cycle by which more than 50% of the patients switch to 2nd treatment, this is the median cycle of discontinuation.
Baseline BASFI score on 2nd line treatment = Baseline BASFI + (increment in BASFI score by the median cycle of discontinuation if any)

Table 12 BASDAI and BASFI baseline and change from baseline for second-line treatment (i.e. conventional care) within the biologic experienced population

	BASDAI		BASFI	
	2^{nd} line baseline	2^{nd} line change from baseline	2^{nd} line baseline	2^{nd} line change from baseline
Secukinumab	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40
Certolizumab	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40
Etanercept	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40
Adalimumab	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40
Infliximab	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40

Golimumab	Responders: 6.24 Non-responders: 6.61	Responders: -2.93 Non-responders: -0.67	Responders: 5.49 Non-responders: 5.85	Responders: -1.61 Non-responders: -0.40
Source	Taken as CC values. Can be found in “Clinical inputs” sheet cells L40, L41	Taken as CC values. Can be found in “Clinical inputs” sheet cells L49, L50	Taken as CC values. Can be found in “Clinical inputs” sheet cells L44, L45	Taken as CC values. Can be found in “Clinical inputs” sheet cells L54, L55

Novartis Clarification Questions Response:

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors [ID719]

Contents

Section A: Clarification on effectiveness data

Definitions

A1. **Priority request**: Please provide definitions for 1) mild, 2) moderate and 3) severe ankylosing spondylitis as used in the submission.

There is currently no consensus on the definitions of mild, moderate or severe ankylosing spondylitis (AS).[1] The classification of AS continues to be a topic of debate and the absence of agreed terminology means that the relevance and importance of this classification is unclear.[2] The inclusion criteria of the MEASURE 2 and MEASURE 1 trials specified that patients had been diagnosed with moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI≥4 (0-10), spinal pain as measured by VAS≥4 (0-10) on BASDAI question 2, and total back pain as measured by VAS≥40 (0-100mm).[3, 4] No further criteria were used to determine whether patients had moderate to severe AS or to distinguish between these classes. This is in line with the approved indication for secukinumab, the population in the final NICE scope, with the British Society for Rheumatology guidelines for prescribing biologics in AS and the EMA CHMP Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis (2005).[5, 6]

- Please state how many people had mild, moderate and severe ankylosing spondylitis in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).

In both MEASURE trials, patients were required to have prior documented radiologic evidence fulfilling the Modified New York criteria for AS with active AS assessed by BASDAI≥4 and spinal pain as measured by VAS≥4 cm, meaning that all patients in the study had active AS, in line with the approved indication for secukinumab and the population in the final NICE scope.

Please see above statements regarding the definitions and available data for MEASURE 1 and MEASURE 2.

Furthermore, this data does not exist for the other trials included in the network meta-analysis (NMA), indicating that such classification lacks clinical relevance.

- Please provide data separately for people with mild, moderate and severe ankylosing spondylitis, for all outcomes specified in the scope (after 12 and 16 weeks) for each of the MEASURE trials (and all other trials included in the network meta-analysis, if available).

See above, these data are not available.

A2. Please provide a definition of conventional care, in both the biologic experienced and biologic naïve populations. Does conventional care include physiotherapy and/or non-steroidal anti-inflammatory drugs (NSAIDS)?

As described in Section 3.5 of the submission, conventional care is defined as treatment with NSAIDs alongside non-pharmacological interventions to help relieve pain and stiffness (e.g. physiotherapy).[5] Therefore, conventional care is considered to include both NSAIDs and physiotherapy. This treatment is variably referred to in the submission as conventional therapy or conventional care; the two terms are considered interchangeable.

- Please provide an overview of the concomitant therapies that were permitted in each of the MEASURE trials (and all other trials included in the network meta-analysis, if available), as well as the prior medications received before starting the trial.

Concomitant Therapies – MEASURE 2 and MEASURE 1

Information on permitted concomitant therapies within the MEASURE 1 and MEASURE 2 trials was provided in Tables 11 and Appendix E (Table 131) of the submission; “Inclusion criteria” and “Guidelines for the use of concomitant medicines”, respectively.

Please find below a summary of the concomitant therapies that were permitted in other trials included in the network meta-analysis.

Concomitant Therapies – Other Trials Included in the NMA

Details of concomitant therapies used in other trials included in the NMA are presented in Table 1 below.

Table 1: Summary of the concomitant therapies that were permitted in other trials included in the NMA

Trial	Treatment	Concomitant Medications
ATLAS[7]	Adalimumab	Remain on the following treatments if dosage has remained stable for at least 4 weeks before the baseline visit: • Sulfasalazine (≤3gm/day) • Methotrexate (≤25mg/week) • Hydroxychloroquine (≤400mg/day) • Prednisone or prednisone equivalent (≤10mg/day) • NSAIDS
Hu (2012)[8]	Adalimumab	Patients could remain taking the following treatments if dosage has remained stable for at least 4 weeks before the baseline visit: • Sulfasalazine (≤3gm/day) • Methotrexate (≤25mg/week) • Prednisone and/or prednisone equivalents (≤10mg/day) and/or NSAIDs
Huang (2014)[9]	Adalimumab	The following treatments were allowed, however dose adjustments, induction and/or discontinuation of therapies was only permitted during the open-label period: • Methotrexate (≤25mg/week) • Sulfasalazine (≤3gm/day) • Prednisone (≤10mg/day) • NSAIDs and/or analgesics
RAPID-axSpA[10]	Certolizumab	NSAIDs DMARDs
Giardina (2010)[11]	Etanercept	NSAIDs
SPINE[10]	Etanercept	NSAIDs – doses had to remain stable for the 2 weeks prior to study entry DMARD (sulfasalazine and methotrexate) – doses had to remain stable in the 4 weeks prior to study entry
ASSERT[12]	Infliximab	Patients could receive concomitant stable doses of: • NSAIDs • Acetaminophen (paracetamol) • Tramadol
GO-RAISE[13]	Golimumab	Patients were allowed to continue the following concomitant treatments at stable doses: • Methotrexate • Sulfasalazine • Hydroxychloroquine • Corticosteroids • NSAIDs Patients receiving NSAIDs had to have received continuous therapy for 3 months at the highest recommended doses or had to have been unable to receive a full 3month course of full dose NSAID therapy because of intolerance, toxicity or contraindications

Abbreviations: DMARD, Disease modifying anti-rheumatic drug; NSAID, Non-steroidal anti-inflammatory drug.
Source: as indicated.

Prior Medications

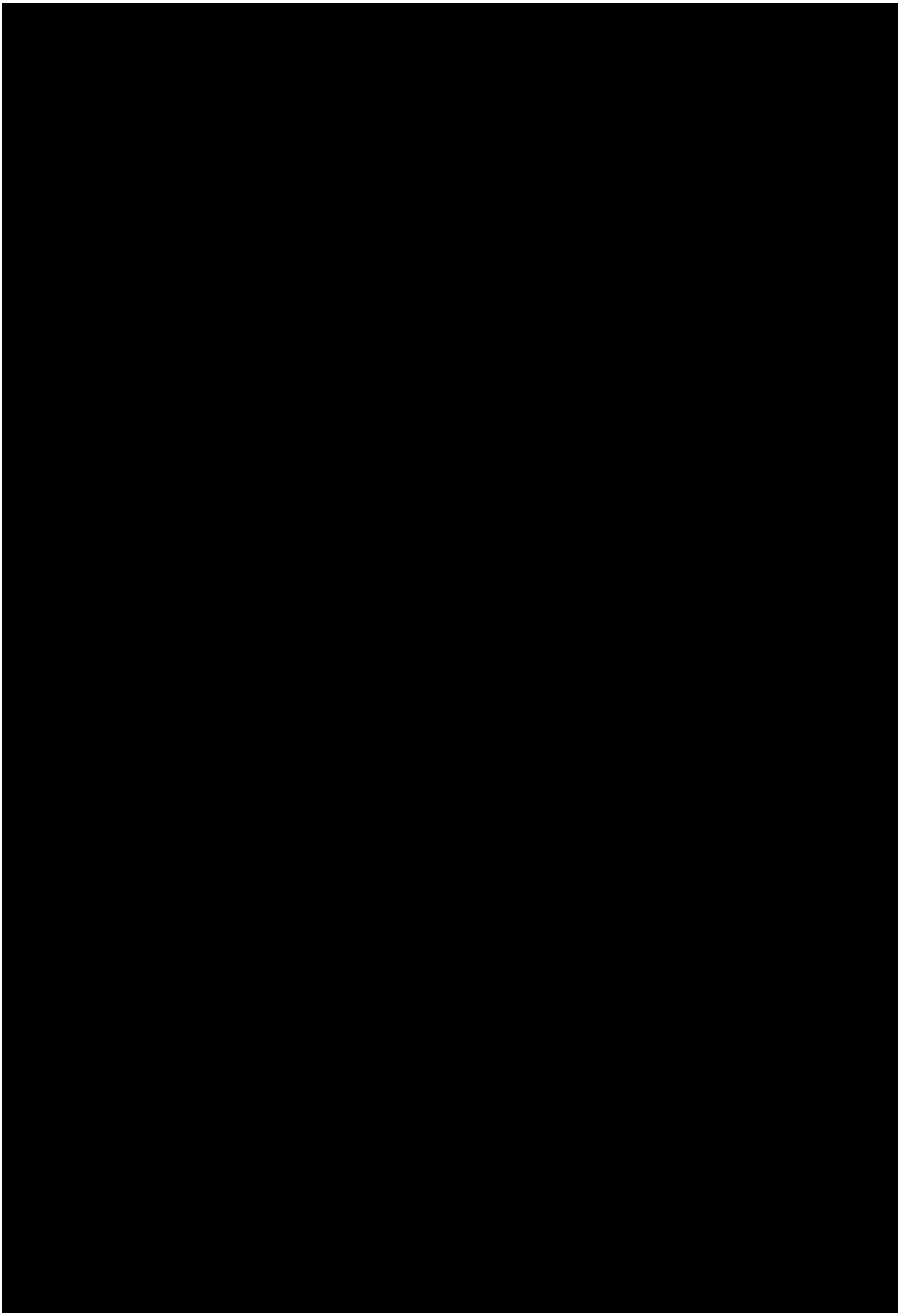
In MEASURE 1 and 2 Prior medications were reported in similar proportions of patients across the treatment groups:

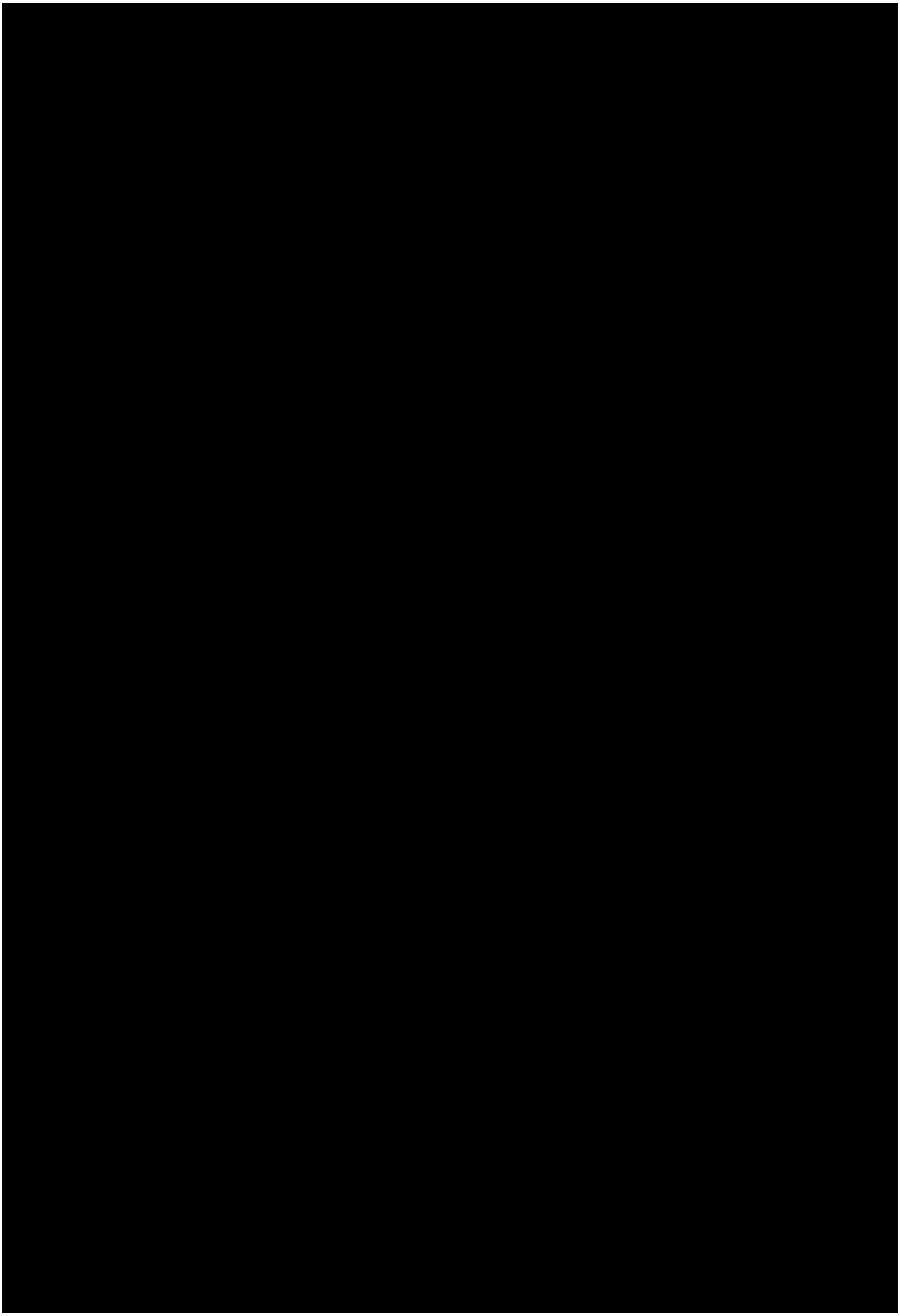
- MEASURE 1: [redacted] and [redacted] for the secukinumab IV-150 mg and placebo groups
- MEASURE 2: prior medications were reported in [redacted] and [redacted] of patients in the secukinumab 150 mg s.c. and placebo groups, respectively.

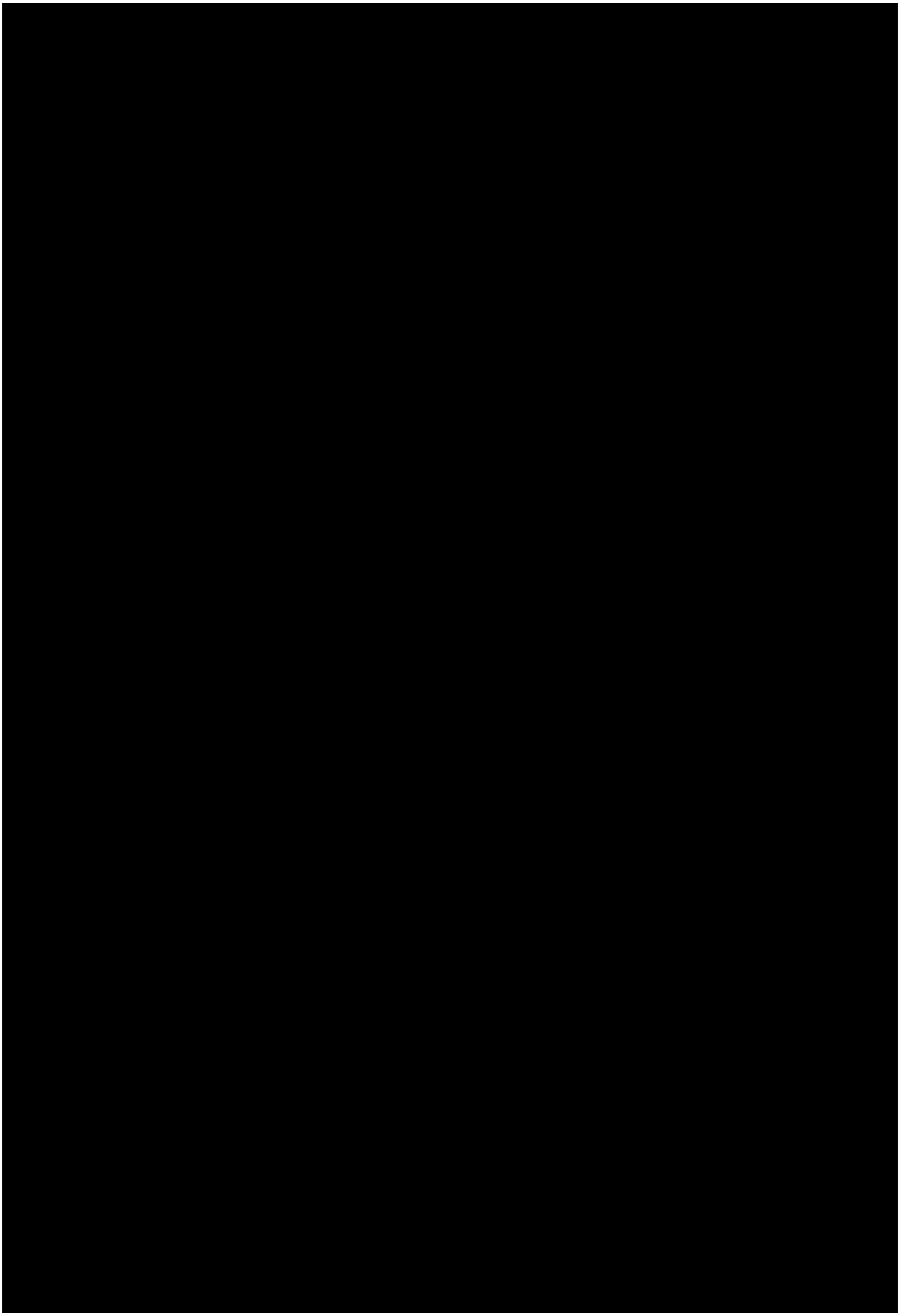
Please find in [redacted] 2 below a summary of the prior medications that patients in MEASURE 1 and 2 had received.

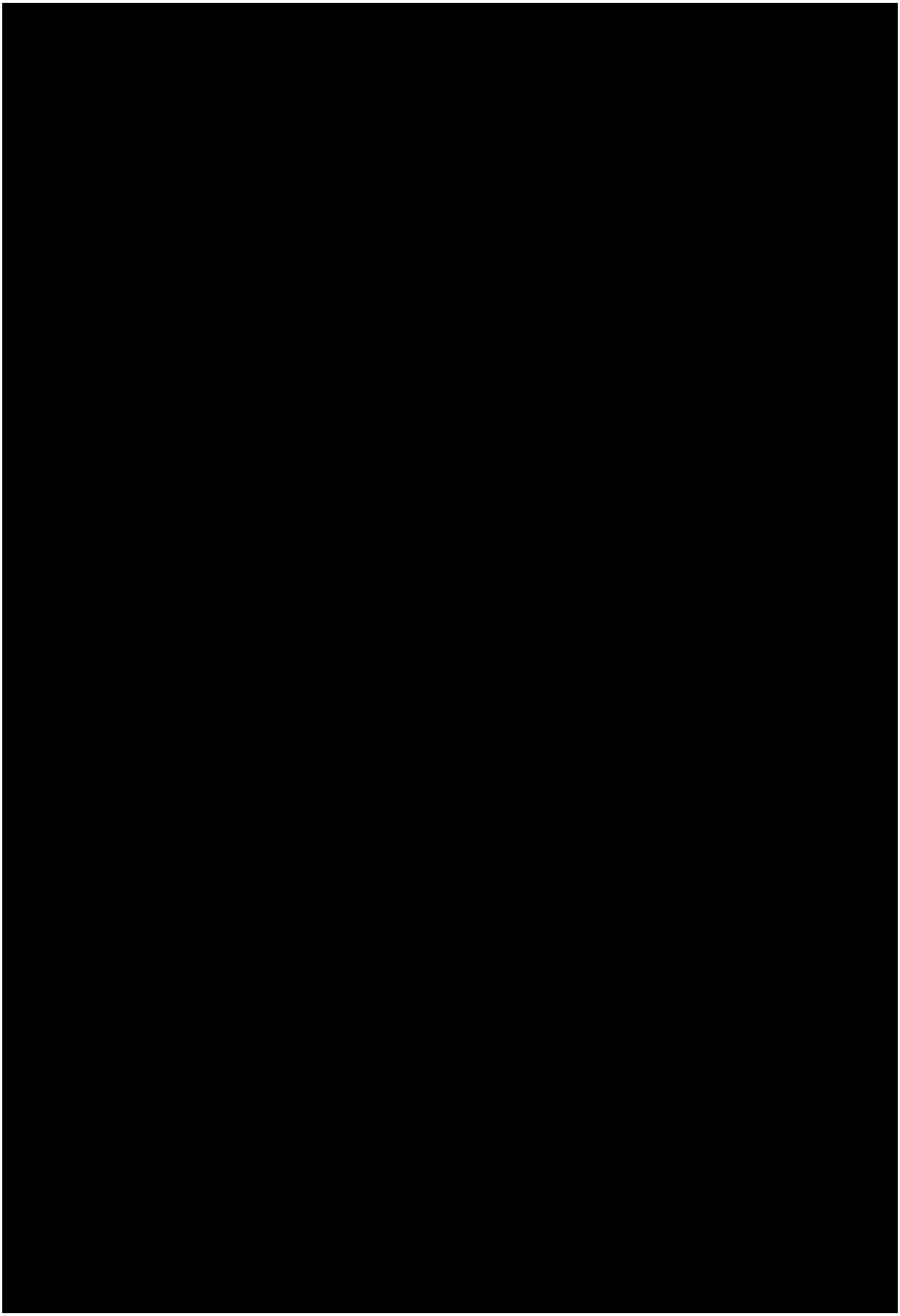
[redacted] 2

[redacted]









[redacted]

A3. Section 3.1 of the company submission provides UK specific prevalence estimates.

- What is the time frame for the "estimated 200,000 cases of AS [that] have been diagnosed in the UK"?

The prevalence estimate of 200,000 cases of AS was provided by the Department of Health in The Musculoskeletal Services Framework published on 12th July 2006.[14] The original source states that "upwards of 400,000 adults in the UK have rheumatoid arthritis, while about 200,000 have been diagnosed with ankylosing spondylitis…", which suggests the figure of 200,000 is an estimate of the number of patients in the UK who, at the time of reporting, had received a diagnosis of AS.

- What is the denominator used to calculate prevalence?

The prevalence estimate of 200,000 is quoted for adults in the UK and therefore, the denominator is assumed to be the adult population in the UK at the time of reporting.[14] Assuming a UK adult population of 47,469,500 as reported in 2006, this would be equivalent to a prevalence estimate of 42.1 cases per 10,000, which is a similar order of magnitude to the alternative European prevalence estimate of 23.8 cases per 10,000.[15, 16]

Literature searching

A4. Please supply the date span of the individual databases searched for the clinical systematic literature review and the cost effectiveness systematic literature review.

a) For the clinical systematic literature review, databases were searched from database inception up to 23rd January 2015 (PubMed, Cochrane), 26th January (Embase), and 27th January 2015 (BIOSIS) for the original review. For the update, all databases were searched from 1st January 2014 to 14th September 2015.

As described in Appendix C of the submission, in the original clinical systematic literature review, databases were searched from database inception up to 23rd January 2015 (PubMed, Cochrane), 26th January (Embase), and 27th January 2015 (BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

b) For the original economic systematic literature review, databases were searched from 1st January 1999 up to 22nd December 2014 (Embase, Cochrane Library), 23rd January 2015 (PubMed), and 27th January 2015 (EconLit, BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

As described in Appendix D of the submission, in the original economic systematic literature review, databases were searched from 1st January 1999 up to 22nd December 2014 (Embase, Cochrane Library), 23rd January 2015 (PubMed), and 27th January 2015 (EconLit, BIOSIS). For the update, all databases were searched from 1st January 2014 to 14th September 2015.

Database inception dates for PubMed, EMBASE and BIOSIS are 1946, 1947 and 1926, respectively.

A5. Please supply the search strategies for the searches conducted in clinicaltrials.gov and the International Clinical Trials Registry (ICTRP).

Search Strategy for clinicaltrials.gov

The following search strategies, listed as Conditions | Interventions | Age Group, were conducted in clinicaltrials.gov:

- "ankylosing spondylitis" | secukinumab OR cosentyx | Adult, Senior
- "ankylosing spondylitis" | certolizumab OR cimzia | Adult, Senior
- "ankylosing spondylitis" | Etanercept OR Enbrel OR Avent OR BX2922 OR CHS-0214 OR ENIA11 OR Etacept OR Etanar OR GP2013 OR GP2015 OR HD203 OR LBEC0101 OR M923 OR PRX-106 OR SB4 OR tunex OR yisapu | Adult, Senior
- "ankylosing spondylitis" | Adalimumab OR Humira OR Trudexa OR ABP 501 OR BI695501 OR CHS-1420 OR GP2017 OR M923 OR PF-06410293 | Adult, Senior
- "ankylosing spondylitis" | infliximab OR Remicade OR CT-P13 OR Remsima OR Inflectra | Adult, Senior
- "ankylosing spondylitis" | Golimumab OR Simponi | Adult, Senior

Search Strategy for the International Clinical Trials Registry (ICTRP)

The following search strategies were conducted in the ICTRP:

- "ankylosing spondylitis" in condition, "Secukinumab" in intervention
- "ankylosing spondylitis" in condition, "certolizumab" in intervention
- "ankylosing spondylitis" in condition, "Etanercept" in intervention
- "ankylosing spondylitis" in condition, "Adalimumab" in intervention
- "ankylosing spondylitis" in condition, "Infliximab" in intervention
- "ankylosing spondylitis" in condition, "Golimumab" in intervention

A6. Inclusion and exclusion criteria:

- Please explain why combination therapies were included in the cost effectiveness inclusion/exclusion criteria (footnote a in table 65) but were not included for clinical effectiveness (table 6).

The clinical systematic literature review was designed to inform the NMA, which did not consider combination therapies as these were considered inappropriate comparators for the decision problem; therefore the inclusion of combination therapies was beyond the scope of the clinical literature review. The economic literature review was designed with broader inclusion criteria in order to allow the collection of data that may have been beneficial for the model design.

- Please explain why non-biologic treatments have been excluded from both the clinical and cost effectiveness inclusion/exclusion criteria.

Non-biologic treatments were excluded from both the clinical and cost effectiveness inclusion/exclusion criteria consistent with the final scope issued by NICE, which is presented in Table 1 of the submission. Whilst we acknowledge that the scope also defines "established clinical management without secukinumab" for the population whose disease has responded inadequately to, or who are intolerant to, TNFα inhibitors, we considered that no appropriate search strategy could be employed to capture this comparator and that this comparator would be addressed by the placebo arms of any clinical studies of biologic treatments identified by the SLR.

Secukinumab trial design and baseline characteristics

A7. According to Table 131 in appendix E of the company submission, concomitant medicines were allowed in MEASURE 1 and MEASURE 2. Please provide details of how many patients were on concomitant medication.

In MEASURE 1, up to Week 16, concomitant medications were used [redacted] in the placebo groups and by [redacted] in the secukinumab IV-150 mg group. In MEASURE 2, up to Week 16, concomitant medications were used by [redacted] in the secukinumab groups and [redacted] patients in the placebo group.

A8. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients whose disease had not responded to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

Feasibility for the above analyses was assessed by determining the patient numbers per sub-group. The results of these analyses are presented in Table 3 below.

Table 3: Patient numbers for sub-groups defined by inadequate response to prior medications

	MEASURE 1		MEASURE 2	
Patients with inadequate response to:	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs and TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs or TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **NSAID, non-steroidal anti-inflammatory drug; TNFα, tumour necrosis factor alpha**

Sub-group analyses were deemed feasible where a minimum of 20 patients were available for both arms of the studies. Based on the above analyses, the sub-group of patients with

inadequate response to both NSAIDs and TNFα inhibitors was deemed too small for meaningful sub-group analysis. Outcome data, on ASAS20, ASAS40, BASDAI 50, BASDAI change from baseline and BASFI change from baseline, for the other three sub-groups, is provided in Table 4 to Table 6 below. No data on these sub-groups is available for any of the other trials included in the network meta-analysis.

Table 4: Results for NSAID inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Results for TNFα inhibitor inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Results for NSAIDs or TNFα inhibitors inadequate responders at week 16

	MEASURE 1		MEASURE 2	
Endpoint	Secukinumab 150 mg	Placebo	Secukinumab 150 mg	Placebo
ASAS20	[redacted]	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline n, LS mean change (SE)	[redacted]	[redacted]	[redacted]	[redacted]

A9. Please state how intolerance was defined in each of the trials included in the network meta-analysis. Please report, for both of the MEASURE trials (and all other trials included in the network meta-analysis, if available), the number of patients who, at baseline, were intolerant to:

- NSAIDs
- TNF-alpha inhibitors
- NSAID and/or TNF-alpha inhibitors

Please provide data separately for each of the patient groups specified above, for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis.

Intolerance to prior medication was based on the individual investigator's assessment. Feasibility for the above analyses was assessed by determining the patient numbers per sub-group. The results of these analyses are presented in Table 7 below.

Table 7: Patient numbers for sub-groups defined by inadequate response to prior medications

	MEASURE 1		MEASURE 2	
Patients with intolerance to:	**Secukinumab 150 mg**	**Placebo**	**Secukinumab 150 mg**	**Placebo**
NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs and TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
NSAIDs or TNFα inhibitors	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: **NSAID, non-steroidal anti-inflammatory drug; TNFα, tumour necrosis factor alpha**

Sub-group analyses were deemed feasible where a minimum of 20 patients were available for both arms of the studies. Based on the above analyses, no meaningful analyses of sub-groups with intolerance to prior medications were possible.

No data on these sub-groups is available in the public domain for any of the other trials included in the network meta-analysis.

A10. Please provide additional detail for the category 'other' in table 15 (baseline characteristics of participants in MEASURE 1 and MEASURE 2) i.e. which ethnic group represented 13.9% and 21.6% of the secukinumab and placebo arms, respectively, in MEASURE 1?

Please find the requested information in Table 8 below.

Table 8: Race data for MEASURE 1 participants

	Secukinumab 150 mg (N=125)	Placebo (N=122)
White, n (%)	69 (55.2)	81 (66.4)
Black or African American, n (%)	0 (0.0)	1 (0.8)
Asian, n (%)	21 (16.8)	19 (15.6)
American Indian or Alaska Native, n (%)	8 (6.4)	3 (2.5)
Native Hawaiian or other Pacific Islander, n (%)	0 (0.0)	1 (0.8)
Other, n (%)	[redacted]	[redacted]
Mestizo / Mestiza, n (%)	[redacted]	[redacted]
White, n (%)	[redacted]	[redacted]
North African, n (%)	[redacted]	[redacted]
Turkish, n (%)	[redacted]	[redacted]
Western European, n (%)	[redacted]	[redacted]

A11. The baseline characteristics for patients in MEASURE 1 appear to differ from the baseline characteristics for patients in MEASURE 2. For example: ethnicity, average weight, time since diagnosis and number of prior TNF-alpha inhibitors. Please discuss the impact these differences may have.

As described by study investigators, the primary publication of MEASURE 2 and MEASURE 1 findings by Baeten et al. (NEJM, 2015) states that the baseline demographic and disease characteristics were similar between MEASURE 2 and MEASURE 1 and among the groups within each study.[17] This manuscript was peer reviewed and approved by external experts outside the secukinumab study group prior to publication. Thus, no impact is expected from any of the above mentioned factors.

Of note, as patients treated with more than one TNF-alpha inhibitor were excluded from both studies, the number of patients exposed to more than 1 TNF-alpha inhibitor in either study was negligible. In addition, as described in the submission dossier, pooled subgroup analyses based on ethnicity and weight revealed no clinically meaningful differences in efficacy or safety results based on these subgroups.

Secukinumab trial results

A12. Please provide an interpretation as to why ASAS20 response improves between weeks 12 and 16, but ASAS40 response deteriorates during this time period, for people receiving secukinumab in the MEASURE 2 trial (section 4.7.1, figures 11 and 13).

ASAS 20 and ASAS 40 are binary clinical variables, and there is a likelihood of seeing variation in the visit-to-visit results of these variables in rheumatology studies. Similar variation was also observed in the ATLAS study for adalimumab, in which a continual improvement in ASAS 20 rate was seen throughout the study, but a slight decrease in ASAS 40 rate was seen between weeks 30-52, even when using the less conservative statistical analysis of observed data.

The numerical decrease in ASAS 40 response in the MEASURE 2 trial was less than 3% (38.9% at week 12 compared with 36.1% at week 16), which is clinically negligible. It is important to note

that after week 16, the ASAS 40 response rate for secukinumab 150 mg continues to improve up to Week 52 at 48.6%. These data for secukinumab 150 mg were analysed using the most conservative method for missing data: non-responder imputation. Any patient data that were missing at any of the time points were imputed as a non-response for ASAS 20 and ASAS 40.

The ASAS 40 response deterioration in the MEASURE 2 trial was less than 3% (38.9% at week 12 compared with 36.1% at week 16). It is important to note that after week 16 the ASAS 40 response rate for secukinumab 150 mg continues to improve through to 48.6% at 52 weeks. It should also be noted that the data for secukinumab 150 mg was analysed using the most conservative method for missing data: non-responder imputation. Any patient data that was missing at any of the time points was imputed as a non-response with baseline values.

BASDAI is a continuous efficacy variable, rather than a binary endpoint, and the data for secukinumab 150 mg during the same time period of MEASURE 2 shows continuous improvement through weeks 0 - 16 as demonstrated in [redacted]1 below.

[redacted]1

A13. Please provide patient-level Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores from MEASURE 1 and MEASURE 2 for biologic naïve and experienced patients separately.

The requested patient-level data is provided in separate excel files. [redacted]

A14. Please provide details of the statistical analysis methods used for subgroup analyses (section 4.8). The p-values in table 44, table 45 and all subgroup analyses in section 4.8 appear to be for the treatment comparison within each subgroup and not from an interaction test between subgroups. Please report the results of a test for an interaction between treatment and the subgroup.

The MEASURE 1 and MEASURE 2 studies were not powered to detect a difference between the TNFα inhibitor-naïve subgroup and the TNFα inhibitor-inadequate responder subgroup, and hence these analyses were not included in the pre-specified analysis plan. However, the test for interaction between treatment and subgroup on the primary endpoint has been carried out as requested. The results are shown in Table 9 and Table 10 below. Relatively small patient numbers in the TNFα inhibitor-inadequate responder subgroup mean that these results should not be relied upon. Anti-TNF-α naïve patients showed numerically higher ASAS 20 response rates at Week 16, and whilst the tests for interaction do not reach statistical significance, we consider them to be clinically meaningful. In addition, switching to an alternative TNFα inhibitor in axial spondyloarthropathies has been shown to be associated with lower response rates.[18] Please note that these analyses were carried out at a trial level, and thus included the unlicensed 75mg dose of secukinumab.

Within the allocated time frame it has not been possible to run tests of interaction for the secondary efficacy endpoints – we will endeavour to supply these by Friday 18th March.

Table 9: MEASURE 1 ASAS20 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.

Table 10: MEASURE 2 ASAS20 response by subgroup at Week 16 using non-responder imputation (full analysis set)

Subgroup	Treatment Group	n/M (%)	Comparator	Odds ratio	95% confidence interval	p-value, unadjusted	P value of treatment by TNF status subgroup interaction
TNFα inhibitor-naïve	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TNFα inhibitor-inadequate responder	Secukinumab 75 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

M=Number of patients in each treatment group; n=Number of ASAS20 responders in each treatment group (missing ASAS responses were considered non-responders);
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; NA, not applicable; TNFα, tumour necrosis factor alpha.

Statistical analysis of secukinumab trials

A15. According to table 14, "the impact of missing data on the analysis results of ASAS20 response was assessed by repeating the logistic regression model using different ways to handle missing data, including multiple imputation and observed data analysis."

None of these results appear to be reported, please provide them for the binary outcomes or clarify why using different assumptions about missing data did not alter the results.

As stated in the submission the sensitivity analyses of the primary endpoint included:

- Same logistic regression model using multiple imputation to handle missing values, to assess the robustness of missing data handling
- Same logistic regression model with observed data (with no rescue penalty), to assess the robustness of missing data handling

Please find below the results of these different analyses for ASAS20 at Week 16 in Table 11.

Table 11: Sensitivity analyses on ASAS20 at Week 16 in MEASURE 1 and 2

Analysis	Response Rate	Comparator	Odds Ratio	95% CI	p-value
MEASURE 1					
Multiple imputation					
Secukinumab 150mg (n=125)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed data (with no rescue penalty)					
Secukinumab 150mg (n=125)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=122)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MEASURE 2					
Multiple imputation					
Secukinumab 150mg (n=72)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=74)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed data (with no rescue penalty)					
Secukinumab 150mg (n=66)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo (n=63)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition, post-hoc analyses using last observation carried forward (LOCF) imputation for missing data have now been performed, and these are provided in Table 12.

Table 12: Post-hoc LOCF analyses on ASAS20 at Week 16 in MEASURE 1 and 2

Analysis	n	N	Response rate	95% CI
MEASURE 1				
LOCF				
Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
MEASURE 2				
LOCF				
Secukinumab 150mg	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; IV, intravenous; LOCF, last observation carried forward

Network meta-analysis

A16. **Priority request:** According to table 8 of the company submission the study by Marzo-Ortega et al. 2005 was excluded from the network meta-analysis on the basis that the study did not connect to the network. This study is a comparison of infliximab with placebo and therefore it is unclear why this study cannot be connected to the network via the placebo arm.

Please provide further details to explain the reason why this study was excluded, or provide revised results from the network meta-analyses including this study.

In the Marzo-Ortega et al. 2005 study all patients were treated with methotrexate and were randomly assigned, in a ratio of 2:1, to receive five infusions of either 5 mg/kg infliximab or placebo over 30 weeks.[19] As such, all patients in the placebo arm were also receiving methotrexate as per the planned treatment regimen. As methotrexate is considered to have some benefit as a treatment in AS, and all patients within the placebo arm of the trial received methotrexate, it was considered inappropriate to use this treatment regimen as a proxy for placebo in the NMA; as such, the study was deemed to be disconnected from the network.

In reviewing the studies included in the network, two omissions from the original set of analyses were identified:

- The ATLAS study had been excluded from the BASFI change from baseline networks in error
- The Huang (2014) study had not been included in the biologic-naïve networks. Initially this study was categorised as being "unclear" regarding whether the population was biologic naïve or biologic experienced. On further review, the article includes the statement "Prior exposure to TNF-α inhibitors, natalizumab or efalizumab at any time, or use of traditional Chinese medicines within 28 days of baseline was not allowed". This indicates that the study was conducted amongst biologic naïve patients. Therefore revised analyses, including Huang (2014) in the biologic naïve networks are, presented in Section D:.

A17. **Priority request:** According to section 4.10.9 of the company submission, both fixed effects and random effects models were applied to all networks. The results for the random effects models are not included in the company submission. Please provide the random effects model results for all networks listed in table 59.

Please see Table 13 to Table 20 for random effects results from both overall and biologic naïve populations in the base case NMA as well as the three sensitivity analyses (excluding MEASURE 1, 12 week data only and both excluding MEASURE 1 and using 12 week data only). Please note that the random effects results presented below are for the updated analyses including ATLAS in the BASFI networks and Huang (2014) in the biologic naïve networks (see response to A16). As discussed in the submission (Section 4.10.9), of the submission, the assessment of model fit by Deviance Information Criterion (DIC) indicated no strong preference for either the FE or RE models in any of the analyses where both model types were possible. Furthermore, for some analyses in the biologic naïve population RE models were not mathematically feasible to conduct. Given this, combined with the low number of trials reporting in each arm and the fact

that no strong evidence of heterogeneity was observed in trial baseline characteristics, FE models were chosen.

Results of comparisons of relative treatment effects – Base case

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Base case)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 13.

Table 13: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Base case NMA: 12-16 weeks, MEASURE 1 & MEASURE 2)

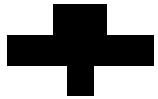
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Base case)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 14.

Table 14: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Base case NMA: 12-16 weeks, MEASURE 1 & MEASURE 2)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 1

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 1)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 15.

Table 15: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 1: 12-16 weeks, MEASURE 2 only)

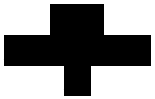
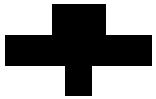
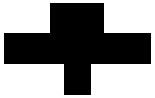
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Sensitivity Analysis 1)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 16.

Table 16: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 1: 12-16 weeks, MEASURE 2 only)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 2

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 2)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 17.

Table 17: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 2: 12 weeks, MEASURE 1 & MEASURE 2)

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Sensitivity Analysis 2)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 18.

Table 18: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 2: 12 weeks, MEASURE 1 & MEASURE 2)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	BASDAI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

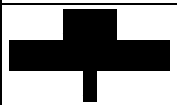
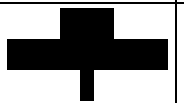
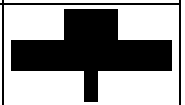
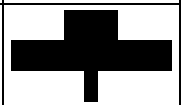
Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Results of comparisons of relative treatment effects – Sensitivity Analysis 3

Binomial endpoints: ASAS20, ASAS40 and BASDAI 50 (Sensitivity Analysis 3)

The relative risks for secukinumab 150 mg compared with comparator treatments for the binomial endpoints of ASAS20, ASAS40 and BASDAI 50 for the whole population and biologic naïve subgroup are summarised in Table 19.

Table 19: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints (Sensitivity Analysis 3: 12 weeks, MEASURE 2 only)

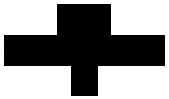
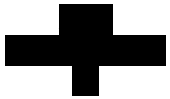
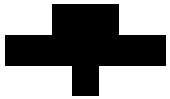
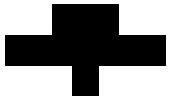
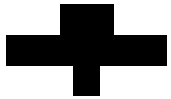
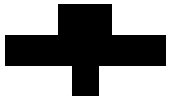
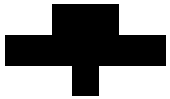
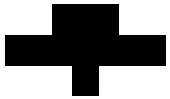
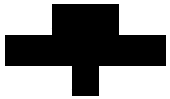
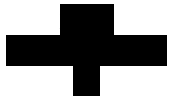
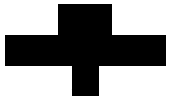
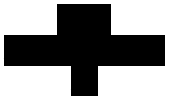
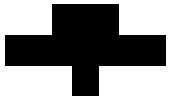
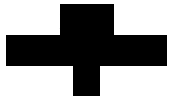
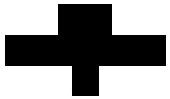
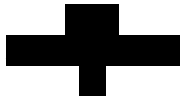
Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20								
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

Continuous endpoints: BASDAI change from baseline and BASFI change from baseline (Scenario 3)

The change from baseline differences for secukinumab 150 mg compared with comparator treatments for the continuous endpoints of BASDAI change from baseline and BASFI change from baseline are summarised in Table 20.

Table 20: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints (Sensitivity Analysis 3: 12 weeks, MEASURE 2 only)

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline								
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly.

A18. Section 4.10.2 of the company submission states that ASAS 5/6 and SF-36 PCS outcomes were analysed. Please provide these results.

Please find the ASAS 5/6 and SF-36 PCS results for both the base case NMA and scenario analyses in Table 21 to Table 28; Table 21 to Table 24 present results of fixed effects models, whilst Table 25 to Table 28 present results of random effects models. Further, please note that random-effects models were not feasible for SF-36 PCS. Cells shaded in light green indicate comparisons that are favourable to secukinumab. Cells shaded in purple indicate comparisons that are not favourable to secukinumab.

Table 21: Base case NMA (12-16 weeks, MEASURE 1 & MEASURE 2) – Fixed Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 22: Scenario 1 (12-16 weeks, MEASURE 2 only) – Fixed Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 23: Scenario 2 (12 weeks, MEASURE 1 & MEASURE 2) – Fixed Effects

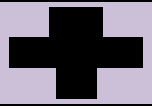
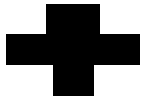
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 24: Scenario 3 (12 weeks, MEASURE 2 only) – Fixed Effects

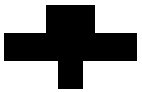
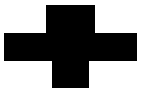
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 25: Base case NMA (12-16 weeks, MEASURE 1 & MEASURE 2) – Random Effects

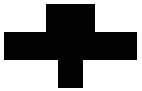
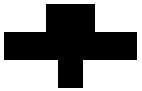
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 26: Scenario 1 (12-16 weeks, MEASURE 2 only) – Random Effects

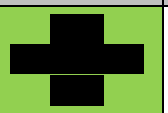
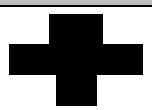
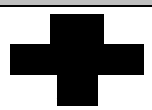
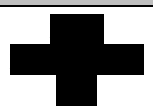
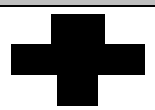
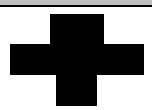
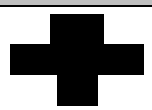
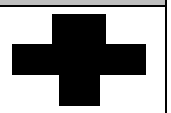
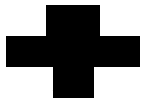
Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 27: Scenario 2 (12 weeks, MEASURE 1 & MEASURE 2) – Random Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

Table 28: Scenario 3 (12 weeks, MEASURE 2 only) – Random Effects

Endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Relative Risks in ASAS 5/6 response								
SF-36 change from baseline								

A19. According to section 4.10.6 the Markov Chain Monte Carlo simulations appear to have been implemented in two different software packages: OpenBUGS and JAGS. Please clarify why 2 different software packages were employed and specify which package was used for which analysis.

The reference to two software packages is an oversight given that in the end all analyses were conducted in JAGS. In the early stages of the project, analyses for the ASAS outcomes were conducted in OpenBUGS, but by the end all analyses were conducted in JAGS.

A20. Section 4.10.7.1 of the company submission reports the predicted absolute response for each treatment for 5 outcomes (ASAS20, ASAS40, BASDAI 50, BASDAI change from baseline, BASFI change from baseline). The analysis methods do not describe how the absolute response was calculated. Please provide full details of how this was calculated.

The primary outputs of Bayesian NMAs were posterior distributions of the relative treatment effects between all interventions in the network for each outcome. In addition, the expected absolute effect (change from baseline for continuous outcomes, proportion for dichotomous outcomes) for each of these outcomes by treatment was modelled by combining the relative treatment effect estimates versus placebo obtained from the NMA with the average outcome with placebo from placebo-controlled trials. For example, change from baseline in continuous outcomes for a given treatment was calculated by adding the mean placebo change from baseline to the posterior distribution of the relative difference between the treatment of interest and placebo. With dichotomous outcomes, transformations were required to go from log odds to proportions. The posterior distributions of modelled outcomes were summarized by the median and 95% credible intervals (CrIs), which were constructed from the 2.5th and 97.5th percentiles. This approach follows the guidance set forth by the NICE Decision Support Unit technical reports.[20, 21]

A21. Section 4.10.8 states that no evidence of inconsistency was found for the base case network. It is unclear from the text which outcome this refers to. According to the network diagrams provided in appendix K there is potential for inconsistency in both the whole population and the biologic naïve population in the ASAS20 networks and the ASAS40 networks (Figures 51-54). In addition, the cited reference describes several methods for the assessment of inconsistency.

- Please specify which method of inconsistency assessment was used.
- Please provide the full results of the inconsistency assessment for each network where inconsistency may be present.

Inconsistency was assessed by comparing direct and indirect evidence. Direct evidence was assessed through independent-means models where we simultaneously obtained pooled estimates for all the different direct comparisons.[22] The findings of a synthesis of direct evidence improved the understanding of the findings of the network meta-analysis where direct and indirect evidence were combined. The DIC was compared between the independent means model, which assumes no consistency, and NMA. Comparing these DICs served as a global test for the assumption of inconsistency. In all cases, the DIC was smaller for the NMA model and no concerns over inconsistency were raised.

In addition to a synthesis of direct evidence, we estimated relative treatment effects for all the possible comparisons in the network based on only indirect evidence using a technique that is called edge-splitting, more commonly referred to as node-splitting.[22] This allowed us to compare direct evidence with the indirect evidence to assess consistency. Edge-splitting was conducted in the ASAS20 and ASAS40 networks, as these were the only networks that contained closed loops of more than one trial. Plots of the estimated indirect and direct effects are provided in Appendix A: Figure 33 to Figure 48.

A22. According to page 140 "...there were very few situations [in this network meta-analysis] in which multiple trials informed a comparison, no formal assessment of heterogeneity was performed."

Please report the I2 values for comparisons involving 2 or more trials, especially MEASURE 1 and 2. For example, the comparison of adalimumab with placebo contained 3 trials so heterogeneity should have been assessed.

I^2 statistics and Cochran's Q statistics for each edge with multiple trials for each outcome have been calculated. Note that the test-based method of calculating confidence intervals for the I^2 statistic require at least three trials. Thus in such cases, no confidence intervals were produced for the I^2 statistic. As can be seen in both Table 29 and Table 30, there was no evidence of concerning heterogeneity outside of the ADA to placebo comparison for SF-36 PCS.

Table 29: Heterogeneity assessment of direct comparisons within the mixed population networks

Outcome	Trials	I^2	Cochran's Q	P-value
BASDAI CfB	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASDAI CfB	ATLAS, Hu (2012), Huang (2014)	[redacted]	[redacted]	[redacted]
BASDAI 50	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASDAI 50	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASFI	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASFI	Hu (2012), Huang (2014), ATLAS	[redacted]	[redacted]	[redacted]
ASAS20	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS20	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS40	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS40	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS 5/6	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS 5/6	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
SF-36	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
SF-36	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]

Table 30: Heterogeneity assessment of direct comparisons within the biologics-naïve population networks

Outcome	Trials	I^2	Cochran's Q	P-value
BASDAI CfB	MEASURE2, MEASURE1	[redacted]	[redacted]	[redacted]
BASDAI CfB	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASDAI 50	MEASURE2, MEASURE1	[redacted]	[redacted]	[redacted]
BASDAI 50	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
BASFI	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
BASFI	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS20	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS20	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS40	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS40	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
ASAS 5/6	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
ASAS 5/6	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]
SF-36	MEASURE1, MEASURE2	[redacted]	[redacted]	[redacted]
SF-36	ATLAS, Huang (2014)	[redacted]	[redacted]	[redacted]

A23. According to page 25, "insufficient data was available to conduct an network meta-analysis in the biologic-experienced only population; outside of the MEASURE 1 and MEASURE 2 studies there is no reported data for TNF-alpha inhibitors in the biologic-experienced population."

- Please provide results for MEASURE 1 and MEASURE 2 in the biologic experienced population.

- The results from MEASURE 1 and 2 in the biologic experienced population are provided in Section 4.8.1 and 4.8.2 of the submission.

We assume this request relates to a pair-wise meta-analysis of the MEASURE 1 and MEASURE 2 studies, results of which are provided in Table 31 and Table 32 below.

Table 31: Meta-analysis results comparing secukinumab to placebo at 12 weeks

Outcome	Effect of SEC relative to Placebo	I^2	Cochran's Q p-value
ASAS20	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]
ASAS 5/6	[redacted]	[redacted]	[redacted]
BASDAI 50	[redacted]	[redacted]	[redacted]
BASDAI CfB	[redacted]	[redacted]	[redacted]
BASFI CfB	[redacted]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects; RE: random effects; RR: relative risk; MD: mean difference; SEC: secukinumab.

Table 32: Meta-analysis results comparing secukinumab to placebo at 16 weeks

Outcome	Effect of SEC relative to Placebo	I2	Cochran's Q p-value
ASAS20	[redacted]	[redacted]	[redacted]
ASAS40	[redacted]	[redacted]	[redacted]
ASAS 5/6	[redacted]	[redacted]	[redacted]
BASDAI 50	[redacted]	[redacted]	[redacted]
BASDAI CfB	[redacted]	[redacted]	[redacted]
BASFI CfB	[redacted]	[redacted]	[redacted]
SF-36 PCS	[redacted]	[redacted]	[redacted]

Abbreviations: FE: fixed effects; RE: random effects; RR: relative risk; MD: mean difference; SEC: secukinumab.

Matched adjusted indirect comparison

A24. Section 4.10.11 and appendix J report the results of a matching adjusted indirect comparison. Please clarify the following points:

- Why were other studies of adalimumab not considered in this analysis?

Huang 2014 could potentially have been included, as it reports the ASAS20/40 outcomes. However, the MAIC method presented in the original Signorovitch papers focuses on a single trial per treatment. It is not clear that the meta-analysis method is appropriate, especially in cases where the baseline characteristics of the comparator trials (ATLAS and Huang, Table 201 of the submission) are not very similar. Furthermore, the single study comparison clearly compares adalimumab and secukinumab in the setting of the ATLAS trial but the setting of the meta-analysis comparison would be unclear. The ATLAS setting may be most appropriate as licensing/reimbursement decisions for adalimumab were based on its population.

- Why were other comparators not considered for this type of analysis?

Comparison of secukinumab versus adalimumab was prioritised since adalimumab currently has the largest share of the UK biologics market, with 39% of patients receiving adalimumab.

- Why was only MEASURE 2 included, but not MEASURE 1?

The MEASURE 1 trial used unlicensed intravenous administration and weight based dose (10mg/kg) of secukinumab for the loading dose, in contrast to the licensed subcutaneous secukinumab 150mg loading dose used in the MEASURE 2 trial. Since the ATLAS study of adalimumab used subcutaneous administration and MEASURE 2 was the only trial employing the licensed subcutaneous administration route and loading dose, inclusion of MEASURE 2 only was considered appropriate. However, as with the network meta-analyses sensitivity analyses with MEASURE 1 have now also been conducted and show similar results as with MEASURE 2 (see Appendix D: which represents an updated version of Appendix J from our original submission document).

Section B: Clarification on cost-effectiveness data

Model structure and assumptions

B1. **Priority question:** In the base case model, response at 12 weeks was defined as an improvement of 50% or more in BASDAI score from baseline (BASDAI 50). A scenario analysis defined response as a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more.

- In TA383, the appraisal committee concluded that the decision to continue treatment in clinical practice should be based on the broader definition of response to treatment outlined in British Society of Rheumatology (BSR) guidelines and the previous technology appraisal[23]: a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more. Please present the results of an additional scenario analysis, where the response assessment for treatment continuation takes into consideration the response definition that was adopted in NICE guidance[23], which also includes 2 cm reduction in spinal pain VAS. Please also provide the details regarding the extent to which data on spinal VAS are missing, and what method was used to adjust for the missing data.

The extent of missing data is indicated in Appendix Table 186 of the submission. The same N numbers are available at both 12 and 16 weeks in both MEASURE 1 and MEASURE 2 for classification according to either “BASDAI 50” or “BASDAI 50 or 2 unit drop in BASDAI” definitions. However, between 13% to 19% of patients cannot be included in the N for classification according to “BASDAI 50 or 2 unit drop in BASDAI and VAS reduction of 2cm or more”. This is due to the requirement for patients to have both BASDAI50 ***and*** VAS data available in the database for these analyses. BASDAI 50 analyses provided in Table 186 of the submission are based on observed data with no imputation for missing data.

Available analyses of conditional changes from baseline in BASDAI and BASFI within the sub-groups, based on the alternative definitions of response (“BASDAI 50 or a 2 unit reduction in BASDAI” as well as “BASDAI 50 or a 2 unit reduction in BASDAI plus a 2cm reduction in VAS”) are based on non-responder imputation i.e. patients unable to classified as responders due to missing VAS scores are classed as non-responders.

Pooled MEASURE 1 and MEASURE 2 efficacy data using alternative definitions of response amongst the biologic naïve and biologic experienced sub-groups are presented in Table 33 to Table 35 below.

Table 33: Response rate at week 12 according to alternative definitions of response

	Secukinumab 150mg			Placebo		
	n	N	%	n	N	%
Biologic naive						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: BASDAI change from baseline at week 12 according to alternative definitions of response

	Secukinumab 150mg		Placebo	
	n	CFB	n	CFB
Biologic naïve - responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]

Table 35: BASFI change from baseline at week 12 according to alternative definitions of response

	Secukinumab 150mg		Placebo	
	n	CFB	n	CFB
Biologic naïve - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced - responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced – non-responders				
BASDAI50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]

From the above data, estimates of relative changes in efficacy parameters have been calculated and are provided in Table 36 below.

Table 36: Relative efficacy estimates for alternative definitions of response

	BASDAI 50 or 2 unit drop		BASDAI 50 or 2 unit drop + 2 cm VAS drop	
	Active treatment	Conventional care	Active treatment	Conventional care
Biologic naive				
Response rate	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Biologic experienced				
Response rate	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASDAI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]
Non-responder BASFI CFB	[redacted]	[redacted]	[redacted]	[redacted]

Please note two errors have been identified in the original response rate model inputs for Scenario 5:

- Week 16 data, rather than week 12 had been used to determine the proportion of responders
- The relative changes in response rate had been mis-calculated, resulting in reductions to the proportion of responders with the alternative definition of response, rather than increases.

The results of Scenario 5 have therefore been revised in the below results. The changes result in cost-effectiveness results that are further in favour of secukinumab; secukinumab now dominates all comparators except golimumab, whereas previously both golimumab and infliximab generated very slightly greater QALYs than secukinumab.

The results of cost-effectiveness analyses employing all three definitions of response are presented in Table 37 and Table 38, for biologic naïve and biologic experienced populations respectively.

Table 37: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population – comparison of alternative definitions of response

	Base Case – BASDAI 50			BASDAI 50 or 2 unit drop			BASDAI 50 or 2 unit drop + 2 cm VAS drop		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	£15,300	-0.359	SEC dominates	£23,265	-0.471	SEC dominates	£20,182	-0.429	SEC dominates
Certolizumab pegol – with PAS	£9,202	-0.359	SEC dominates	£14,903	-0.474	SEC dominates	£12,725	-0.430	SEC dominates
Etanercept	£2,033	-1.046	SEC dominates	£1,792	-1.378	SEC dominates	£2,027	-1.250	SEC dominates
Etanercept biosimilar	£1,018	-1.046	SEC dominates	£325	-1.378	SEC dominates	£738	-1.250	SEC dominates
Golimumab	£16,703	0.025	£674,914	£25,783	0.029	£874,073	£22,222	0.028	£798,038
Infliximab	£26,223	-0.216	SEC dominates	£37,686	-0.122	SEC dominates	£33,238	-0.153	SEC dominates
Infliximab biosimilar	£22,649	-0.216	SEC dominates	-£32,454	0.122	SEC dominates	£28,658	-0.153	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

Table 38: Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population – comparison of alternative definitions of response

	Conventional care		
	Incr. Costs	Incr. QALYs	ICER
Base Case – BASDAI 50	£1,747	0.778	£2,245
BASDAI 50 or 2 unit drop	£3,704	1.036	£3,574
BASDAI 50 or 2 unit drop + 2 cm VAS drop	£2,938	0.978	£3,004

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

B2. For people who whose disease has not responded to treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, are biologics used as the next line of treatment? If so:

- What proportion of the ankylosing spondylitis population in England use a second biologic after the first has failed?

There are limited data on the proportion of the ankylosing spondylitis population in England that use a second biologic after the first has failed, perhaps reflecting the lack of clear formal guidelines on the sequencing of biologic therapies in AS.

As noted in Section 5.2.2 of our submission, expert clinical feedback gathered during model development suggested that approximately 25% of patients might transition to conventional care rather than a biologic therapy, and that therefore 75% of patients would be expected to use a biologic therapy after failure of the first biologic.

- What proportion use 'conventional' treatment after the first biologic has failed?

As noted above, there are limited sources to estimate the proportion of patients who would go on to use conventional treatment after the first biologic has failed. As described in Section 5.2.2 of our original submission, clinical expert feedback has suggested that 25% of patients experiencing failure of their first-line biologic would be expected to use conventional care.

B3. **Priority question:** When modelling treatment sequencing, an efficacy reduction of 0.55 for the second biologic treatment in the sequence was assumed (Excel model, "Clinical Inputs" sheet, Cell F26). Please explain how the value of 0.55 was derived. Please provide and justify the other assumptions in the modelling of second-line biologics. Include the baseline BASDAI/BASFI values used at the start of second-line treatment and the values used for change from baseline.

Derivation of relative reductions in BASDAI 50, BASDAI change from baseline and BASFI change from baseline are explained in Table 39 to Table 41. Please refer to Tables 45 & 47 in the submission for sub-group data from MEASURE 1 and MEASURE 2.

Table 39: BASDAI 50 relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg			Placebo			Treatment effect (SEC response minus PBO response)	Relative reduction in BASDAI 50 response
	n	N	% response	n	N	% response		
Biologic naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. response rates in the experienced group are (1-0.45) = 0.55 x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 40: BASDAI change from baseline relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg		Placebo		Treatment effect (SEC response minus PBO response)	Relative reduction in BASDAI change from baseline
	n	Change from baseline	n	Change from baseline		
Biologic naive	132	-2.67	122	-0.87	-1.80	(-1.80 – (-1.04)/-1.80 = 41.9% i.e. response rates in the experienced group are (1-0.42) = 0.58 x those of the naïve group
Biologic experienced	56	-1.67	50	-0.62	-1.04	

Table 41: BASFI change from baseline relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150mg		Placebo		Treatment effect (SEC response minus PBO response)	Relative reduction in BASFI change from baseline
	n	Change from baseline	n	Change from baseline		
Biologic naive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. response rates in the experienced group are (1-0.50) = **0.50** x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Another assumption underlying the modelling of second line biologics is that decline in efficacy with TNFα inhibitors when used in an experienced population is the same as that observed in MEASURE 1 and MEASURE 2. There is no randomised controlled data available on efficacy of the TNFα inhibitors when used in biologic experienced patients. Since secukinumab has a different mechanism of action to TNFα inhibitors it seems plausible to assume that the reduction in efficacy observed between naïve and experienced patients treated with secukinumab, all of whom are receiving their first IL-17A inhibitor, will be at least as large as the reduction in efficacy observed between naïve and experienced patients treated with TNFα inhibitors, some of whom will then be taking their second treatment from the same drug class. If the efficacy reduction between naïve and experienced patients is larger for the TNFα inhibitors than for secukinumab, our assumption of an equivalent reduction would disfavour secukinumab in the cost-effectiveness analyses.

B4. On pages 185-186, the company submission highlights a "lack of robust clinical data to support use of the TNF-alpha inhibitors in this setting" as a reason for not comparing secukinumab to TNF-alpha inhibitors in the biologic experienced population. Please explain why non-randomised data was not used to compare secukinumab with TNF-alpha inhibitors in the biologic experienced population in an exploratory analysis.

The NICE Guide to the Methods of Technology Appraisal 2013 states that data from non-randomised studies may be required to supplement RCT data.[24] Due to the considerable body of randomised data that was available for secukinumab and the comparator therapies, it was not felt necessary to supplement the RCT data with non-randomised studies and non-randomised data was not included in the search strategy for the clinical systematic literature review. Furthermore, the inclusion of randomised data sources only in the systematic literature review is consistent with the approach taken by the Assessment Group in the recent MTA of biologic therapies in AS.[25]

Although non-randomised data can be used in the absence of randomised data, and we acknowledge a lack of randomised data in biologic experienced populations, non-randomised data is associated with a number of well-established limitations. The NICE Guide to the Methods of Technology Appraisal 2013 notes a number of issues more frequently associated with non-randomised data, including confounding, lack of blinding and incomplete follow-up.[24] These limitations, amongst others, can result in biased estimates of treatment effect. Taking into account the uncertainty surrounding estimates from non-randomised data, and the methodological difficulties in incorporating this type of data into a NMA, it was considered appropriate to base the main cost-effectiveness analysis of secukinumab in the biologic experienced population on the MEASURE 1 and MEASURE 2 RCTs, and to compare versus conventional care only, based on the placebo arm of these trials.

B5. The model includes an infliximab biosimilar as a comparator, but not the recently approved etanercept biosimilar (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004007/WC500196736.pdf). Please rerun the analyses including the etanercept biosimilar.

At the time of submission, the UK list price for biosimilar etanercept was not available. This has subsequently become available and comparison versus biosimilar etanercept is included in the revised results (see Section E:). Secukinumab dominates biosimilar etanercept in the base case

and all scenarios except one; in which biosimilar etanercept falls in the south-west quadrant, with only a £1,701 saving per QALY lost.

We also omitted to include the certolizumab patient access scheme in our original analyses. The revised analyses incorporate the free loading doses of certolizumab available to the NHS through UCB's patient access scheme. These changes do not impact the overall conclusions of the cost-effectiveness analysis, as secukinumab continues to dominate certolizumab pegol,

Treatment effect in cost effectiveness model

B6. **Priority request:** Different values for the change from baseline in BASDAI scores for biologic naïve patients are reported in table 73 and the Excel model (worksheet "Clinical inputs", Cells "F49:L50").

- Please explain which values are the correct ones and why there is a discrepancy.

The discrepancy between the model and Table 73 in the submission was a mis-labelling issue in an early version of the NMA report. This mis-labelling issue was identified and the correction applied in the model, however, updates to Table 73 were overlooked. Therefore the values in the model were considered correct at the time of submission. Please note they have now been updated to reflect an error identified as a result of clarification question B15.

Revised versions of Table 73 and Table 74 from the submission, reflecting the corrections identified in response to clarification question B15, are presented below. We recognise that the BASDAI change from baseline with infliximab is now greater than the baseline value. This is due to the limitations of assuming a fixed ratio for responder to non-responder changes from baseline (see Estimation of conditional change from baseline in BASDAI and BASFI

), in the absence of conditional data for infliximab. BASDAI values less than zero will be treated as zero within the model.

Table 42. Change from baseline in BASDAI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-4.65	-5.63	-4.49	-4.61	-8.09	-5.35	-
BASDAI 50 non-responders	-1.09	-1.29	-1.03	-0.81	-1.85	-1.38	-
Biologic experienced population							
BASDAI 50 responders	-4.98	-	-	-	-	-	-3.81
BASDAI 50 non-responders	-0.94	-	-	-	-	-	-0.36

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

Table 43. Change from baseline in BASFI at 3 months

	SEC	CZP	ETN	ADA	INF	GOL	CC
Biologic naive population							
BASDAI 50 responders	-3.59	-3.96	-3.53	-3.22	-5.16	-4.18	-
BASDAI 50 non-responders	-1.12	-0.98	-0.87	-0.79	-1.27	-0.73	-
Biologic experienced population							
BASDAI 50 responders	-3.79	-	-	-	-	-	-2.73
BASDAI 50 non-responders	-0.73	-	-	-	-	-	0.06

Abbreviations: ADA, adalimumab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP, certolizumab pegol; ETN, etanercept; GOL, golimumab; INF, infliximab; SEC, secukinumab.

- Please explain in detail the calculations in the "Subgroup data" sheet, formulae in columns "M:CU". How were the BASDAI 50 response, BASDAI change from baseline and BASFI change from baseline calculate? Which regression coefficients were used?

Main analysis of biologic experienced population

Rows 11, 17, 51, 57, 91, 97, 131, 137, 171 and 177 relate to the biologic experienced population and utilise data from the pre-specified TNF-IR sub-groups of the MEASURE 1 and MEASURE 2 studies.

Rows 11 & 17 relate to the BASDAI 50 response:

- Column O is the BASDAI 50 response rate at 16 weeks pooled from MEASURE 1 and MEASURE 2 (see Tables 45 & 47 of the submission):
  - Secukinumab 150mg = (5+7)/(28+33) = 12/61 = 19.7%
  - Placebo = (1+1)/(29+33) = 2/62 = 3.2%
- Column P is the Log Odds ratio of BASDAI 50 treatment effect calculated as:
  - Secukinumab 150mg = (LN(19.7%/(1-19.7%))-(LN(3.2%/(1-3.2%))
  - Placebo = LN(3.2%/(1-3.2%)
- Column Q is the standard error of the Log Odds of BASDAI 50 response calculated as:
  - Secukinumab 150mg = 1/SQRT((61*19.7%*(1-19.7%)))
  - Placebo = 1/SQRT((62*3.2%*(1-3.2%)))

Rows 51, 57, 91 & 97 relate to the BASDAI changes from baseline; rows 51 & 57 amongst BASDAI 50 responders, and rows 91 & 97 amongst BASDAI 50 non-responders.

- Column O are weighted averages of change from baseline amongst patients identified as BASDAI 50 responders to secukinumab 150mg and placebo at week 12 in MEASURE 1 and MEASURE 2 (see conditional BASDAI change from baseline data in Table 44 below)
- Column P are the treatment effect coefficients calculated as the differences in change from baseline versus placebo

- Column Q is the standard error of the pooled, weighted changes from baseline for both secukinumab 150mg and placebo. Please note there was an error in the placebo calculations (SE values from MEASURE 2 used as SDs) which has resulted in corrections to the placebo SE values in the model (cells Q57, Q97, Q137, Q177 and equivalent cells in columns AB, AM and AX).

Table 44: Conditional BASDAI Change from baseline from MEASURE 1 and MEASURE 2

BASDAI Change from Baseline	Secukinumab 150mg			Placebo		
	n	Mean CFB	SD	n	Mean CFB	SD
BASDAI 50 responders at 12 weeks						
MEASURE 1	7	-4.48	1.265	3	-3.90	1.782
MEASURE 2	7	-5.48	2.459	2	-3.69	1.068
BASDAI 50 non-responders at 12 weeks						
MEASURE 1	25	-1.04	1.487	24	-0.29	2.143
MEASURE 2	19	-0.81	1.531	24	-0.43	1.499

Rows 131, 137, 171 & 177 relate to the BASFI changes from baseline; rows 131 & 137 amongst BASDAI 50 responders, and rows 171 & 177 amongst BASDAI 50 non-responders

- Explanation for Columns O – P is as above for BASDAI changes from baseline. Conditional BASFI change from baseline data is presented in Table 45.

Table 45: Conditional BASFI Change from baseline from MEASURE 1 and MEASURE 2

BASFI Change from Baseline	Secukinumab 150mg			Placebo		
	n	Mean CFB	SD	n	Mean CFB	SD
BASDAI 50 responders at 12 weeks						
MEASURE 1	7	-3.15	2.411	3	-2.83	2.547
MEASURE 2	7	-4.43	3.243	2	-2.57	0.453
BASDAI 50 non-responders at 12 weeks						
MEASURE 1	25	-0.79	1.531	24	0.10	1.685
MEASURE 2	19	-0.64	1.534	24	0.02	1.597

Biologic naive population

Rows 22-28, 62-68, 102-108, 142-148, 182-188 relate to the biologic naïve population and use data from the naïve network meta-analyses.

Rows 22-28 relate to the BASDAI 50 response:

- Column O is the predicted absolute response rate calculated as:
    - EXP(Sum of Log Odds for active treatment + placebo)/((1+EXP(Sum of Log Odds for active treatment + placebo)))
- Column P is the Logs odds of BASDAI 50 response from the network meta-analyses

- Column Q is the standard error of the Logs odds of BASDAI 50 response from the network meta-analyses

Rows 62-68 and 102-108 relate to the BASDAI changes from baseline; rows 62-68 amongst BASDAI 50 responders, and rows 102-108 amongst BASDAI 50 non-responders.

- Column P is the co-efficient of BASDAI change from baseline treatment effect from the network meta-analyses
- Column Q is the standard error of the BASDAI change from baseline from the network meta-analyses

Estimation of conditional change from baseline in BASDAI and BASFI

- Calculations in row 45 are utilised in Column O, which represent the ratios of BASDAI change from baseline amongst responders versus non-responders.
- Conditional changes from baseline are only available for adalimumab and golimumab (from ATLAS and GO-RAISE respectively, in Table 78 of the assessment report for TA383), as well as for secukinumab (from both MEASURE 1 and MEASURE 2).
- For secukinumab a straight average of the MEASURE 1 and MEASURE 2 ratios was used.
- For comparators with no available conditional change from baseline data, the ratio of change from baseline amongst responders versus non-responders has been assumed to be a straight average of the four trials with available conditional data.
- The available conditional BASDAI change from baseline data, as well as the average ratios, are summarised in Table 46 below.

Table 46: Available ratios of conditional BASDAI changes from baseline

BASDAI Change from baseline	MEASURE 1	MEASURE 2	ATLAS	GO-RAISE	Overall average	MEASURE 1 & 2 average
Responders	-4.77	-4.51	-4.64	-4.74	4.37	4.27
Non-responders	-1.42	-0.99	-0.82	-1.22		
Ratio of responders to non-responders	3.96	4.57	5.66	3.89		

Rows 62-68:

- Column O is the predicted change from baseline amongst responders with a calculation based on the premise that:
    - Overall Δ = (Responder Δ x % responders) + (Non-responder Δ x % non-responders)
- Therefore; Responder Δ = Overall Δ x ((Ratio / (% responders x ratio) + (1 - % responders))

Rows 102-108:

- Column O is the predicted change from baseline amongst non-responders and utilises ratios in row 85 (which are a repeat of those in row 45):
    - Non-responder Δ = Overall Δ x (1 / (% responders x ratio) + (1 - % responders)))

Rows 142-148 and 182-188 relate to the BASFI changes from baseline; rows 142-148 amongst BASDAI 50 responders, and rows 182-188 amongst BASDAI 50 non-responders.

- Columns O, P & Q are as above for BASDAI changes from baseline
- Ratios of BASFI change from baseline amongst responders versus non-responders are at rows 125 and 165.
- The available conditional BASFI change from baseline data, as well as the average ratios, are summarised in Table 47 below.

Table 47: Available ratios of conditional BASFI changes from baseline

BASFI Change from baseline	MEASURE 1	MEASURE 2	ATLAS	GO-RAISE	Overall average	MEASURE 1 & 2 average
Responders	-3.76	-4.28	-2.92	-3.03	4.06	3.21
Non-responders	-1.15	-1.34	-0.72	-0.53		
Ratio of responders to non-responders	3.23	3.19	4.06	5.72		

Exploratory analysis of biologic experienced population

Rows 33-39, 73-79, 113-119, 153-159, 193-199 relate to the biologic experience population and are based on the naïve population network meta-analyses. The data in the Subgroup data sheet are identical to the blocks of cells directly above, relating to the biologic naïve population. When "Model sequential treatment" and "Model decline in efficacy" are set to "Yes" on the Settings sheet, efficacy reductions (as explained in response to B3), are applied with the Markov engines for second line treatments. The efficacy reductions are consistent across all comparators and are based on MEASURE 1 and MEASURE 2 data for biologic naïve vs. biologic experienced patients (see response to B3).

Other columns in the Subgroup data sheet

- Columns M:V relate to the base case NMA scenario which uses data from both MEASURE 1 and MEASURE 2, with data for each trial taken from the primary endpoint where this fell within the 12-16 week window (with the exception of the ASSERT study on infliximab where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab.
- Columns X:AG relate to the NMA scenario which uses data from both MEASURE 1 and MEASURE 2, with data for each trial taken at 12 weeks. This is presented as scenario 6b in the submission.

- Columns AI:AR relate to the NMA scenario which uses only data from MEASURE 2, with data for each trial taken from the primary endpoint where this fell within the 12-16 week window (with the exception of the ASSERT study on infliximab where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab. This is presented as scenario 6a in the submission.
- Columns AT:BC relate to the NMA scenario which uses only data from MEASURE 2, with data for each trial taken at 12 weeks. This is presented as scenario 6c in the submission.
- Columns BE:CU were placeholders for random effects network meta-analyses. Prior to the inclusion of ATLAS and Huang (see response to A16), it was not possible to solve for random-effects models in the biologic naïve networks since none of the comparisons were informed by more than a single trial, so in the original model the random effects columns were not utilised. With the inclusion of ATLAS and Huang in the biologic naïve networks, random effects models are possible, and base case random effects network meta-analysis results are included in columns BE:BN.
- In the latest version of the model, columns BP:CU include the analyses requested at B8;
    - Columns BP:BY reflect the assumption of identical effects across TNFα inhibitors and a fixed effects network meta-analysis (York Assessment Group approach A3)
    - Columns CA:CJ reflect the assumption of identical effects across TNFα inhibitors and a random effects network meta-analysis (York Assessment Group approach A4)
    - Columns CL:CU reflect the assumption of exchangeable effects across TNFα inhibitors (York Assessment Group approach A5)

In the above analyses, trial-specific ratios of responder change from baseline to non-responder change from baseline (at rows 45, 85, 125 and 165) are no longer used. Instead, the average ratio is used for all comparators, to reflect the assumed lack of differentiation between the TNFα inhibitors.

B7. **Priority request:** Baseline BASDAI, BASDAI 50 and absolute BASDAI change from baseline are correlated parameters. BASDAI 50 and absolute BASDAI change from baseline were modelled separately; the dependence of these 2 parameters was not reflected in the probabilistic sensitivity analysis. By contrast, the assessment group for TA383 (herein referred to as York) used joint modelling approaches for BASDAI and BASFI-related treatment outcomes (approaches B and C, see sections 6.1.4 and 6.1.5 as well as appendix 9 of the assessment report for TA383).

Please rerun the economic model using input data based on the results of the network meta-analysis models (including secukinumab), which incorporate dependencies between BASDAI, BASDAI 50 and BASFI. Please follow the approaches B1, B2, C1 and C2 (independent treatment effects) in the York assessment report for TA383.[26]

We have made best efforts at implementing this request. We identified some errors with the winBUGS code provided in Appendix 9 of the York Assessment Group report suggesting the included code may not have been the final version; further detail is provided in Appendix B: .

Although there are some similarities and trends in results excluding the secukinumab data, we were unable to replicate the York results exactly. The reasons for this could be:

- Number of chains, iterations, burn-in etc. MCMC conditions in winBUGS, which are not specified
- Initial values for the prior distribution, which are not specified.

Nonetheless we implemented both Models B and C using random effects and the following MCMC specifications; number of chains=1, Inits generated by winbugs, burn-in=10000, Total iterations =50000.

Please note that these analyses do not use conditional changes from baseline, as our approach to modelling conditional changes differs from the York evidence synthesis model (see Estimation of conditional change from baseline in BASDAI and BASFI

). The outputs from this model are provided in Table 48 to Table 51 below.

Table 48: Modelling approach B: results

	Estimated difference in change score from baseline	Assumed * probability of having a BASDAI50 response, placebo	Predicted probability of having a BASDAI50 response, anti-TNF	OR for BASDAI50 response, anti-TNF vs Placebo
Anti-TNFs	-1.867 (0.8684)	0.1412	0.4389 (0.1448)	6.057 (9.377)
D	-1.868 (0.3147)			
γ	0.7586 (0.2835)			
$\rho placebo$	0.6075 (0.2088)			
ρ**anti-tnf**	0.738 (0.2156)			
DIC	99.470			

Based on a BASDAI baseline score of 6.38 (sd=1.52) and a placebo change score of -0.97 (sd=1.94), which represent the average across trials (weighted by number of patients)

Table 49: Shrunken estimates of treatment effect from model B

	Change in BASDAI
ADA 40 mg	-1.663 (0.1288)
GOL 100 mg	-1.94 (0.2349)
GOL 50 mg	-2.009 (0.2363)
SEC 150 mg	-1.629 (0.1711)
CZP 200 mg	-1.683 (0.239)
CZP 400 mg	-1.61 (0.2283)
ETN 50 QW	-1.237 (0.3104)
INF 5 mg	-3.186 (0.441)

Table 50: Modelling approach C: results

	Estimated difference in change score from baseline	Assumed * probability of having a BASDAI50 response, placebo	Predicted probability of having a BASDAI50 response, anti-TNF	OR for BASDAI50 response, anti-TNF vs Placebo
Effect of anti-TNFs on BASDAI	-1.704 (0.419)	0.1415	0.406 (0.07447)	4.377 (1.745)
Effect of anti-TNFs on BASFI	-1.333 (0.3676)			
D(BASDAI)	-1.703 (0.2724)			
D(BASFI)	-1.332 (0.1952)			
$\gamma BASDAI$	0.4162 (0.1923)			
$\gamma BASFI$	0.2145 (0.1298)			
$\rho placebo$	0.6107 (0.2067)			
ρanti-tnf	0.7281 (0.2146)			
ρm	0.7049 (0.2624)			
σre	0.255 (0.1857)			
DIC	141.757			

Based on a BASDAI baseline score of 6.38 (sd=1.52) and a placebo change score of -0.97 (sd=1.94), which represent the average across trials (weighted by number of patients)

Table 51: Shrunken estimates of treatment effect from model C

	Change in BASDAI	Change in BASFI
ADA 40 mg	-1.682 (0.2684)	-1.271 (0.1853)
GOL 100 mg	-1.723 (0.3293)	-1.389 (0.2601)
GOL 50 mg	-1.744 (0.3338)	-1.409 (0.261)
SEC 150 mg	-1.638 (0.2885)	-1.387 (0.2111)
CZP 200 mg	-1.701 (0.3171)	-1.23 (0.2458)
CZP 400 mg	-1.672 (0.3174)	-1.266 (0.2502)
ETN 50 QW	-1.443 (0.3761)	-1.194 (0.2711)
INF 5 mg	-2.018 (0.5259)	-1.511 (0.3649)

Base case cost-effectiveness results using the above models are provided in Table 52 and Table 53.

Table 52: Based on Model B approach in York report: BASDAI 50 and BASDAI change from baseline correlations

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)

Secukinumab	£112,596	9.159				
Etanercept biosimilar	£116,068	8.647	£3,472	-0.512	Dominated	Dominated
Etanercept	£117,306	8.647	£4,710	-0.512	Dominated	Dominated
Certolizumab pegol – with PAS	£123,470	8.996	£10,874	-0.163	Dominated	Dominated
Adalimumab	£127,205	9.012	£14,609	-0.147	Dominated	Dominated
Golimumab	£129,438	9.260	£16,842	0.101	£167,423	£167,423
Infliximab biosimilar	£137,615	9.205	£25,019	0.045	£551,654	Dominated
Infliximab	£141,328	9.205	£28,732	0.045	£633,529	Dominated

Table 53: Based on Model C approach in York report: BASDAI and BASFI change from baseline correlations

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£116,433	8.868				
Etanercept biosimilar	£116,981	8.561	£547	-0.307	Dominated	Dominated
Etanercept	£118,152	8.561	£1,719	-0.307	Dominated	Dominated
Certolizumab pegol – with PAS	£125,761	8.755	£9,328	-0.113	Dominated	Dominated
Adalimumab	£129,254	8.786	£12,821	-0.082	Dominated	Dominated
Golimumab	£132,705	8.877	£16,272	0.009	£1,739,468	£1,739,468
Infliximab biosimilar	£139,509	8.782	£23,076	-0.086	Dominated	Dominated
Infliximab	£143,019	8.782	£26,586	-0.086	Dominated	Dominated

B8. In TA383, the appraisal committee concluded that TNF-alpha inhibitors were clinically effective compared with placebo and that they should be considered as a class with broadly similar, even if not completely identical, effects.[23] In the company submission for secukinumab there were no statistically significant differences between secukinumab and TNF-alpha inhibitors (except infliximab) for all trial outcomes in the network meta-analyses.

Please rerun the economic model using input data based on the results of the network meta-analysis models, which assume that all TNF-alpha inhibitors have the same treatment effect. Please follow the approaches A3, A4 and A5 in section 6.1.3 and appendix 9 of the York assessment report for TA383.[26]

The JAGS code for the exchangeable effects model is provided in Appendix C:

Cost-effectiveness results for the biologic naïve population based on the York assumptions are provided in Table 54 to Table 56 below. Please note that in these three scenarios a consistent

biologic withdrawal rate has been applied to all comparators; 11% per annum aligned to the York Assessment Group assumption. In both the scenarios in which TNFα inhibitors are assumed to have identical effects, secukinumab dominates the TNFα inhibitors as a class.

Table 54: Based on A3 approach in York report: Identical effects for TNFα inhibitors (fixed effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	[redacted]	9.383				
Etanercept biosimilar	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Etanercept	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Certolizumab pegol – with PAS	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Adalimumab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Golimumab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Infliximab biosimilar	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated
Infliximab	[redacted]	9.219	[redacted]	0.164	Dominated	Dominated

Table 55: Based on A4 approach in York report: Identical effects for TNFα inhibitors (random effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	[redacted]	9.501				
Etanercept biosimilar	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Etanercept	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Certolizumab pegol – with PAS	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Adalimumab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Golimumab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Infliximab biosimilar	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated
Infliximab	[redacted]	9.360	[redacted]	0.141	Dominated	Dominated

Table 56: Based on A5 approach in York report: Exchangeable effects for TNFα inhibitors (fixed effects model)

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£112,151	9.516				
Etanercept biosimilar	£123,503	9.204	-£11,352	0.312	Dominated	Dominated
Etanercept	£123,791	9.457	-£11,640	0.059	Dominated	Dominated
Certolizumab pegol – with PAS	£125,290	9.511	-£13,139	0.005	Dominated	Dominated
Adalimumab	£125,737	9.204	-£13,586	0.312	Dominated	Dominated
Golimumab	£126,511	9.382	-£14,360	0.134	Dominated	Dominated
Infliximab biosimilar	£139,226	9.653	-£27,074	-0.137	£197,687	£197,687
Infliximab	£143,140	9.653	-£30,989	-0.137	£226,269	Dominated

B9. Please provide all relevant input data for the model so that the other approaches described in the York assessment report for TA383 (A1-5, B3-5, C3-5) can be conducted.

The requested data and treatment / study codes are provided in Table 57 to Table 60 .

Table 57: Data table for Model B

s[]	t[]	n[]	r[]	b[]	prec[]	y[]	y.prec[]
1	2	208	94	6.3	1.7	-2.6	0.207
1	1	107	17	6.3	1.7	-0.8	0.206
2	3	140	56	6.9	1.5	-2.69	0.216
2	4	138	61	6.5	1.6	-2.83	0.216
2	1	78	12	6.6	1.5	-0.69	0.216
3	2	229	114	6	1.4	-2.8	0.127
3	1	115	19	6.2	1.4	-1.4	0.179
4	1	122	10	6.5	1.5	-0.59	0.18
4	5	125	47	6.4	1.6	-2.32	0.172
5	1	74	8	6.8	1.3	-0.85	0.252
5	5	72	22	6.6	1.5	-2.19	0.248
6	6	65	27	6.5	1.7	-2.6	0.224
6	7	56	23	6.2	1.3	-2.5	0.212
6	1	57	6	6.4	1.9	-1.1	0.174
7	8	39	18	6.4	1.2	-2.6	0.324
7	1	43	10	5.8	1.5	-1.4	0.32
8	8	25	NA	6.6	1.1	-1.16	0.216
8	9	25	NA	6.5	1.2	-3.39	0.216
9	2	26	NA	5.9	1.4	-3.6	0.216
9	1	20	NA	6.2	1.1	-2	0.216

Table 58: Data table for Model C

s[]	t[]	n[]	r[]	b[]	prec[]	y[]	y.prec[]	y.f[]	y.prec.f[]
1	2	208	94	6.3	1.7	-2.6	0.207	-1.86	0.156
1	1	107	17	6.3	1.7	-0.8	0.206	-0.45	0.225
2	3	140	56	6.9	1.5	-2.69	0.216	-1.55	0.208
2	4	138	61	6.5	1.6	-2.83	0.216	-1.63	0.208
2	1	78	12	6.6	1.5	-0.69	0.216	0.06	0.208
3	2	229	114	6	1.4	-2.8	0.127	-1.75	0.135
3	1	115	19	6.2	1.4	-1.4	0.179	-0.47	0.154
4	1	122	10	6.5	1.5	-0.59	0.18	-0.37	0.171
4	5	125	47	6.4	1.6	-2.32	0.172	-1.84	0.165
5	1	74	8	6.8	1.3	-0.85	0.252	-0.68	0.235
5	5	72	22	6.6	1.5	-2.19	0.248	-2.15	0.231
6	6	65	27	6.5	1.7	-2.6	0.224	-1.8	0.224
6	7	56	23	6.2	1.3	-2.5	0.212	-1.9	0.232
6	1	57	6	6.4	1.9	-1.1	0.174	-0.8	0.164
7	8	39	18	6.4	1.2	-2.6	0.324	-2.2	0.292
7	1	43	10	5.8	1.5	-1.4	0.32	-1	0.288
8	8	25	NA	6.6	1.1	-1.16	0.216	-1.49	0.208
8	9	25	NA	6.5	1.2	-3.39	0.216	-2.6	0.208
9	2	26	NA	5.9	1.4	-3.6	0.216	-1.9	0.208
9	1	20	NA	6.2	1.1	-2	0.216	-1	0.208

Table 59: Treatment codes

PBO	1
ADA 40 mg	2
GOL 100 mg	3
GOL 50 mg	4
SEC 150 mg	5
CZP 200 mg	6
CZP 400 mg	7
ETN 50 QW	8
INF 5 mg	9

Table 60: Study codes

ATLAS	1
GO-RAISE	2
Huang (2014)	3
MEASURE-1	4
MEASURE-2	5
RAPID-axSpA	6
SPINE	7
Giardina (2010)	8
Hu (2012)	9

B10. According to table 70, BASDAI 50 responses for biologic naïve patients are obtained from the network meta-analysis results (figure 26). However, results reported in table 70 differ from the results in figure 26. Please explain these differences and clarify how average values were calculated when corresponding outcomes for a comparator were lacking in the network meta-analysis.

An update to Table 70 was overlooked following identification of the mis-labelling issue mentioned at B6. The values in the original model (Clinical inputs sheet, cells F22:L22) were within 0.1% of the values in Figure 26. An updated version of Table 70, reflecting the updates to the NMA described at A16, is provided below in Table 61. For the included comparators, these figures align with the values in Figure 10 of this response to within 0.1%. The value for adalimumab differs very slightly due to rounding within the calculations.

Table 61. BASDAI 50 response applied in the model base case

Therapy	BASDAI 50 response for the modelled biologic naïve population	BASDAI 50 response for the modelled biologic experienced population
Secukinumab 150 mg	[redacted]	[redacted]
Adalimumab	[redacted]	
Etanercept	[redacted]	
Golimumab	[redacted]	
Infliximab	[redacted]	

Certolizumab pegol	[redacted]	
CC	[redacted]	[redacted]

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CC, conventional care.

For comparators missing from the network meta-analysis, the log odds of BASADI 50 response was assumed to be a straight average of log odds of BASADI 50 response for available TNFα inhibitors was assumed.

B11. The BASDAI 50 responses for TNF-alpha inhibitors (Table 70) appear to be inconsistent with the results in the York assessment report for TA383 (Table 7).[26] Please explain why they are different.

There are several potential sources of differences between the results using our model versus those generated by the York assessment group report:

- The NMA informing our cost-effectiveness model is based exclusively on studies reporting efficacy of biologic treatments amongst biologic naïve populations. The York assessment group did not differentiate between evidence for biologic naïve versus mixed populations (no evidence amongst biologic experienced populations was available to them since there is no published data on TNFα inhibitors in biologic experienced sub-groups).
- There are some differences in the studies which were included in the NMA, the results of which inform the model parameters (please see Table 48 of the submission and Table 2 of the York assessment report).[25] In the recent MTA in AS, 20 trials were eligible for inclusion in the NMA, 19 of which recruited an AS patient population, and one trial that recruited an AS and non-radiographic axial spondyloarthritis (nr-axSpA) population.[25] By comparison, the NMA presented in this submission included only 10 trials; studies such as Barkham et al. 2010; Calin et al. 2004 and Davis et al. 2003 were included in the MTA NMA but not included in the NMA presented in this submission. The reason for exclusion of these studies from our NMA is that it was unclear whether the populations included were intolerant or had inadequate response to conventional treatments. These differences are likely to be responsible for any differences seen in the NMA results.
- The York Assessment Group had access to additional conditional response data for etanercept and certolizumab, which was redacted in the report (Table 78) and addendum (Appendix page 10).[25, 27]
- Conditional baseline and changes from baseline in BASDAI and BASFI within the York model base case are derived from their synthesis model. Comparison of Tables 77 and 78 in the York Assessment Group report suggest that this model provides poor predictions for conditional baseline BASDAI scores.[25] In contrast conditional baseline scores within the submitted model are based on patient-level analyses of the secukinumab trial data.

B12. In TA383, recommendations were based on severe active ankylosing spondylitis. However, the inclusion criteria for MEASURE 1 and MEASURE 2 were not limited only to "severe" active ankylosing spondylitis. The scope for secukinumab is for adults with active ankylosing spondylitis.

Were any of the values used in the company model, which came from TA383[23] or the York assessment repor[t26] adjusted for the severity of the ankylosing spondylitis?

As discussed in response to Question A1, there is no agreed consensus on the terms used to classify the severity of AS. The scope, the licensed indication for secukinumab and clinical guidelines all refer to adults with active ankylosing spondylitis and as a result data were not adjusted according to severity.

B13. The text above table 71 suggests that the difference in baseline BASDAI and BASFI scores between responders and non-responders was based on response at week 12. However, the text following table 72 suggest that response was derived from pooled data from the MEASURE 1 and MEASURE 2 trials, which suggests that response at week 16 was used.

- Please specify the definition, including time point, of response used to differentiate between responders and non-responders when estimating baseline BASDAI and BASFI scores in table 72.

Within the model, response, defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the baseline total BASDAI score, is always assessed at week 12, based on NICE guidance and BSR guidelines.[5, 28] Different network meta-analyses inform the probability of patients on each treatment meeting this response criterion;

  - Network meta-analyses used for the base case and scenario 6a employ data for each trial taken at the primary endpoint where this fell within the 12-16 week window (the only exception being the infliximab ASSERT study where the primary endpoint was 24 weeks and 12 week data was used as it was the only available data within the 12-16 week window) i.e. 16 week secukinumab data, 14 week golimumab data and 12 week data for etanercept, certolizumab, adalimumab and infliximab.
  - Network meta-analyses used for scenarios 6b and 6c, employed 12 week data for all comparators. Post hoc analyses of MEASURE 1 and MEASURE 2 informed these network meta-analyses.

However, regardless of the NMA data selected to model response probabilities, the model applies response assessment at 12 weeks.

- Please provide the number of patients (n) for each result in table 72.
- Please provide response-based BASDAI and BASFI figures not differentiated by treatment.

A revised version of Table 72 is provided below, including n numbers and conditional baseline BASDAI and BASFI scores for all responders and non-responders, regardless of treatment arm.

Table 62. Treatment-specific baseline BASDAI and BASFI conditional on BASDAI 50 response

Input	Biologic naïve						Biologic experienced					
	Biologics		CC		Pooled		Biologics		CC		Pooled	
	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score
Baseline BASDAI												
Responders	51	6.42	22	6.12	73	6.33	14	6.59	5	6.24	19	6.50
Non-responders	85	6.39	112	6.73	197	6.58	47	6.48	57	6.61	104	6.55
Baseline BASFI												
Responders	51	5.44	22	4.75	73	5.23	14	5.39	5	5.49	19	5.42
Non-responders	85	6.07	112	6.22	197	6.15	47	6.04	57	5.85	104	5.93

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CC, conventional care.

In the Excel model, the same baseline BASDAI and BASFI scores (given in table 72) are used even though different secukinumab trial data (week 12 and week 12-16) were chosen (sheet “Settings”, range “E60:F60”).

- Please provide BASDAI 50 response specific baseline BASDAI and BASFI scores based on different (week 12 or week 12-16) time point responses.

As discussed above, response was always defined at week 12 within the model. All conditional response analyses have defined responders at 12 weeks, not 16 weeks. There is no difference in baseline scores depending on choice of network meta-analysis scenario.

B14. Section 5.3.3.1 is difficult to follow. Please provide a step by step explanation showing all formulae used to calculate mean change in BASDAI and BASFI from the various sources (MEASURE 1 & 2 trials, network meta-analyses, York assessment report[26], TA383[23] and any other sources).

Please see explanation at B6 regarding the Subgroup data sheet, specifically the “Estimation of conditional change from baseline in BASDAI and BASFI

” onwards.

B15. By definition, the absolute BASDAI change from baseline at 3 months for the BASDAI 50 responders should be at least 50% of their baseline BASDAI. However, this does not appear to be the case for some of the model inputs (e.g. etanercept, adalimumab and conventional care; (tables 72 and 73).

Please explain this discrepancy for BASDAI 50 responders.

This question has led to the identification of an error in the way that NMA outputs were applied within the Subgroup Data sheet of the model. An original set of NMA results required placebo responses to be deducted from each comparator before entering the data into the model. In subsequent NMA results, this calculation had already been applied. However, a miscommunication resulted in placebo responses being once more deducted during data entry to

the model. Hence, placebo responses were effectively being deducted twice from comparator changes from baseline in the original version of the model. See response to B6 for updated versions of Tables 72 & 73. Updated results, which are now further in favour of secukinumab, are provided in Section E:.

B16. In the Excel model, differing baseline BASDAI and BASFI scores are used in subgroup (biologic experienced and biologic naïve) and scenario (only MEASURE 2 trial data as a data source for secukinumab) analyses.

Please justify why other baseline characteristics (age, weight and percentage males) are not varied in these subgroup/scenario analyses.

Amending patient baseline characteristics based on choice of NMA scenario was not prioritised as we did not anticipate these differences would have a material impact on results. A comparison of baseline characteristics pooled across MEASURE 1 and MEASURE 2 versus from MEASURE 2 alone is provided in Table 63 below.

Table 63: Baseline patient characteristics, pooled data vs MEASURE 2 only

	MEASURE 1 & 2 pooled (used in base case and Scenario 6b)	MEASURE 2 only (used in scenarios 6a and 6c)
% male	69.5%	69.9%
Mean age (years)	42.37	43.31
Mean weight (kg)	78.20	81.34
Weight SD (kg)	16.882	16.887

Comparison of results the MEASURE 2 scenario analyses (6a and 6c), utilising the MEASURE 2 specific baseline characteristics vs pooled baseline characteristics are provided in Table 64 and Table 65 below.

Table 64: Incremental costs, incremental QALYs and ICERs for Scenario 6a, with pooled baseline characteristics vs. MEASURE 2 baseline characteristics

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	-£17,762	0.095	SEC dominates	-£17,704	0.092	SEC dominates
Certolizumab pegol – with PAS	-£11,829	0.133	SEC dominates	-£11,779	0.129	SEC dominates
Etanercept	-£4,029	0.877	SEC dominates	-£3,978	0.870	SEC dominates
Etanercept biosimilar	-£2,948	0.877	SEC dominates	-£2,897	0.870	SEC dominates
Golimumab	-£19,009	-0.318	£59,771	-£18,925	-0.317	£59,737
Infliximab	-£30,252	0.072	SEC dominates	-£31,537	0.066	SEC dominates
Infliximab biosimilar	-£26,472	0.072	SEC dominates	-£27,628	0.066	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab **Abbreviations:** ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

Table 65: Incremental costs, incremental QALYs and ICERs for Scenario 6c, with pooled baseline characteristics vs. MEASURE 2 baseline characteristics

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Adalimumab	-£11,280	0.312	SEC dominates	-£11,207	0.307	SEC dominates
Certolizumab pegol – with PAS	-£4,768	0.367	SEC dominates	-£4,702	0.361	SEC dominates
Etanercept	£834	1.056	£790*	£903	1.046	£863*
Etanercept biosimilar	£1,796	1.056	£1,701*	£1,863	1.046	£1,781*
Golimumab	-£9,880	0.065	SEC dominates	-£9,788	0.063	SEC dominates
Infliximab	-£20,730	0.293	SEC dominates	-£21,823	0.286	SEC dominates
Infliximab biosimilar	-£17,450	0.293	SEC dominates	-£18,431	0.286	SEC dominates

	Pooled baseline characteristics			MEASURE 2 baseline characteristics		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab. **Abbreviations:** ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.

B17. BASDAI and BASFI change from baseline of TNF-alpha inhibitors in tables 73 and 74 appear to be inconsistent with the results reported in the York assessment report for TA383 (for example table 69 on page 167 of the York report).[26] Please explain these differences.

As discussed in response to Question B11, results would be expected to differ from those in the York assessment report due to the fact that different studies were included in the respective NMAs.

B18. Please provide details of the methods used to derive the values in table 73 of the company submission (especially for etanercept, certolizumab pegol and infliximab).

Please see explanation at B6 regarding application the Subgroup data sheet, specifically the "Estimation of conditional change from baseline in BASDAI and BASFI

" onwards.

B19. Please explain how the value of 0.15 for the annual BASFI progression rate for secukinumab (section 5.3.3.2, second paragraph on page 193) was derived from Ramiro et al. and MEASURE 1 week 104 rates.[29]

Haroon et al. report that the relative rate of mSASSS change with TNFα inhibitors is 0.42 i.e. the ratio of mSASSS change with TNFα inhibitors to mSASSS change with conventional care is 0.42.[30]

Over two years of treatment with secukinumab, mean mSASSS change of 0.3 units was observed (see Section 4.7.2.4 of submission). Assuming linear progression, which is supported by Ramiro et al., who found that "At the group level, a linear time course model fitted the data best", the estimated annual rate of mSASSS change with secukinumab is 0.3 / 2 = 0.15 units.[31]

Ramiro et al. provide an estimate for the background annual rate of mSASSS change, across the total cohort studied, of 0.98 mSASSS units.[31]

The relative rate of mSASSS change with secukinumab was therefore calculated as 0.15 / 0.98 = 0.15.

It should be noted that the York Assessment Group selected a higher background mSASSS progression rate, from a sub-group of patients within the Ramiro et al. study;[31] those with a baseline mSASSS≥10, who had an annual rate of mSASSS change of 1.44 units. Had this higher background rate been assumed, the relative rate of mSASSS change with secukinumab would have been even lower (0.15 / 1.44 = 0.10), and cost-effectiveness results more strongly in favour of secukinumab.

Adverse events

B20. Please justify why switching to a second TNF-alpha inhibitor was not allowed following an adverse event.

Within the model exploratory analysis in which biologic sequencing was incorporated, patients experiencing a serious adverse event on their first biologic were modelled to discontinue this biologic in line with BSR guidelines that biologic therapy should be withdrawn upon evidence of

severe adverse events or evidence of inefficacy.[5] However, patients experiencing an adverse event *were* permitted to switch to a second biologic therapy. Page 181 explains that second line TNFα inhibitors were only included in the exploratory sequencing analyses; "In the base case analysis of the biologic naïve population, transition to conventional care occurred on biologic discontinuation as it was assumed that patients could not receive a second-line biologic therapy". In the exploratory sequencing analyses all discontinuations switched to the "basket" therapy. Page 188 mentions that the included discontinuations could be for any reason: "Within the model, this [withdrawal of TNFα inhibitors upon development of severe adverse events or evidence of inefficacy] is captured by discontinuation of biologic therapy, which could be for any reason including adverse events or loss of efficacy". We acknowledge that this was not may not have been made sufficiently explicit in the write-up of the economic model, but clarify here that patient movement to a second-line biologic was permitted following discontinuation of a first biologic due to an adverse event.

Utilities

B21. Priority request: Please provide the details of the methods used to generate the utility regression equation (section 5.4.5.4, page 198) used for mapping to EQ-5D.

- Please provide details of the regression models considered, the explanatory variables assessed, and the variable selection method used to obtain the final model.

A linear mixed model was used to fit EQ-5D utility score as a response variable with BASDAI, BASFI, age and sex as predictors. The choice of predictive variables was aligned to the MacLeod 2007 and Wailoo 2015 utility analyses in ankylosing spondylitis.[32, 33] The effect of correlation within the data was explored using subject as a random effect to account for the within-subject correlation between assessments.

- Please provide all related regression outputs, e.g. coefficients, test scores and goodness of fit.

The requested data is provided in Table 66 and
Table 67 below.

Table 66: EQ-5D Utility Model Outputs: MEASURE 1 & MEASURE 2, Full Analysis Set

		Estimate (SE)	95% CI	p value
Intercept		0.9610 (0.02503)	0.9118, 1.0101	<.0001
BASDAI score		-0.0442 (0.00312)	-0.0503, -0.0380	<.0001
BASFI score		-0.0330 (0.00316)	-0.0391, -0.0268	<.0001
Sex	**Male**	-0.0111 (0.01335)	-0.0374, 0.0151	0.4049
	Female	reference		
Age (years)		-0.0005 (0.00049)	-0.0015, 0.0005	0.2939

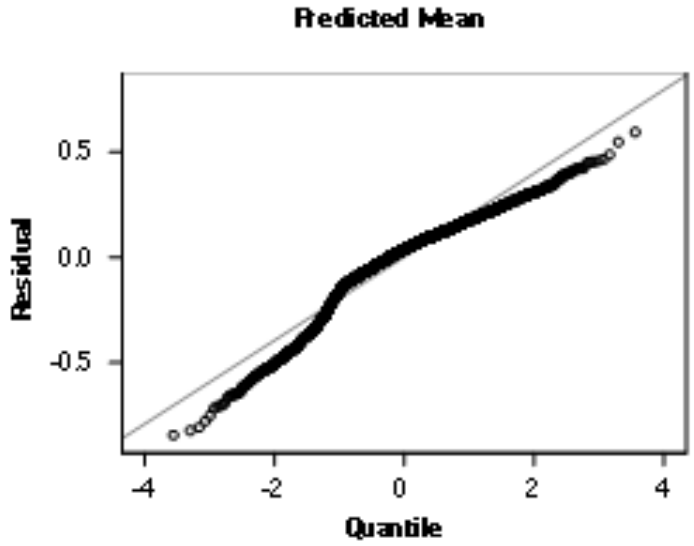
Table 67: EQ-5D Utility Model Fit Statistics: MEASURE 1 & MEASURE 2, Full Analysis Set

Objective / Log likelihood	-2098.6
AIC	-2094.6

- Please provide a Q-Q plot for all 3 utility regression methods (MEASURE 1-2 model, Wailoo et al. 2015 method and McLeod et al. 2007 method) to compare the 3 utility mapping models.[34, 35]

The Q-Q plot for the utility model generated from the MEASURE 1 and MEASURE 2 trial data is provided in Figure 2.

Figure 2: Q-Q plot for the utility model generated from MEASURE 1 and MEASURE 2 trial data



Wailoo et al. 2015 and McLeod et al. 2007 are published algorithms.[32, 33] Since the patient level data from which these algorithms were generated is not available, it is not possible to provide Q-Q plots for them. However, the Wailoo et al. paper include some similar information regarding observed versus predicted EQ-5D utility scores, which is provide in Table 68 below.[33]

Table 68: Observed versus predicted EQ-5D utility scores for the Wailoo et al. linear algorithm.

Percentiles	Observed	Linear Model
1%	-0.184	-0.160
5%	-0.016	0.054
10%	-0.003	0.170
25%	0.516	0.363
50%	0.689	0.570
75%	0.796	0.765
90%	0.883	0.935
95%	1.000	1.033
99%	1.000	1.213

Costs

B22. Please update the cost regression (section 5.5.5, page 157) used for active disease health state according to 2016 NHS prices.

Please check the study on which this regression method is based and whether the assumptions of the regression model are still relevant for the UK clinical setting.[36]

The value of £1,284.19 applied in the cost regression was taken directly from the York assessment report, for consistency with TA383. The cost year for this value is not determinable from the assessment report, with this value being referenced to the Abbvie submission.

We would highlight that the results of the deterministic sensitivity analysis (Figure 43 in our original submission), in which the intercept value of the cost regression equation (£1,284.19) was varied, did not find this model parameter to be a key cost driver. Further detail on the results of one-way sensitivity analyses of both the regression intercept and BASFI co-efficient are provided in Table 69 below. In these analyses the cost equation intercept was varied between a lower bound of £929.35 and an upper bound of £1774.50, whilst the BASFI co-efficient was varied between a lower bound of 0.139 and an upper bound of 0.287. Therefore, a small update to this figure based on inflation would not be anticipated to influence the overall conclusions of the cost-effectiveness analyses.

Table 69: OWSA of both cost regression parameters

	Total cost with upper bound	Total cost with upper bound	Total QALYs	ICER vs baseline with upper bound	ICER vs baseline with lower bound
Cost equation intercept					
Secukinumab	£148,501	£87,680	9.805		
Adalimumab	£165,141	£102,011	9.446	SEC dominates	SEC dominates
Certolizumab pegol – with PAS	£159,371	£95,675	9.447	SEC dominates	SEC dominates
Etanercept	£154,287	£86,997	8.759	SEC dominates	£653*
Etanercept biosimilar	£153,272	£85,982	8.759	SEC dominates	£1,623*
Golimumab	£165,437	£104,215	9.830	£684,332	£668,098
Infliximab	£176,149	£112,873	9.590	SEC dominates	SEC dominates
Infliximab biosimilar	£172,574	£109,299	9.590	SEC dominates	SEC dominates
BASFI co-efficient					
Secukinumab	£170,627	£78,601	9.805		
Adalimumab	£189,179	£92,017	9.446	SEC dominates	SEC dominates
Certolizumab pegol – with	£184,278	£85,352	9.447	SEC dominates	SEC dominates

PAS					
Etanercept	£182,268	£75,232	8.759	SEC dominates	£3,220*
Etanercept biosimilar	£181,253	£74,217	8.759	SEC dominates	£4,190*
Golimumab	£188,289	£94,870	9.830	£713,655	£657,355
Infliximab	£201,222	£102,566	9.590	SEC dominates	SEC dominates
Infliximab biosimilar	£197,648	£98,991	9.590	SEC dominates	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab.

B23. The drug acquisition costs are the same as those in the York assessment report for TA383, from 2014.[26] Please verify that these drug prices have not changed since 2014.

All drug acquisition costs have been verified against the BNF 2016 [online] and no changes to the drug prices for certolizumab pegol, etanercept, adalimumab, infliximab or golimumab have been made since 2014.[37] Since our submission was sent to NICE on February 5th 2016, a list price for biosimilar etanercept has become available – Benepali is priced at 1 x 1 ml = £164.00; 4 x 1ml = £656.00. Therefore we have now updated the acquisition costs to include this information (Table 70). As mentioned at B5, cost-effectiveness analyses are now provided versus biosimilar etanercept (see Section E:). Secukinumab dominates biosimilar etanercept in the base case and all scenarios except one; in which biosimilar etanercept falls in the south-west quadrant, with only a £1,701 saving per QALY lost.

Table 70: Unit costs associated with drug acquisition – etanercept biosimilar added

Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
Acquisition costs						
List price: £1,218.78 per pack of two 150 mg pre-filled syringes/ SensoReady® pens **PAS price:** [redacted] per pack of two 150 mg pre-filled syringes/ SensoReady® pens	£357.50 per 200 mg pre-filled syringe The NICE MTA in AS also indicates that there is an agreed PAS with the department of health for certolizumab pegol, such that the first 12 weeks of treatment are provided free. This PAS is taken	**Originator Etanercept:** £178.75 per 50 mg pre-filled syringe **Biosimilar Etanercept:** Benepali: £164.00 per 50mg/ml solution for injection in pre-filled syringe or	£352.14 per 40 mg pre-filled syringe	**Originator infliximab:** Remicade®: £419.62 per 100 mg vial Average cost per dose calculated as £1,850.59 – see "Infliximab cost calculations"	£762.97 per pre-filled syringe Although the 100 mg pre-filled syringe of golimumab has a higher list price than that of golimumab 50 mg, a PAS has been agreed with the department	BNF 2016 and MIMS

	into account in the cost-effectiveness analysis.	pre-filled pen, 1 x 1ml=£164.00		**Biosimilar infliximab:** Remsima: £377.66 per 100 mg vial Inflectra: £377.66 per 100 mg vial Average cost per dose calculated as £1,665.54 – see "Infliximab cost calculations"	of health that provides the 100 mg dose of golimumab at the same price as the 50 mg dose.	

Abbreviations: AS, ankylosing spondylitis; BNF, British National Formulary; PAS, patient access scheme; MIMS, Monthly Index of Medical Specialties; MTA, multiple technology appraisal; NICE, National Institute for Health and Care Excellence; QW, once a week.

B24. Please explain the calculation methods for the number of doses for all interventions (especially for certolizumab pegol) (Excel Model Sheet "Resource Use Inputs", Range G15:I20).

See Table 68 of the submission for details of the posology secukinumab and biologic comparators.

Secukinumab and golimumab are dosed monthly so the number of doses reflects the number of months per 3 month period (with an increased number of secukinumab doses in the first 3 months reflecting the loading doses).

For certolizumab pegol and adalimumab adjustments were applied to account for fortnightly dosing, given that model cycles reflect periods of 3 calendar months.

The calculation of the number of fortnights per 3 month model cycle is:

- Number of weeks per year = 365.25 / 7 = 52.18
- Number of fortnights per year = 52.18 / 2 = 26.09
- Number of fortnights per 3 month model cycle = 26.09 / 4 = 6.52

For certolizumab pegol, the double doses required at loading were accounted for by multiplying the number of fortnights in the first 3 months by 150%. This does over-estimate the certolizumab doses during the first 3 months since loading is only required for the first 3 doses. However, these dose assumptions do not account for the patient access scheme in place for certolizumab pegol. In the revised analyses (see Section E:) the number of doses for certolizumab pegol in the

first 3 months has been reduced to zero, to reflect that the NHS does not incur drug acquisition costs for these doses. Simultaneously, the oversight of not applying the adjustment to the subsequent 3 month periods for certolizumab pegol has been corrected. These changes do not impact the overall conclusions of the cost-effectiveness analysis, as secukinumab continues to dominate certolizumab pegol,

The same adjustment was applied for etanercept and infliximab in subsequent 3 month periods, based on 4-weekly dosing and 8-weekly dosing, respectively. Whilst the adjustment could also be applied to the first 6 month periods for etanercept and infliximab (and would favour secukinumab), the impact on results will be negligible since these small adjustments only relate to a small proportion of the total model time horizon.

B25. According to the NHS choices website, surgery is part of the treatment pathway. The model does not include costs related to surgeries. Please justify the assumption of excluding surgery costs.

Surgery costs were not explicitly included in the model based on the fact that the York assessment report for TA383 did not include the cost of surgery.[25] In addition, the disease-related costs derived from the Boonen et al. study reflect hospital admissions and therefore include surgery costs.[38]

Validation

B26. Please provide a table similar to table 110 for the comparison of total QALYs in the company model for secukinumab and the York model for TA383. Please provide a comparison for disaggregated costs in table 110.

A comparison with QALYs reported for TA383 is provided in Table 71.

Table 71: Comparison of total QALYs by intervention in submission model and York model in AS

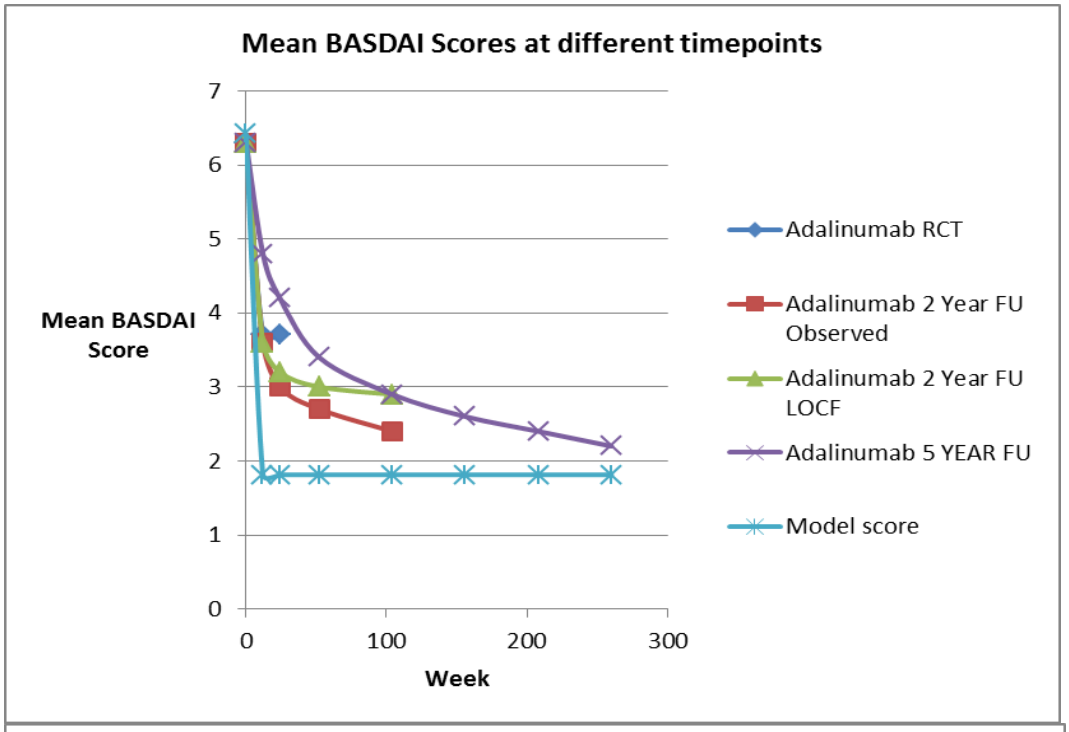
	Total QALYs – model presented in this submission	Total QALYs – York model in AS (base case)
Conventional care	8.537	7.245
Etanercept	8.759	8.163
Certolizumab pegol – with PAS	9.447	8.163
Adalimumab	9.446	8.163
Golimumab	9.830	8.163
Infliximab	9.590	8.163

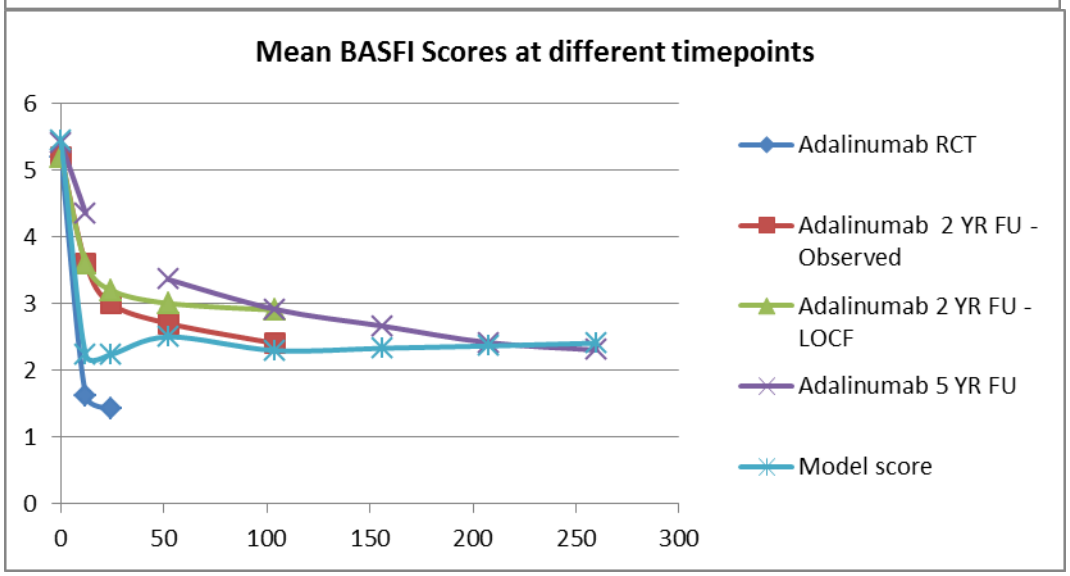
No comparison with disaggregated costs is possible, since these are not reported in the assessment report for TA383.

B27. Please provide a figure that compares the average BASDAI and BASFI scores at different time points from the model with average BASDAI and BASFI scores at different time points from relevant clinical trials.

Please find below figures comparing the average BASDAI and BASFI scores over time from relevant clinical trials versus the cost-effectiveness model. The general trend is that the model is predicting lower BASDAI and BASFI scores than have been observed in clinical trials, due to the model assumption that non-responders discontinue biologic treatment, whilst within clinical trials both responders and non-responders continue treatment.

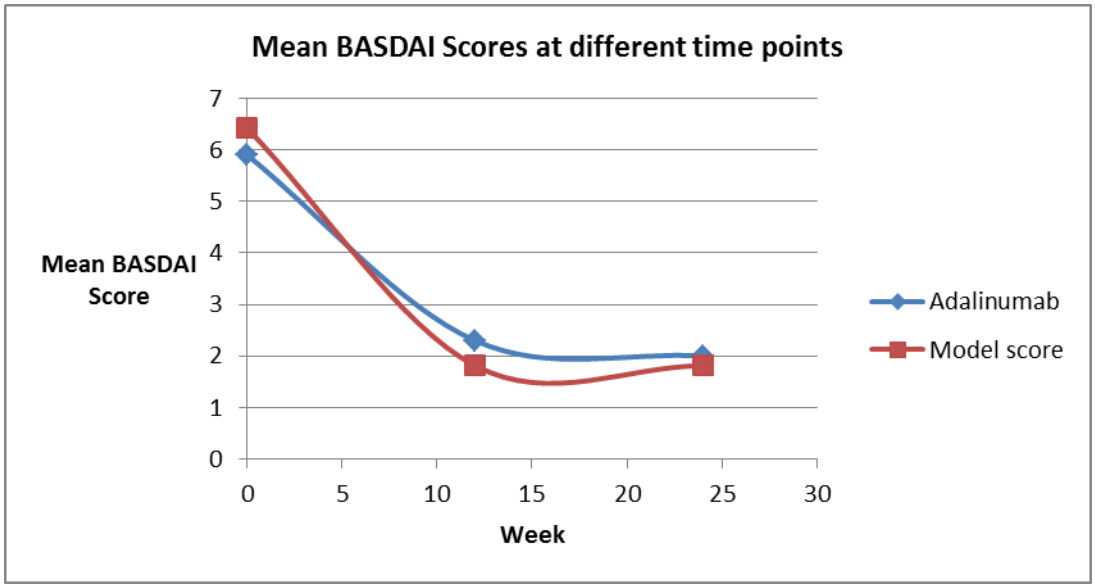
ATLAS

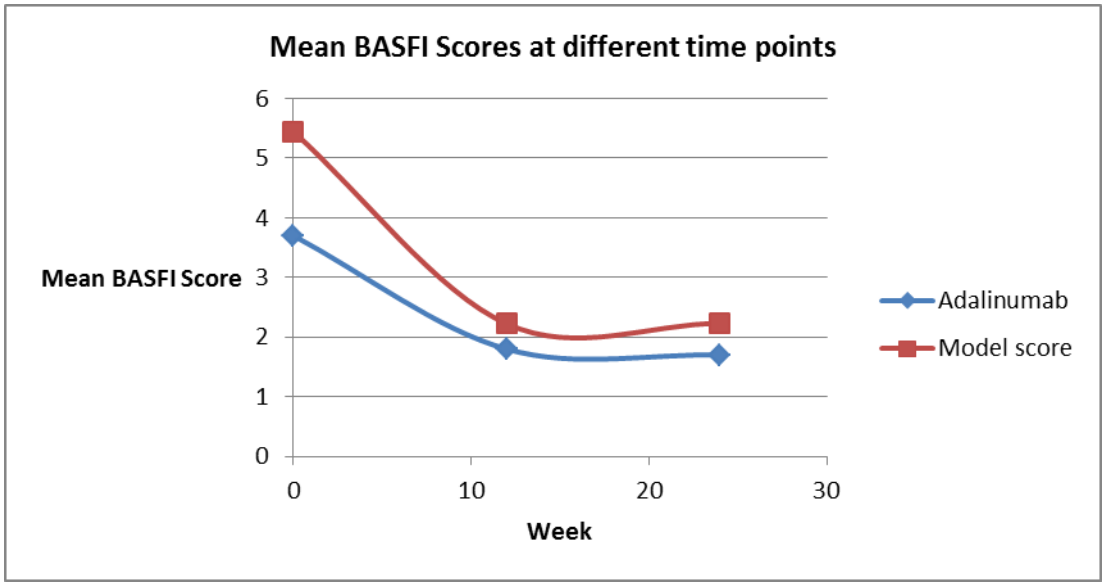




References: van der Heijde 2006,[7] van der Heijde 2009,[39] van der Heijde 2015[40]

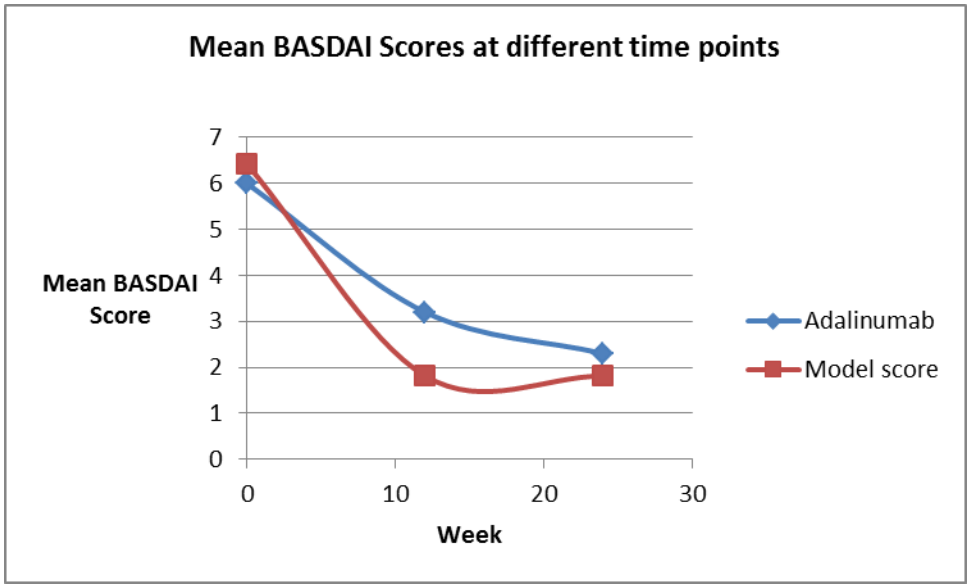
HU

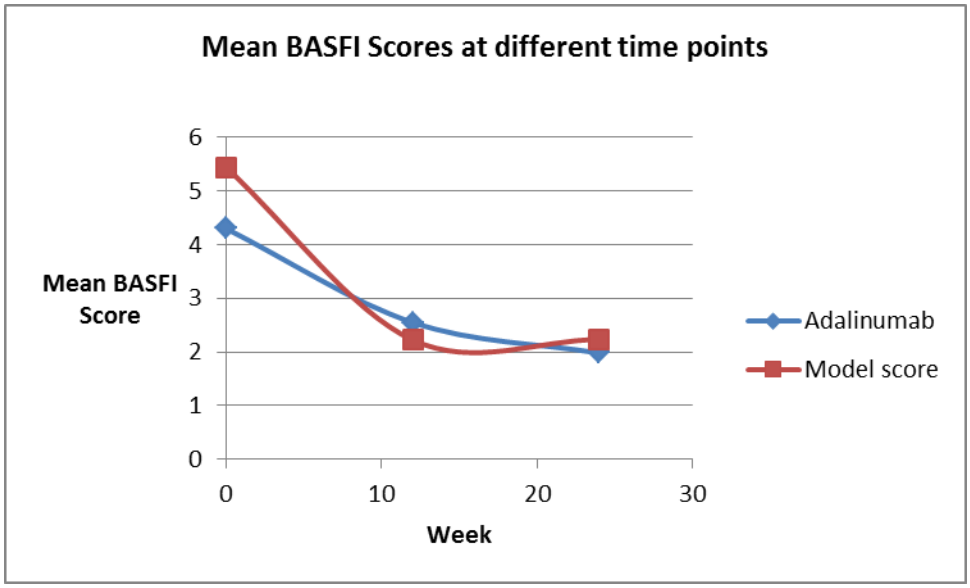




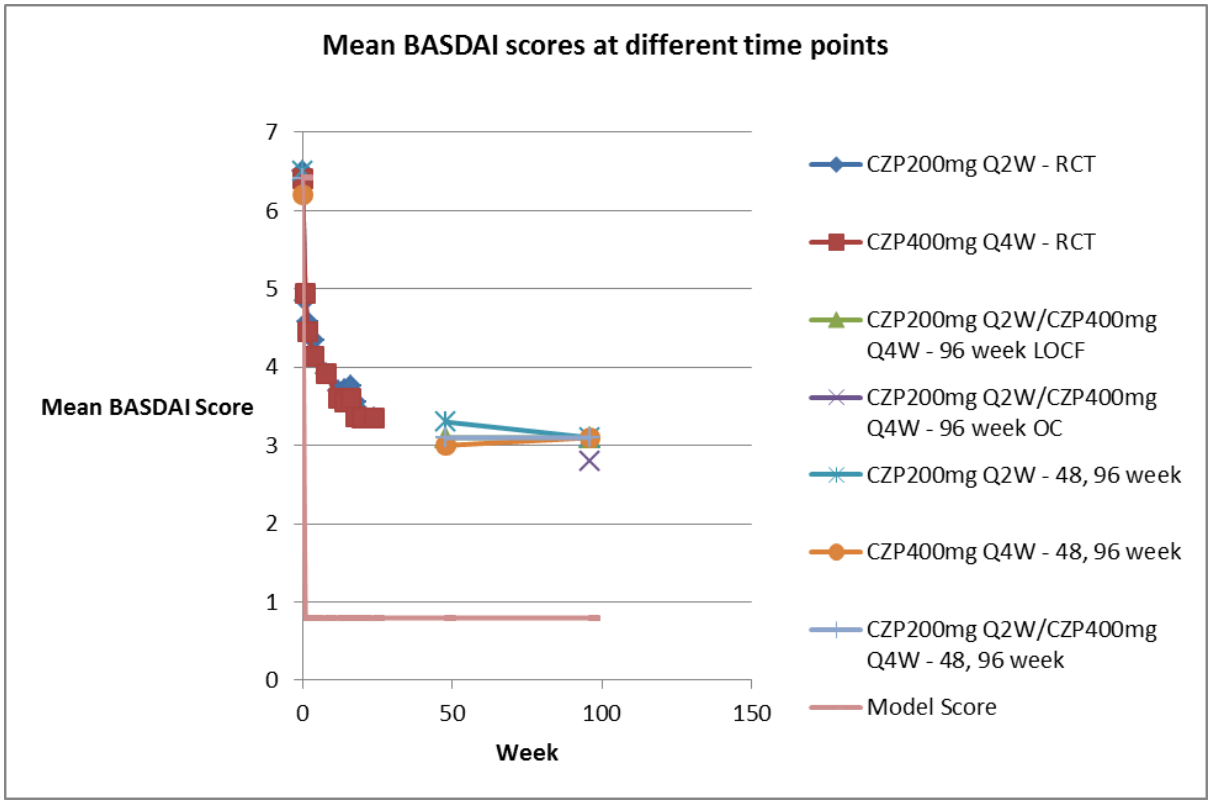
Reference: Hu 2012[41]

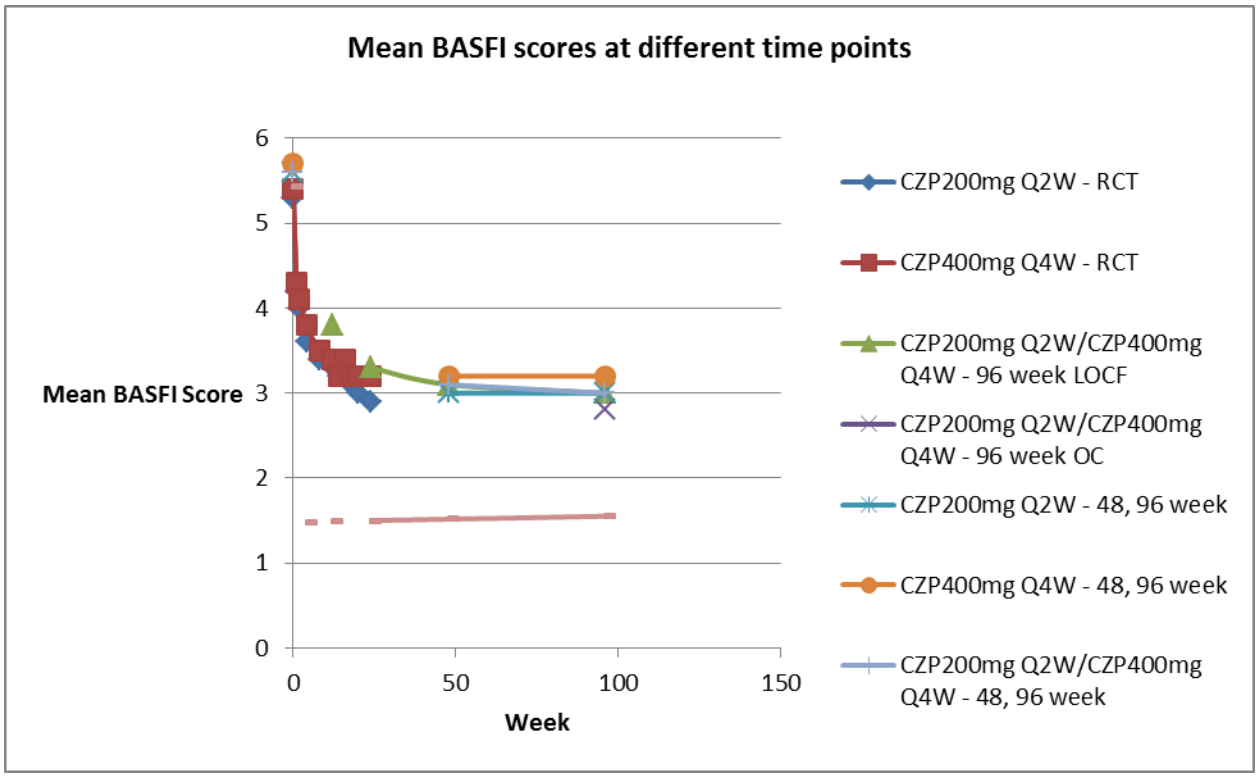
HUANG





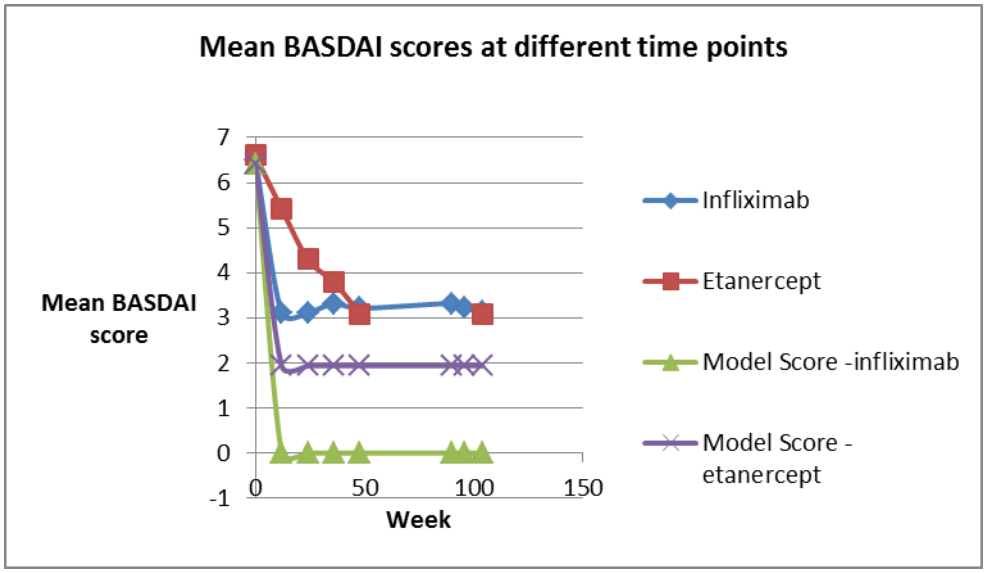
Reference: Huang 2014[42]

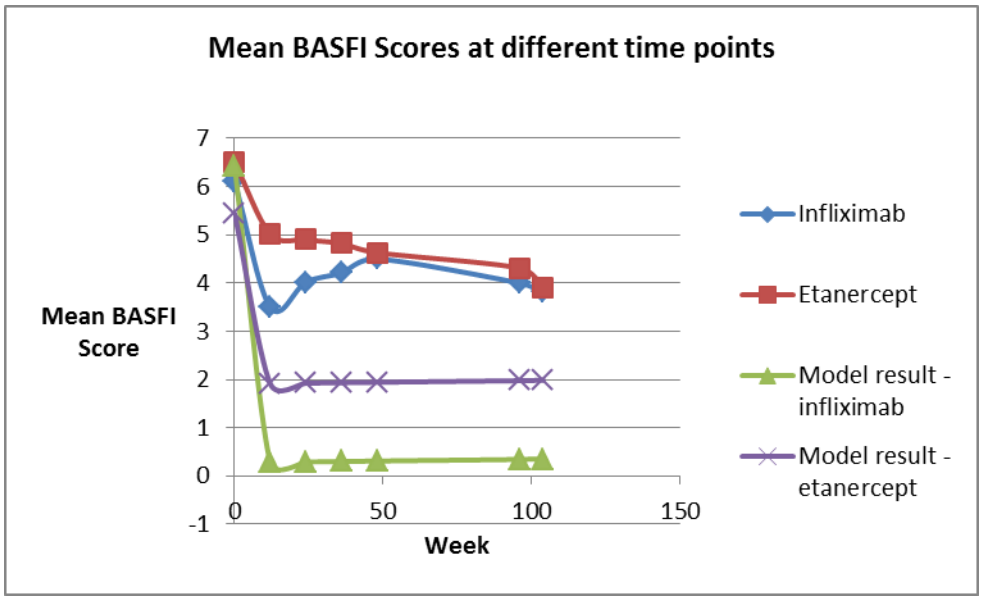




References: Landewe 2013,[43] Landewe 2013 Supplementary information,[44] Sieper 2015[45]

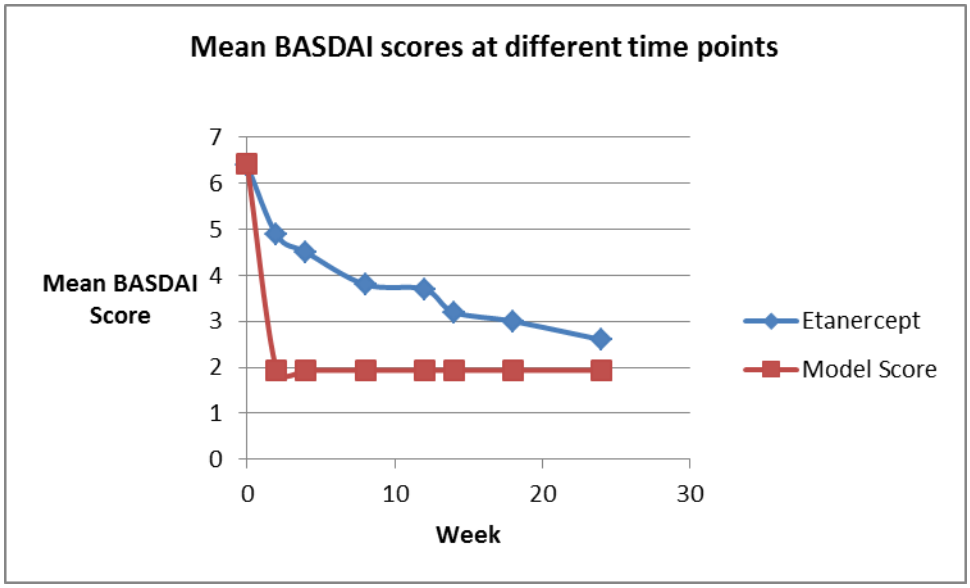
GIARDINA

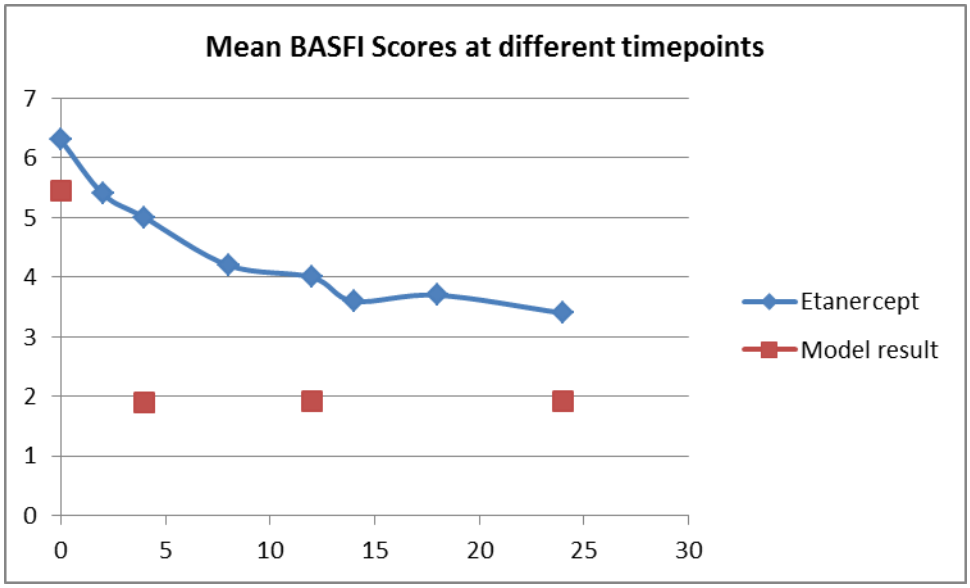




Reference: Giardina et al 2010[46]

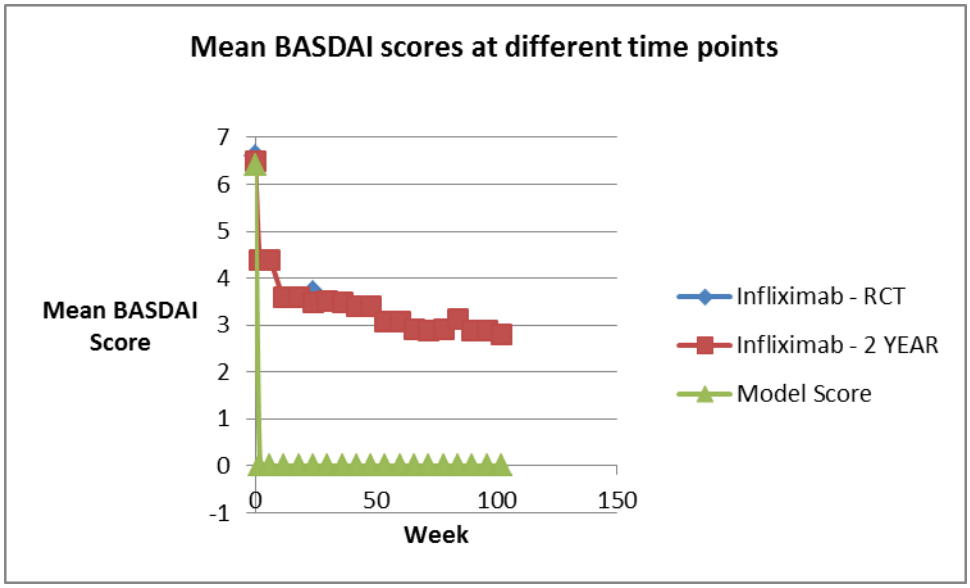
SPINE

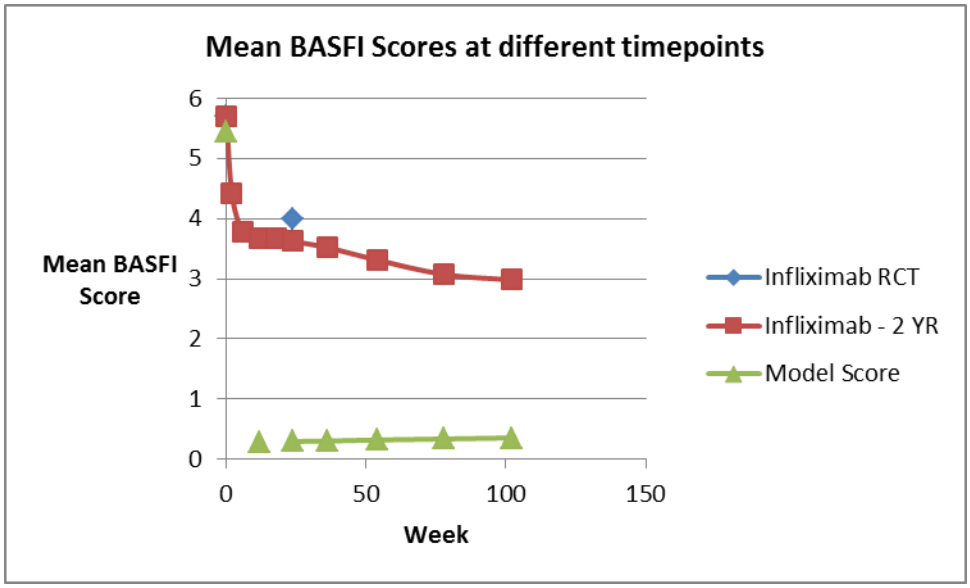




References: Dougados 2011[47], Dougados 2012[48]

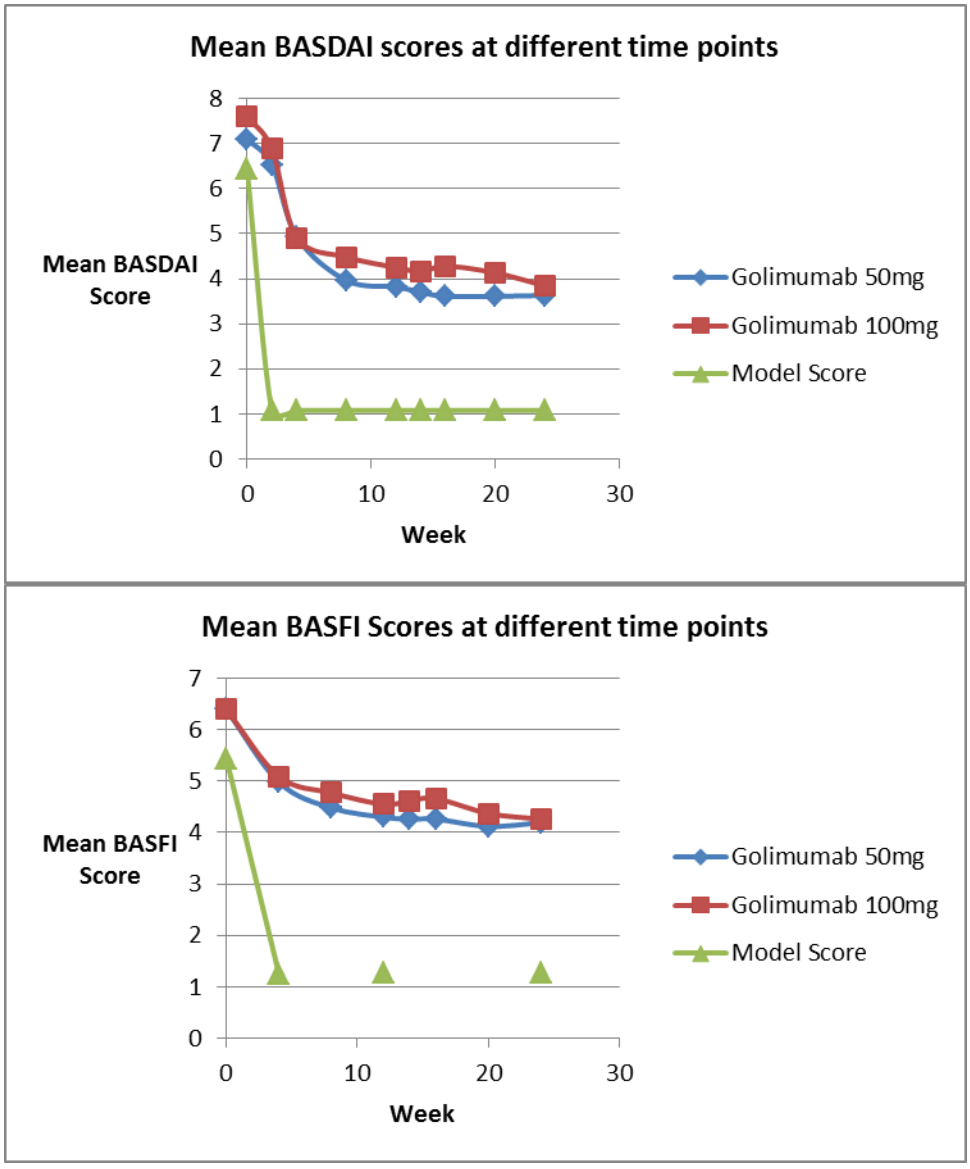
ASSERT





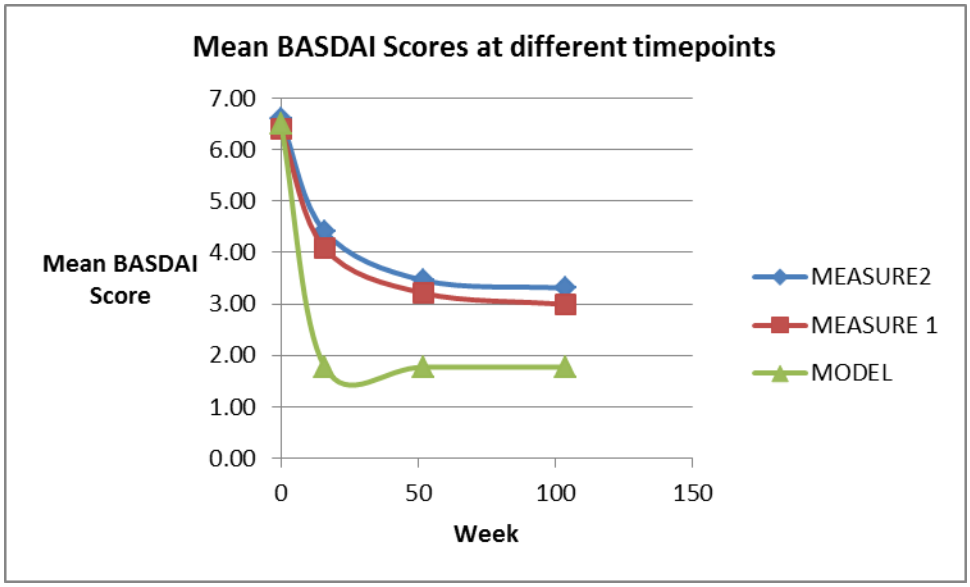
References: van der Heijde 2005,[49] Braun 2008[50]

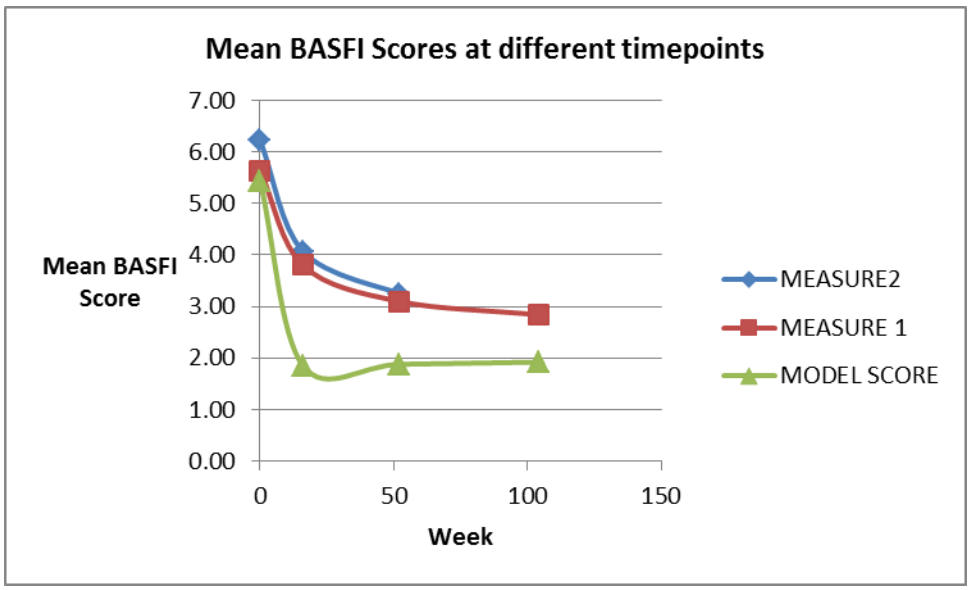
GO-RAISE



Reference: Inman 2008[13]

MEASURE1 and MEASURE 2





B28. In the excel model, it seems that the model estimates are not the same for total QALYs and LYs, even though a utility of 1 is used for each alive state (and no disutilities for adverse events were considered). Please confirm if this is a programming error. If this is the case, please provide a corrected version.

Due to the application of half-cycle correction, some patients are counted in the initial treatment health state in the second cycle of the model. This was not taken into account in the calculation of QALYs but has now been corrected.

B29. In the excel model it appears that the discount rate for costs was used when discounting both costs and health outcomes. Please confirm if this is a programming error and if so, provide a corrected version.

This has been corrected in the revised version of the model.

B30. In the excel model it seems that variations in non-responder BASFI baseline value, and in non-responder change in BASDAI and BASFI, have no effect at all on costs and QALYs. Please confirm if this is meant to be the case and provide an explanation.

Baseline BASDAI for non-responders does have a slight impact on QALYs. This is because patients who discontinue biologic therapy are assumed to immediately revert to baseline BASDAI, in line with the York Assessment Group assumptions.

Baseline BASFI for non-responders has a small impact on QALYs when the BASFI rebound assumption is Natural History, but not with the base case setting of rebound to Initial Gain i.e. baseline.

With base case settings the model does not include non-responder baseline BASFI or change in BASDAI / BASFI for non-responders within the calculations. This is a minor limitation of the latest model version. However, since these parameters would only affect the first cycle for non-responders, the impact on QALYs of implementing a correction would be extremely small.

B31. In the excel model, there is a big difference between the averages from probabilistic sensitivity analyses (PSA) and base case deterministic results, especially in QALYs. Please explain the underlying reasons for this.

BASDAI and BASFI changes from baseline are calculated based on the coefficient of the respective treatment added to the coefficient for conventional care. This is done on the Subgroup data sheet and then feeds into the SA inputs sheet. The probabilistic changes from baseline in BASDAI and BASFI were calculated on the SA inputs sheet using treatment specific changes from baseline, and then adding conventional care changes from baseline. This resulted in BASDAI and BASFI changes from baseline for conventional care being double counted in the probabilistic values, and hence sampled values that were on average much higher than the mean change for the respective treatment.

To prevent this from happening, the probabilistic values are now calculated on the subgroup data sheet. They use coefficients and SEs only, and not calculated change values. Probabilistic values are now calculated using the same method as is used for calculating the lower and upper bounds.

B32. In the excel model, some of the model input parameters were not included in the PSA (e.g. relative risk of BASDAI 50 response for biologic experienced patients). Please justify the inclusion criteria that were applied to the input parameters for PSA.

Three parameters relating to analysis of secukinumab versus conventional care in the biologic experienced population, based on the results of the MEASURE 1 and MEASURE 2 studies, were omitted from the PSA in error; relative risk of BASDAI 50 response, relative risk of BASDAI change from baseline and relative risk of BASFI change from baseline. This has been corrected in the revised version of the model. See Section E: for updated PSA results.

B33. Please provide the BASDAI and BASFI changes from baseline used in Scenario 3 described in section 5.8.3 (page 232).

Scenario 3 was executed in a simplistic manner, by setting the ratio data in rows 45 and 85 of the Subgroup data sheet to 1. As previously run, the scenario did not consider the implication of

assuming no difference between change scores for responders and non-responders, on baseline scores. The scenario has now been re-run, using overall pooled baseline scores (in F40:F45 of the Clinical Inputs sheet) calculated as weighted averages of MEASURE 1 and MEASURE 2 baseline scores, which can be found in Table 15 of the submission , with pooled data provided in Table 72. A comparison of revised results with and without this adjustment to baseline scores is provided in Table 73.

Table 72: Baseline BASDAI and BASFI scores pooled across MEASURE 1 & MEASURE 2

	Secukinumab 150mg	Placebo
BASDAI	5.85	5.92
BASFI	6.47	6.61

Table 73: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population – Scenario 3 with and without non-conditional baseline BASDAI and BASFI scores

	Scenario 3 – with conditional baseline scores			Scenario 3 – without conditional baseline scores		
	Inc. costs	Inc. QALYs	ICER	Inc. costs	Inc. QALYs	ICER
Adalimumab	£14,979	-0.290	SEC dominates	£15,273	-0.291	SEC dominates
Certolizumab pegol – with PAS	£8,847	-0.311	SEC dominates	£9,216	-0.313	SEC dominates
Etanercept	£467	-0.726	SEC dominates	£1,227	-0.730	SEC dominates
Etanercept biosimilar	-£547	-0.726	£754	£212	-0.730	SEC dominates
Golimumab	£17,426	-0.063	SEC dominates	£17,549	-0.063	SEC dominates
Infliximab	£25,904	-0.132	SEC dominates	£26,218	-0.134	SEC dominates
Infliximab biosimilar	£22,330	-0.132	SEC dominates	£22,643	-0.134	SEC dominates

Section C: Textual clarifications and additional points

C1. Table 6: The inclusion criteria list patients with intolerance or inadequate response. However, the exclusion criteria list “treatment-naïve patients”. Please explain this discrepancy.

We do not consider there to be a discrepancy here. To clarify, studies that considered patients who had received conventional treatments, regardless of response (i.e. including those who were intolerant or had inadequate response to those prior conventional treatments) were included. In contrast, studies of patients who were treatment-naïve (ie. had not received any prior therapy) were excluded. No distinction between intolerance and inadequate response as the reason for failure of prior therapy was made in applying the eligibility criteria.

C2. Details of how many patients remain in MEASURE 2 at different time points were provided. However, outcomes reported in tables and appendices do not always reflect these numbers. For example, table 139 reports on 68 patients at 16 weeks in the secukinumab arm yet there were only 66 patients in study at this point. Please add reasons for any differences in the patient numbers to each table.

At the end of week 16 there were 66 patients who remained in the study on the secukinumab 150 mg arm of MEASURE 2, these patients were assessed for all of the study endpoints. In addition to these 66 patients there were 5 patients who withdrew from the study due to adverse events, of these 5 patients data were available for 2 of these patients for some of the secondary and exploratory endpoints. As the data were available for some of the endpoints it was included for completeness.

To confirm the actual patient numbers at week 16 for secukinumab 150 mg for these endpoints:

- hsCRP change from baseline - Full analysis set: **68 patients**
- Patient's global assessment of disease activity (VAS) change from baseline - Full analysis set: **67 patients**
- ASDAS-CRP change from - Full analysis set: **67 patients**

C3. Cross-references are missing on page 58 and 213 (the text says “please see section 0”). Please confirm the correct section numbers that should be referenced here.

The cross-references on page 58 and page 213 should read Section 4.7.1 and Section 5.3.7, respectively.

Additional textual clarifications

On page 193 there is a statement “However, this may be a conservative assumption as secukinumab has demonstrated efficacy upon radiographic outcomes (Section 4.8.3) that may be better than that of TNFα inhibitors”. The cross-reference here is incorrect – it should refer to Section 4.7.2.4.

Table 190 (Appendix J): The title is misleading as it indicates that response is relative to placebo, however this is not the case for the week 24 and week 52 results since no placebo data at these time points is available. The week 12 and week 16 results are the risk differences relative to placebo. The week 24 and week 52 results are absolute probabilities of response.

Section D: Revised NMA Results

Since our original submission was made, Novartis has identified two genuine errors in the analyses run as part of the NMA:

- The ATLAS study should have been included in the networks relating to the BASFI outcome but was omitted in error from the analyses performed.
- The Huang et al. study should have been included in all networks for the biologic naïve population but was omitted in error from the analyses performed.

Therefore, Novartis has revised the analyses to correct for these errors. The updated network diagrams and results of the base case and sensitivity analysis NMAs are provided below.

Revised network diagrams

Figure 3: Network Diagram of Evidence for BASFI Change from Baseline – whole population *[correction of Figure 59 in submission appendices]*

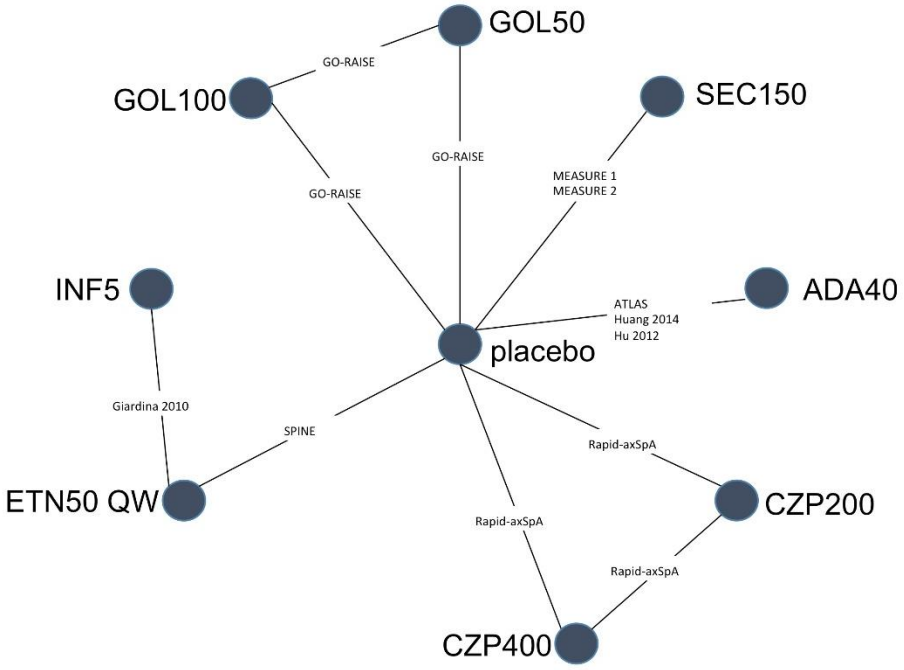


Figure 4: Network Diagram of Evidence for ASAS20 Response – biologic naïve population *[correction of Figure 52 in submission appendices]*

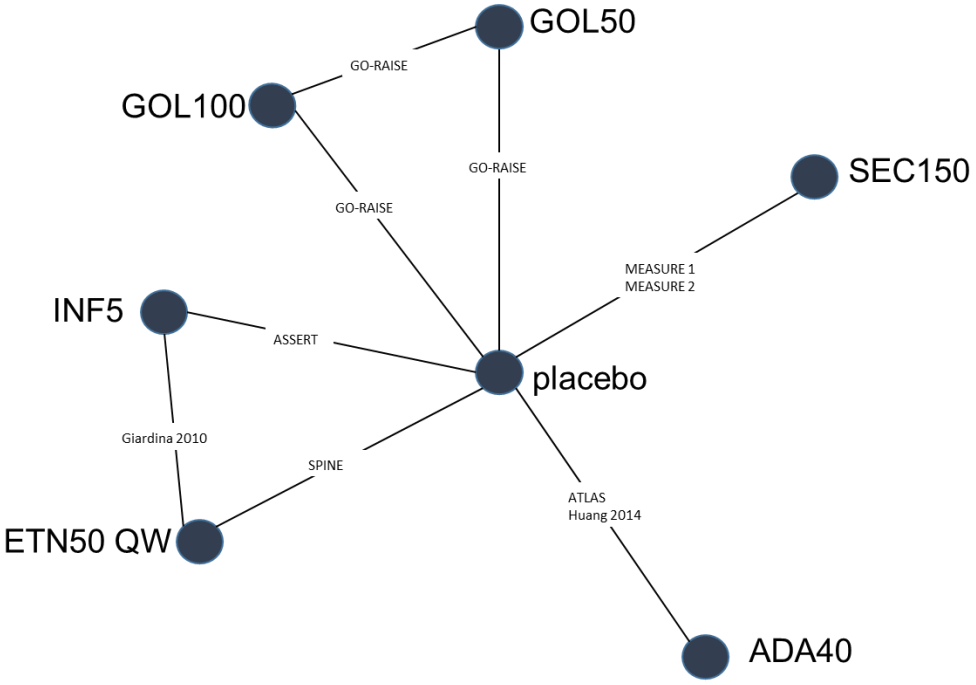


Figure 5: Network Diagram of Evidence for ASAS40 – biologic naïve population *[correction of Figure 54 in submission appendices]*

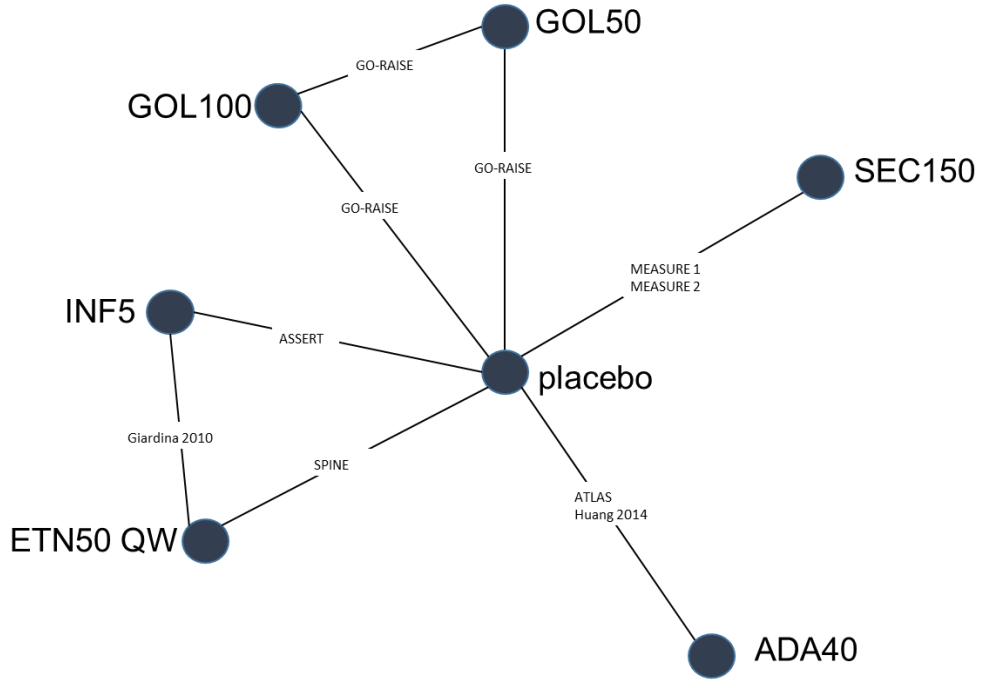


Figure 6: Network Diagram of Evidence for BASDAI 50 – biologic naïve population ***[correction of Figure 56 in submission appendices]***

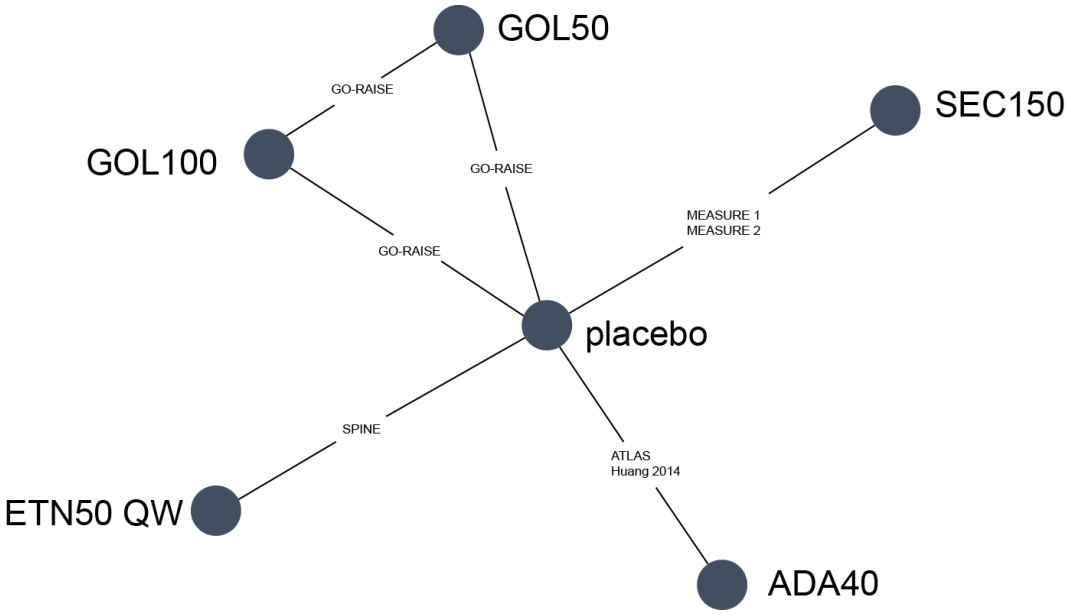


Figure 7: Network Diagram of Evidence for BASDAI Change from Baseline – biologic naïve population ***[correction of Figure 58 in submission appendices]***

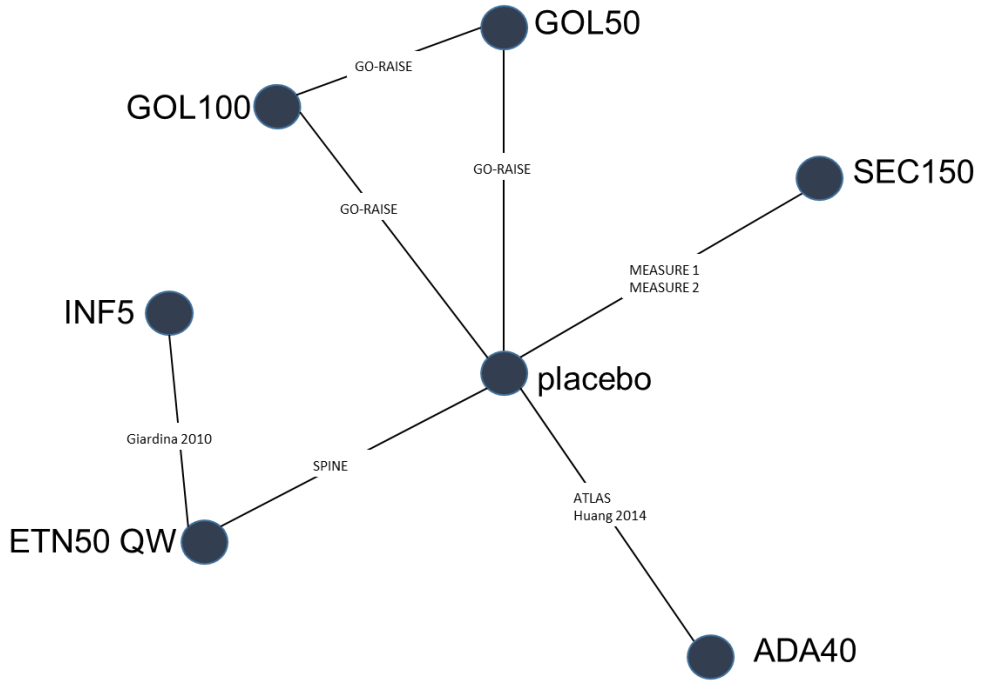
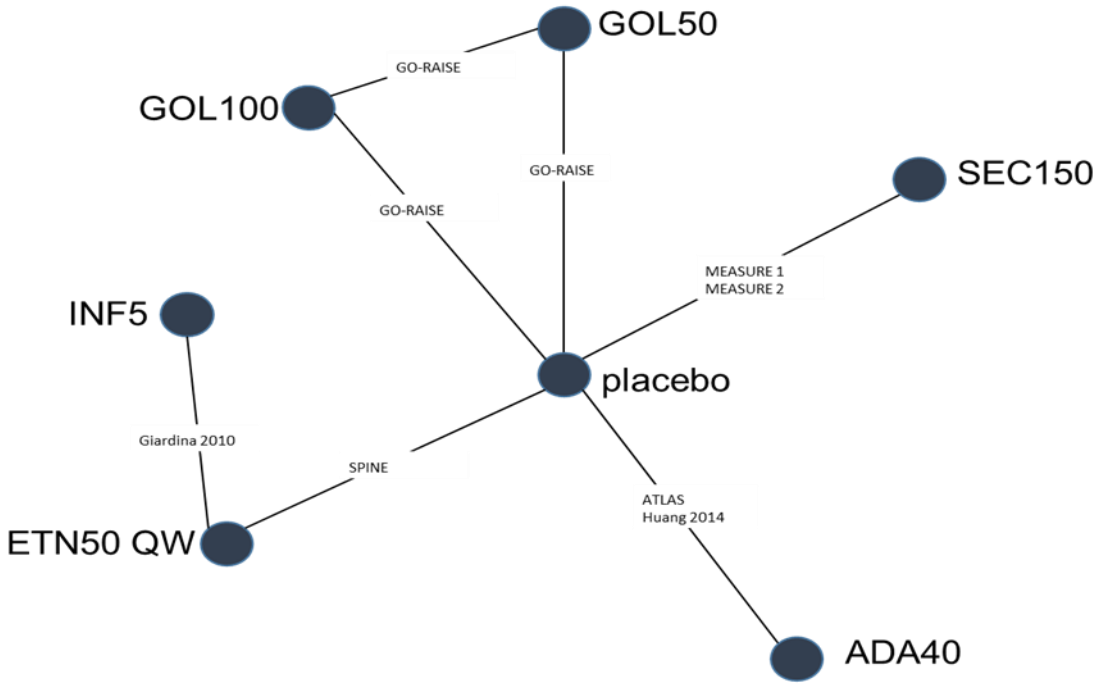


Figure 8: Network Diagram of Evidence for BASFI Change from Baseline – biologic naïve population *[correction of Figure 60 in submission appendices]*



Revised results – base case analysis

Results tables and figures for the base case analysis from the original submission are replicated below, with results updated taking into account the corrections required to the NMA. Where results have not changed, this is indicated in the following tables.

Revised summary of statistical significance of relative treatment comparisons

Table 74: Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – whole population *[correction of Table 51 in submission main body]*

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

Table 75: Overall summary of significance or non-significance of relative comparisons of secukinumab 150 mg versus comparators – biologic naive population *[correction of Table 52 in submission main body]*

Outcome		PBO	ADA40	CZP200	CZP400	ETN50QW	GOL50	GOL100	INF5
ASAS20	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
ASAS40	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	No significant difference
BASDAI 50	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	-
BASDAI change from baseline	**SEC 150**	SEC 150 mg significantly superior	No significant difference	-	-	No significant difference	No significant difference	No significant difference	INF5 significantly superior
BASFI change from baseline	**SEC 150**	SEC 150 mg significantly superior	-	-	-	No significant difference	No significant difference	No significant difference	No significant difference

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; SEC150, secukinumab 150 mg.

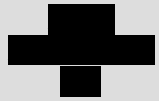
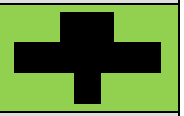
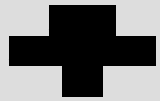
Revised results of comparisons of relative treatment effects

Table 76: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints *[correction of Table 52 in submission main body]*

Population	Binomial endpoint	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
Whole population	ASAS20	*No changes to any of these results versus the original submission Table 52*							
	ASAS40								
	BASDAI 50								
Biologic naïve population	ASAS20								
	ASAS40								
	BASDAI 50								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA 40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BN, biological naïve; CZP 200, certolizumab pegol 200 mg; CZP 400, certolizumab pegol 400 mg; ETN 50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Table 77: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints *[correction of Table 54 in submission main body]*

Population	Continuous endpoint	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
Whole population	BASDAI change from baseline	*No changes to any of these results versus the original submission Table 54*							
	BASFI change from baseline								
Biologic naïve population	BASDAI change from baseline								
	BASFI change from baseline								

Green cells represent statistically meaningful result; - =not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BN, biological naïve; CZP200, certolizumab pegol 200 mg; CZP400, certolizumab pegol 400 mg; ETN50, etanercept 50 mg; GOL, golimumab; INF, infliximab; PBO, placebo; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SEC 150, secukinumab 150 mg.

Revised predicted absolute responses for each treatment

Whole population:

- ASAS20, ASAS40, BASDAI 50 and BASDAI change from baseline – no change versus figures 21, 23, 25 and 27, respectively, in the original submission
- BASFI change from baseline – see Figure 9 for corrected results

Figure 9: Modelled mean change from baseline BASFI response according to the fixed-effects NMA at 12 to 16 weeks in the mixed population with MEASURE-1 included ***[correction of Figure 29 in submission main body]***

Biologic naïve population:

- All absolute results in the biologic naïve population have altered. Corrected versions of figures 22, 24, 26, 28 and 30 from the original submission are provided below.

Figure 10: Absolute ASAS20 response – biologic naïve population *[correction of Figure 22 in submission main body]*

Figure 11: Absolute ASAS40 response – biologic naïve population *[correction of Figure 24 in submission main body]*

Figure 12: Absolute BASDAI 50 response – biologic naïve population *[correction of Figure 26 in submission main body]*

Figure 13: Absolute BASDAI change from baseline – biologic naïve population *[correction of Figure 28 in submission main body]*

Figure 14: Absolute BASFI change from baseline – biologic naïve population *[correction of Figure 30 in submission main body]*

Revised results – sensitivity analysis

Results tables for the sensitivity analyses from the original submission are replicated below, with results updated taking into account the corrections required to the NMA. Where results have not changed, this is indicated in the following tables.

Revised results of comparisons of relative treatment effects

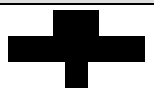
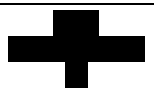
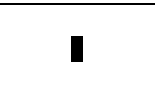
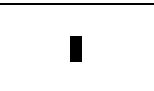
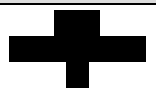
Table 78: Relative risks for secukinumab 150 mg versus comparators on binomial endpoints – sensitivity analyses *[correction of Table 55 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	ASAS20	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
	ASAS40	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
	BASDAI 50	1	*No changes to any of these results versus the original submission Table 55*							
		2	*No changes to any of these results versus the original submission Table 55*							
		3	*No changes to any of these results versus the original submission Table 55*							
Biologic naïve population	ASAS20	1								
		2								
		3								
	ASAS40	1								
		2								
		3								
	BASDAI 50	1								
		2								
		3								

Green cells represent a statistically significantly meaningful result. -=not analysed (i.e. could not be included in network)

Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 79: Change from baseline differences for secukinumab 150 mg versus comparators on continuous endpoints – sensitivity analyses ***[correction of Table 56 in submission main body]***

Population	Continuous endpoint	Sensitivity analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL50	INF5
Whole population	BASDAI change from baseline	1	*No changes to any of these results versus the original submission Table 56*							
		2	*No changes to any of these results versus the original submission Table 56*							
		3	*No changes to any of these results versus the original submission Table 56*							
	BASFI change from baseline	1								
		2								
		3								
Biologic naïve population	BASDAI change from baseline	1								
		2								
		3								
	BASFI change from baseline	1								
		2								

		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent a statistically significantly meaningful result; -=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Revised predicted absolute responses for each treatment

Table 80: Absolute results for binomial endpoints – sensitivity analyses *[correction of Table 57 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	ASAS20	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
	ASAS40	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
	BASDAI 50	1	*No changes to any of these results versus the original submission Table 57*								
		2	*No changes to any of these results versus the original submission Table 57*								
		3	*No changes to any of these results versus the original submission Table 57*								
Biologic naïve population	ASAS20	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ASAS40	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	BASDAI 50	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

-=not analysed (i.e. could not be included in network)
Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Table 81: Absolute results for continuous outcomes – sensitivity analyses *[correction of Table 58 in submission main body]*

Population	Binomial endpoint	Sensitivity analysis	SEC150	ADA40	CZP200	CZP400	ETN50 QW	GOL50	GOL100	INF5	PBO
Whole population	BASDAI change from baseline	1	*No changes to any of these results versus the original submission Table 58*								
		2	*No changes to any of these results versus the original submission Table 58*								
		3	*No changes to any of these results versus the original submission Table 58*								
	BASFI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologic naïve population	BASDAI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	BASFI change from baseline	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

-=not analysed (i.e. could not be included in network)

Abbreviations: ADA40, adalimumab 40 mg; ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CZP200, certolizumab pegol 200 mg Weeks 0, 2 and 4 then every 2 weeks; CZP400, certolizumab pegol 400 mg Weeks 0, 2 and 4 then every 4 weeks; ETN50QW, etanercept 50 mg once weekly; GOL50, golimumab 50 mg; GOL100, golimumab 100 mg; INF5, infliximab 5 mg/kg; PBO, placebo; SD, standard deviation; SEC150, secukinumab 150 mg.

Section E: Revised Cost-effectiveness Results

Base-case incremental cost effectiveness analysis results

The summary results of the base case analysis are presented in Table 82 for the biologic naïve population and Table 83 for the biologic experienced population.

Table 82. Revised Summary base case results – biologic naïve population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£113,216	9.805				
Etanercept	£114,234	8.759	£1,018	-1.046	Dominated	Dominated
Etanercept biosimilar	£115,249	8.759	£2,033	-1.046	Dominated	Dominated
Certolizumab pegol – with PAS	£122,418	9.447	£9,202	-0.359	Dominated	Dominated
Adalimumab	£128,516	9.446	£15,300	-0.359	Dominated	Dominated
Golimumab	£129,919	9.830	£16,703	0.025	£674,914	£674,914
Infliximab biosimilar	£135,865	9.590	£22,649	-0.216	Dominated	Dominated
Infliximab	£139,439	9.590	£26,223	-0.216	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 83. Revised Summary base case results – biologic experienced population population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£107,417	8.161			
Secukinumab	£109,164	8.939	£1,747	0.778	£2,245

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Exploratory cost-effectiveness analyses in biologic naïve and biologic experienced populations

The summary results for the exploratory analysis of the biologic naïve population, including sequencing, are provided in Table 84 below.

Table 84. Summary results – exploratory sequencing analyses on biologic naïve population

Treatment pathway	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Secukinumab -> Mixed Tx	£121,209	9.987			
Etanercept -> Mixed Tx	£124,499	9.047	-£3,684	0.940	Dominated
Etanercept biosimilar-> Mixed Tx	£125,886	9.047	-£4,677	0.940	Dominated
Certolizumab pegol -> Mixed Tx	£131,066	9.655	-£9,857	0.332	Dominated
Adalimumab -> Mixed Tx	£136,401	9.648	-£15,192	0.339	Dominated
Golimumab -> Mixed Tx	£137,515	10.017	-£16,305	-0.030	£545,767*
Infliximab biosimilar -> Mixed Tx	£142,884	9.791	-£22,069	0.196	Dominated
Infliximab -> Mixed Tx	£146,628	9.791	-£25,419	0.196	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The summary results for the exploratory analysis of the biologic experienced population, comparing secukinumab to the other biologic therapies, are provided in Table 85.

Table 85. Summary results – exploratory comparison with TNFα inhibitors in biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,379	8.166			
Etanercept	£110,928	8.463	£3,549	0.297	Extendedly Dominated
Etanercept biosimilar	£111,571	8.463	£4,192	0.297	Extendedly Dominated
Secukinumab	£112,125	8.791	£4,746	0.625	£7,597
Certolizumab pegol – with PAS	£115,344	8.678	£7,965	0.512	Dominated
Adalimumab	£119,876	8.680	£12,497	0.514	Dominated
Golimumab	£121,114	8.796	£13,736	0.630	£1,614,375
Infliximab biosimilar	£125,438	8.778	£18,059	0.612	Dominated
Infliximab	£127,650	8.778	£20,271	0.612	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Probabilistic sensitivity analysis

Probabilistic mean costs, QALYs and resultant ICERs for the analysis of the biologic naïve population are presented in Table 86, followed by the scatterplots for the comparison of secukinumab to each comparator (Figure 15 to Figure 20) and the CEAC (Figure 22) in this population. The ICERs for the probabilistic analysis in the biologic experienced population are presented in Table 87, followed by the scatterplot (Figure 23) and CEAC (Figure 24).

Table 86. Summary probabilistic base case results – biologic naïve population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Secukinumab	£116,011	£29,355	10.494	0.959			
Etanercept	£120,471	£35,462	9.500	0.959	£4,459	-0.994	Dominated
Etanercept biosimilar	£120,614	£34,936	9.456	0.953	£4,602	-1.038	Dominated
Certolizumab pegol – with PAS	£127,032	£32,659	10.124	0.989	£11,020	-0.370	Dominated
Adalimumab	£131,609	£31,241	10.152	0.952	£15,598	-0.342	Dominated
Golimumab	£134,921	£31,933	10.465	1.008	£18,910	-0.029	Dominated
Infliximab biosimilar*	£156,555	£42,181	9.945	1.052	£40,544	-0.549	Dominated
Infliximab	£160,533	£47,027	9.865	1.070	£44,522	-0.629	Dominated

Abbreviations: SD, standard deviation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SEC, secukinumab.
*Please note results for infliximab and etanercept biosimilars require separate PSA runs in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 15. Scatterplot for secukinumab vs etanercept – biologic naïve population

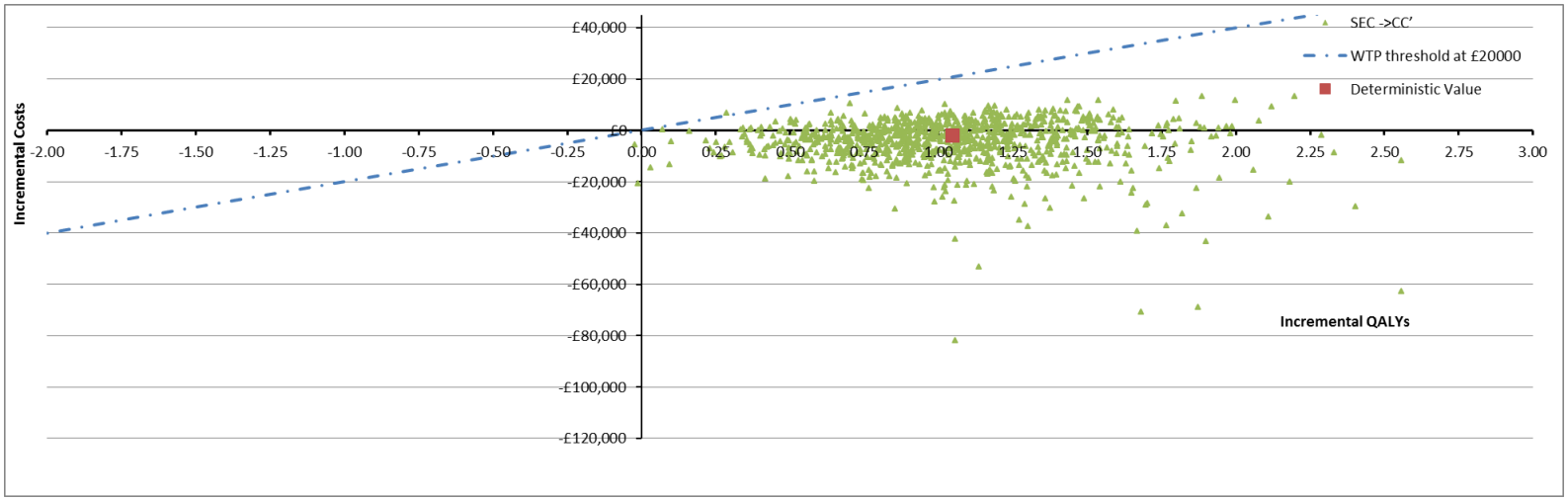


Figure 16. Scatterplot for secukinumab vs etanercept biosimilar – biologic naïve population

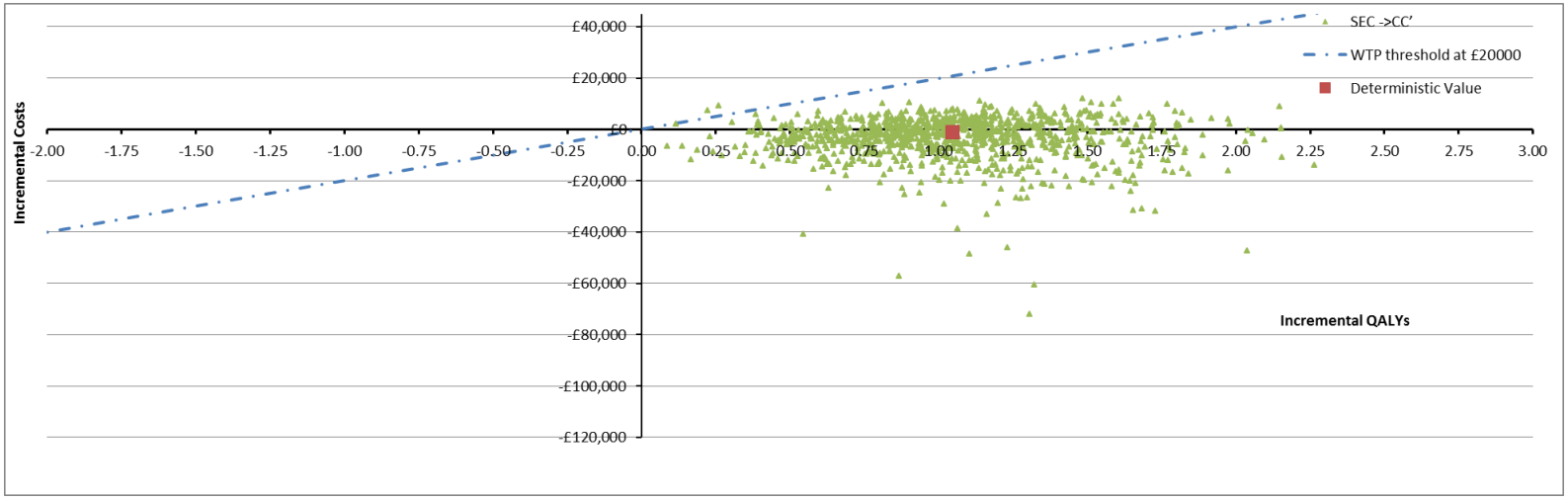


Figure 17. Scatterplot for secukinumab vs certolizumab pegol – biologic naïve population

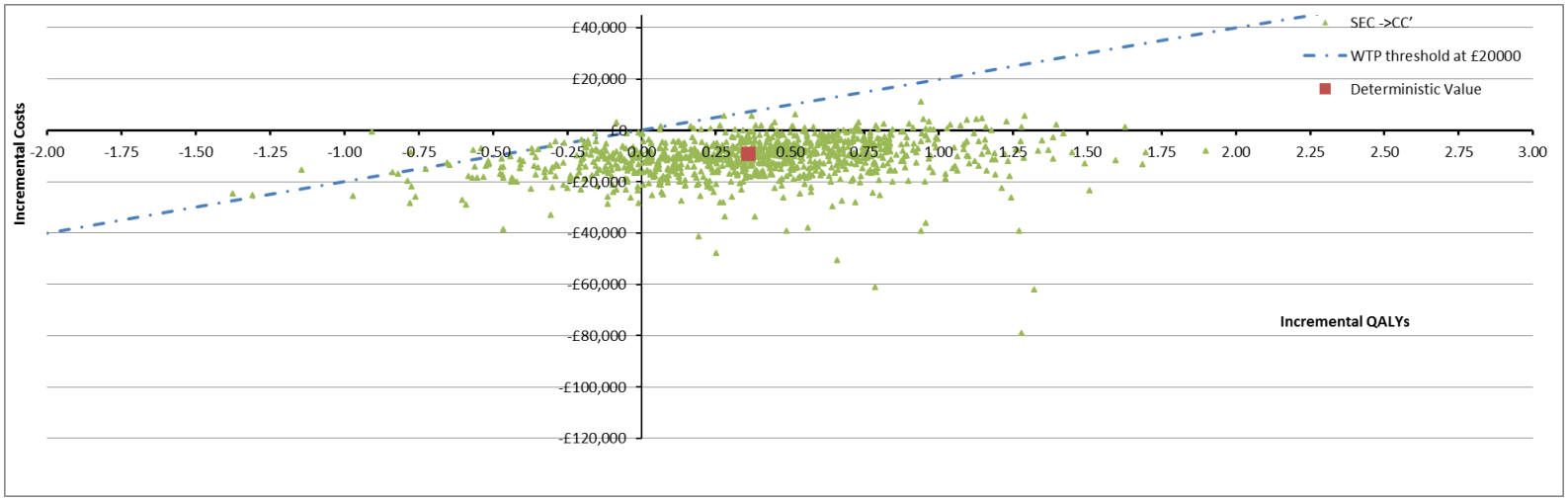


Figure 18. Scatterplot for secukinumab vs adalimumab – biologic naïve population

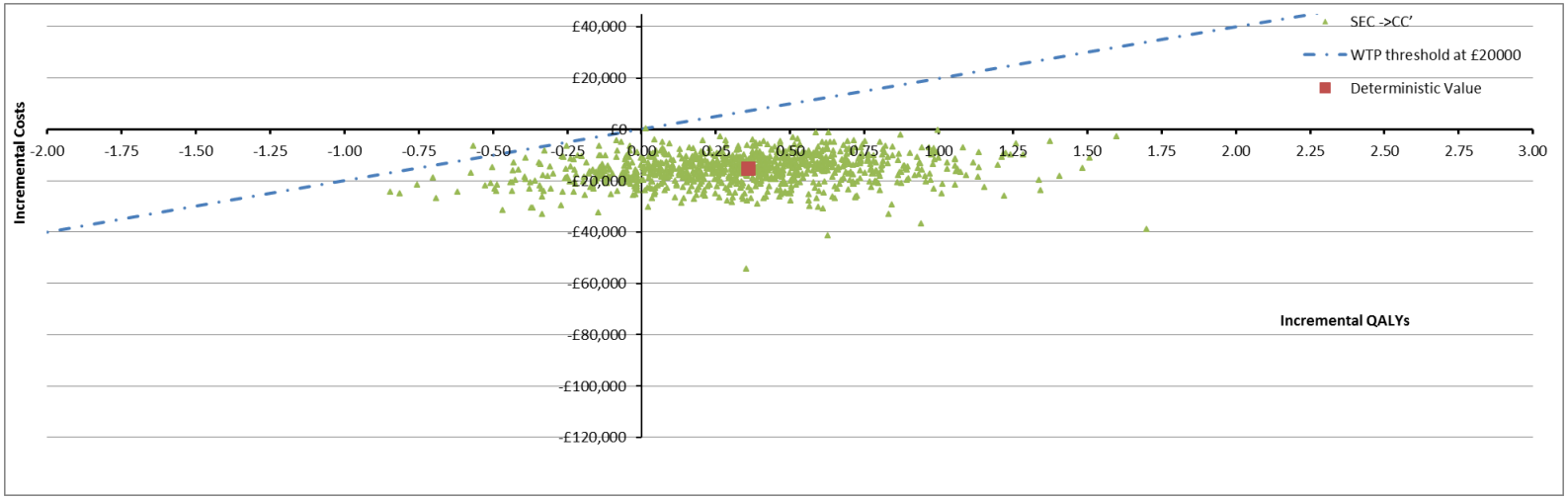


Figure 19. Scatterplot for secukinumab vs golimumab – biologic naïve population

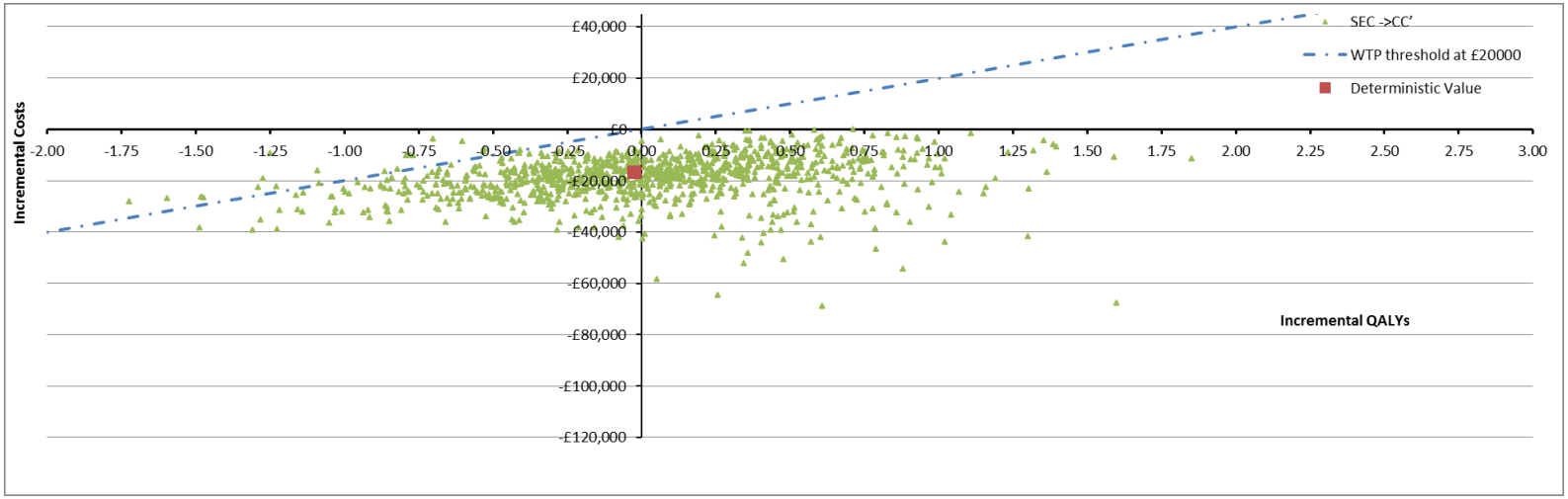


Figure 20. Scatterplot for secukinumab vs infliximab – biologic naïve population

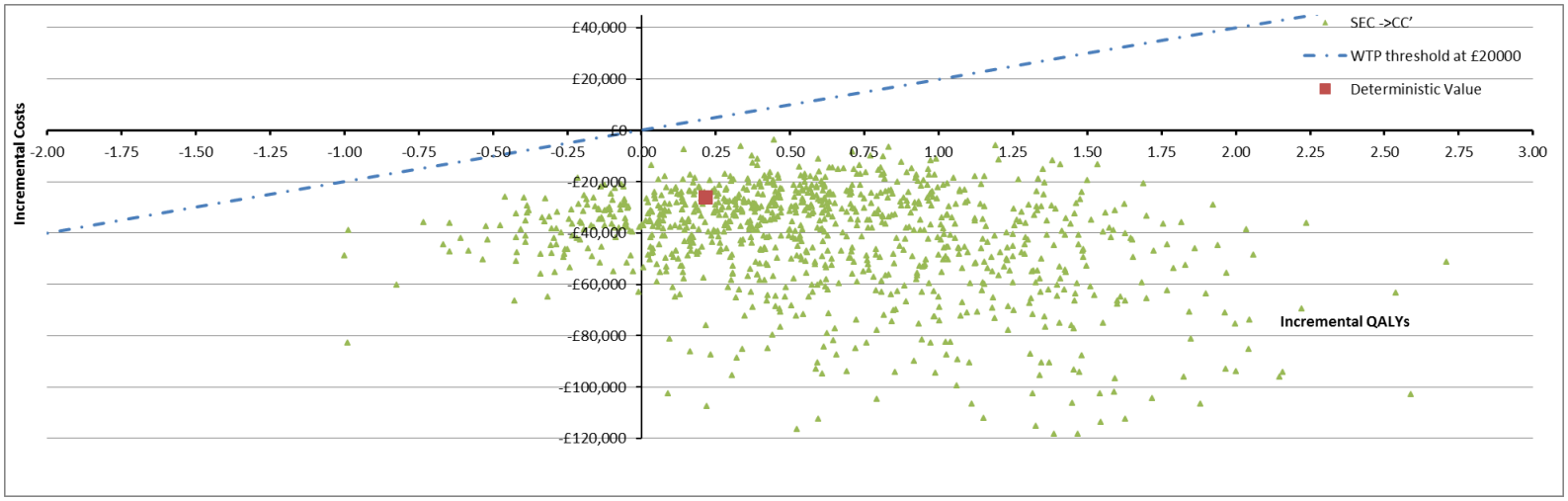
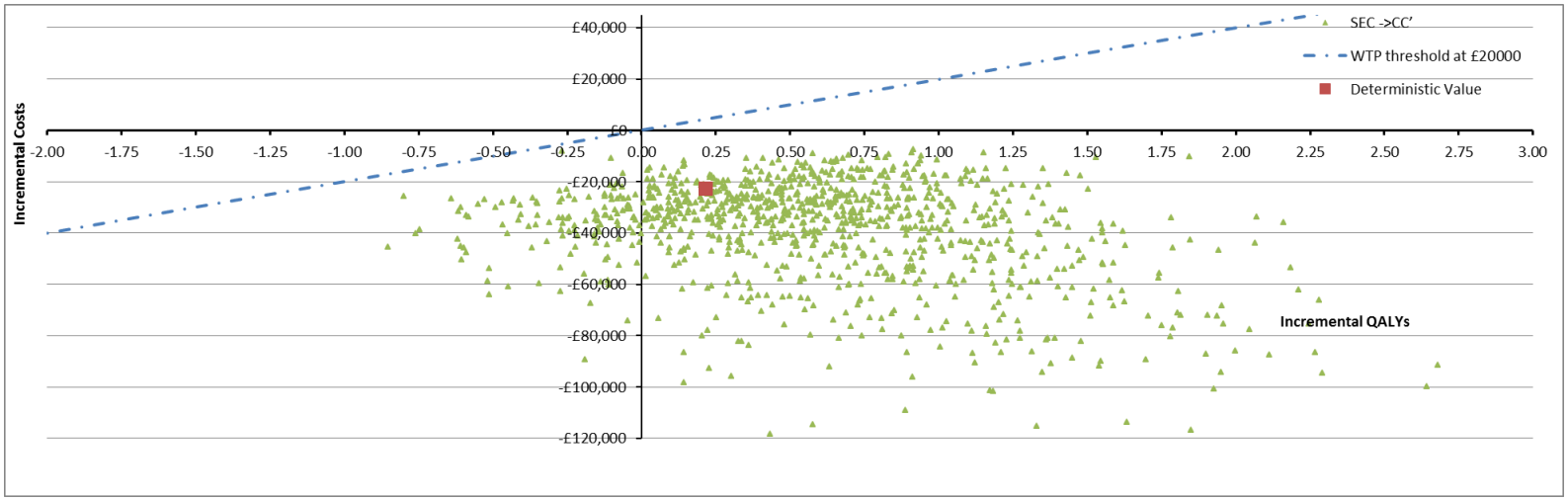
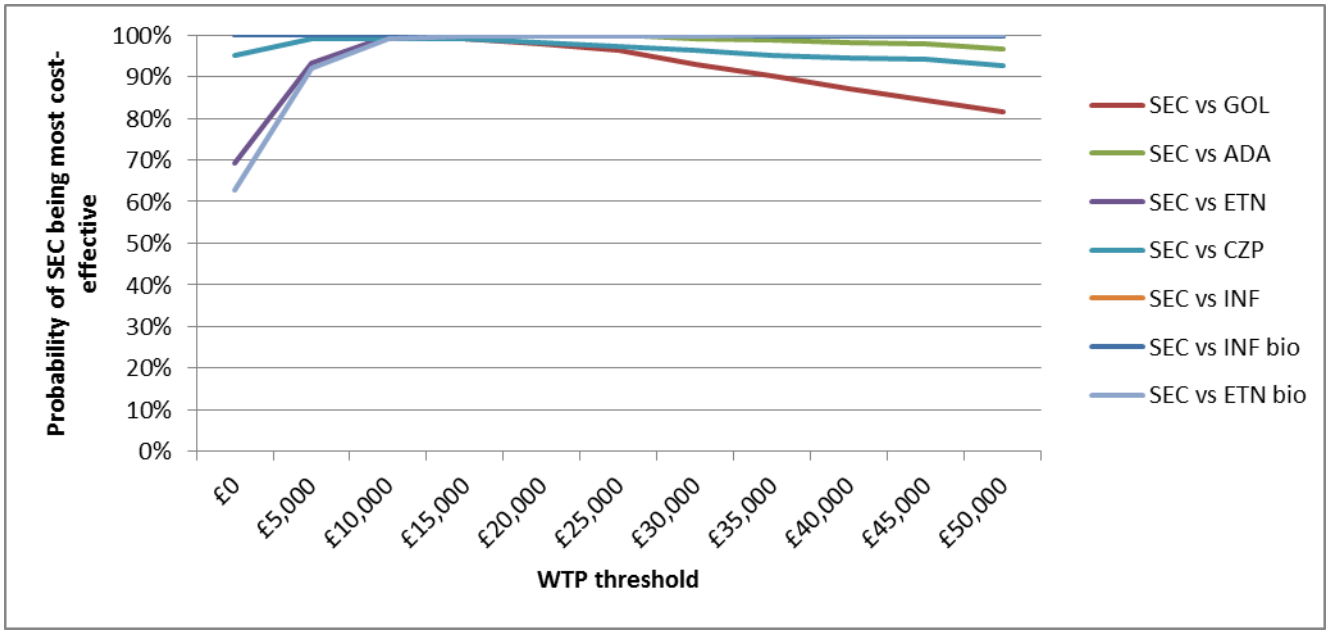


Figure 21. Scatterplot for secukinumab vs infliximab biosimilar – biologic naïve population*



*Please note results for infliximab biosimilar require a separate PSA run in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 22. CEAC for secukinumab versus comparators in the biologic naïve population*



*The above chart combines results of two comparator CEAC results for secukinumab versus each comparator.

Table 87. Summary probabilistic base case results – biologic experienced population

Treatment	Total mean costs (£)	Mean costs SD (£)	Total mean QALYs	Mean QALYs SD	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Conventional care	£111,974	£36,811	8.858	0.972			

Secukinumab	£113,433	£32,639	9.662	1.016	£1,458	£1	£1,815

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; SEC, secukinumab.

Figure 23. Scatterplot for secukinumab vs conventional care – biologic experienced population

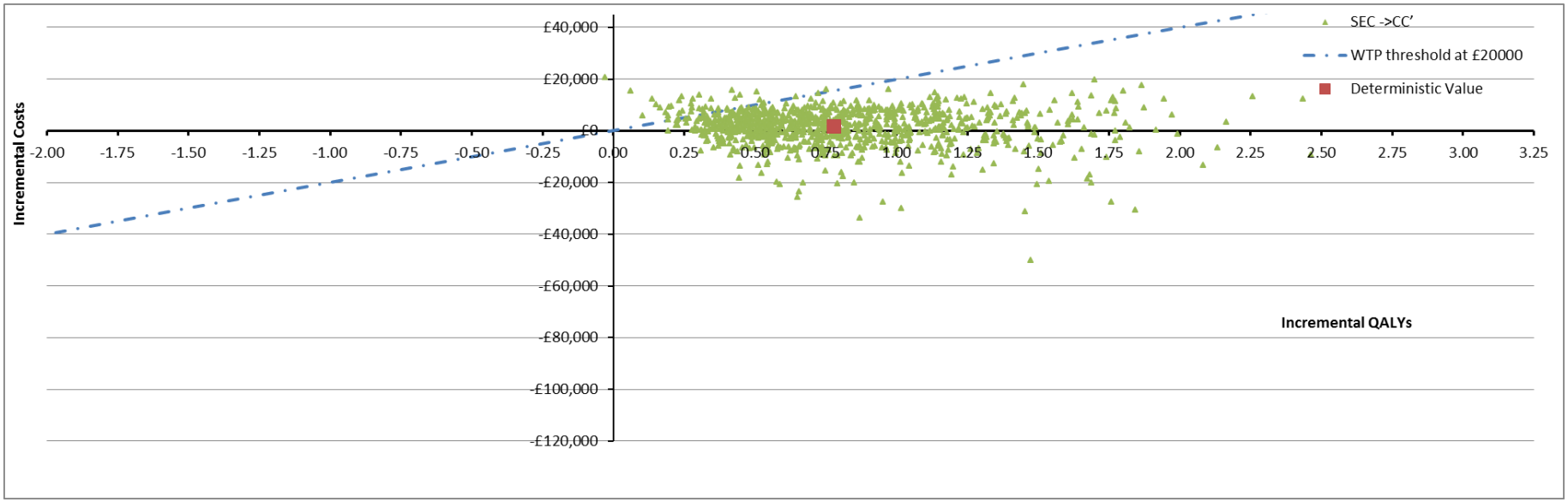
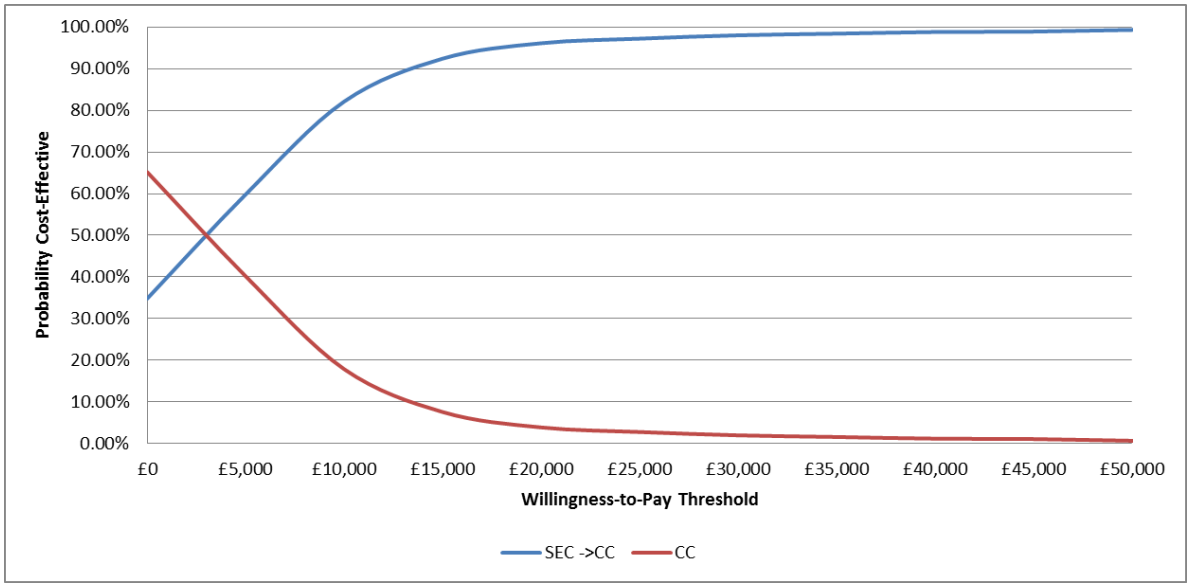


Figure 24. CEAC for secukinumab vs. conventional care – biologic experienced population



Deterministic sensitivity analysis

The tornado diagrams below present the variation in base case model results from OWSA in terms of net monetary benefits (valuing one QALY at £20,000). Net monentary benefits are presented instead of ICERs due to incremental costs of secukinumab being negative versus all comparators i.e. in the southern quadrants of the cost-effectiveness plane, where ICERs are not informative. Tornado diagrams for the biologic naïve population are provided in Figure 25 to Figure 31. The tornado diagram for the analysis in the biologic experienced population is provided in Figure 32.

Figure 25. OWSA results for secukinumab vs etanercept – biologic naïve population

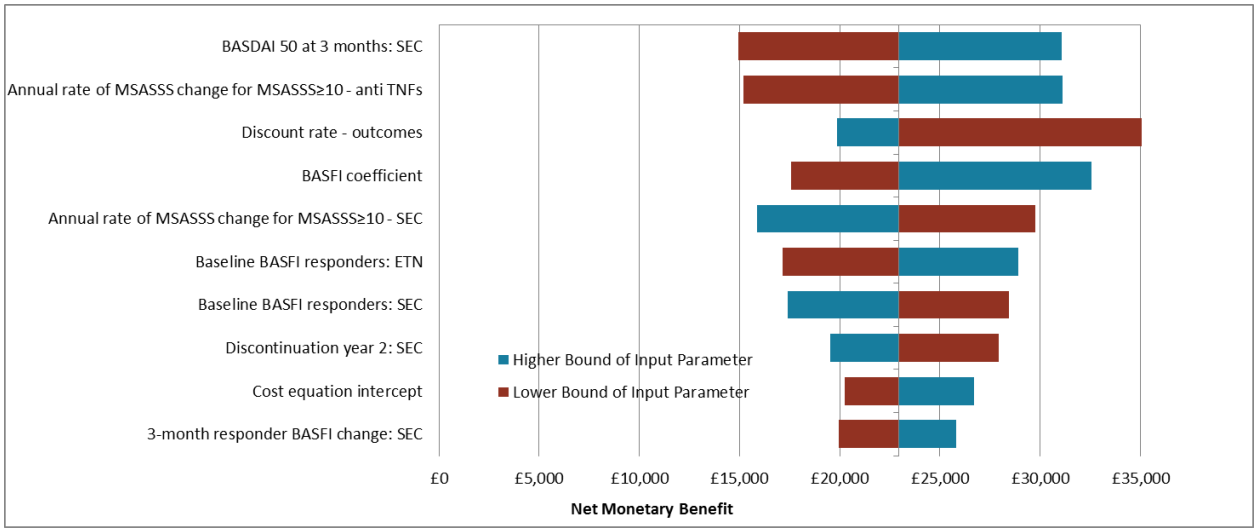


Figure 26: OWSA results for secukinumab vs biosimilar etanercept – biologic naïve population

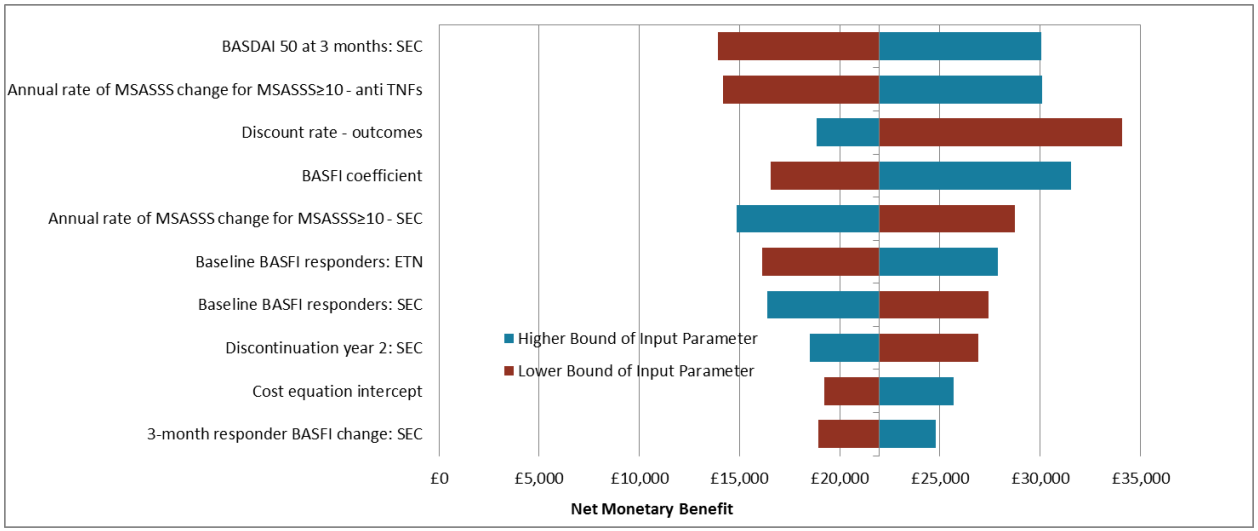


Figure 27. OWSA results for secukinumab vs certolizumab – biologic naïve population

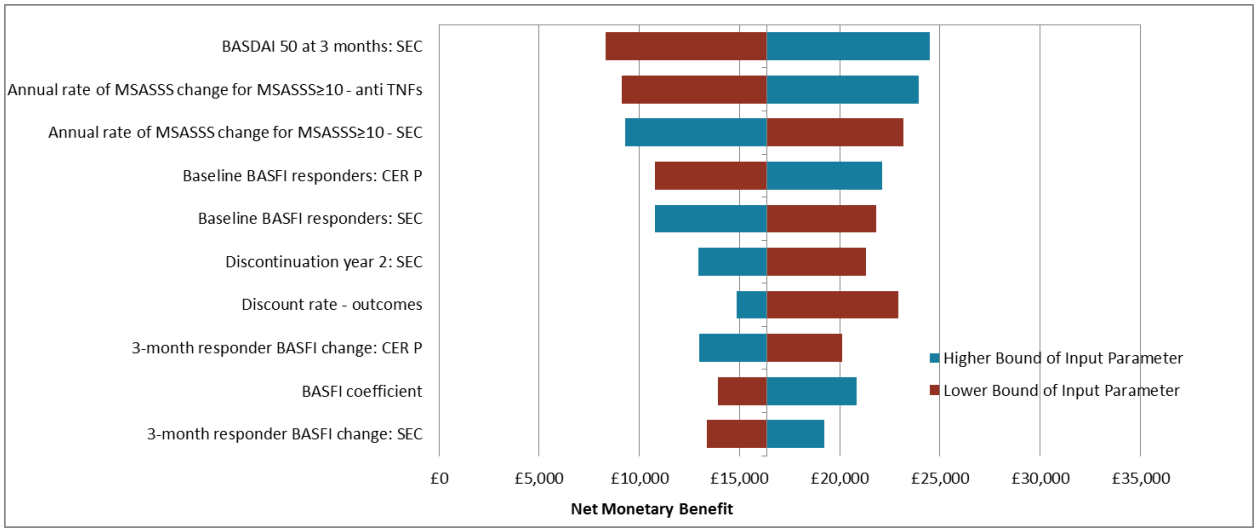


Figure 28. OWSA results for secukinumab vs adalimumab – biologic naïve population

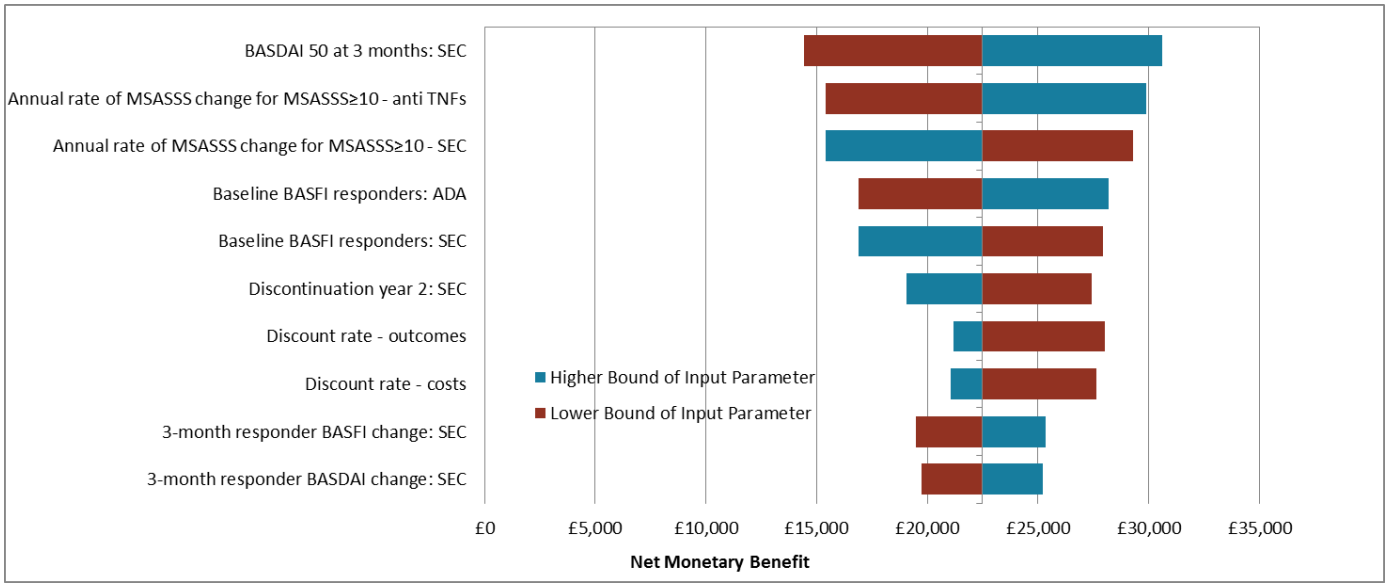


Figure 29. OWSA results for secukinumab vs golimumab – biologic naïve population

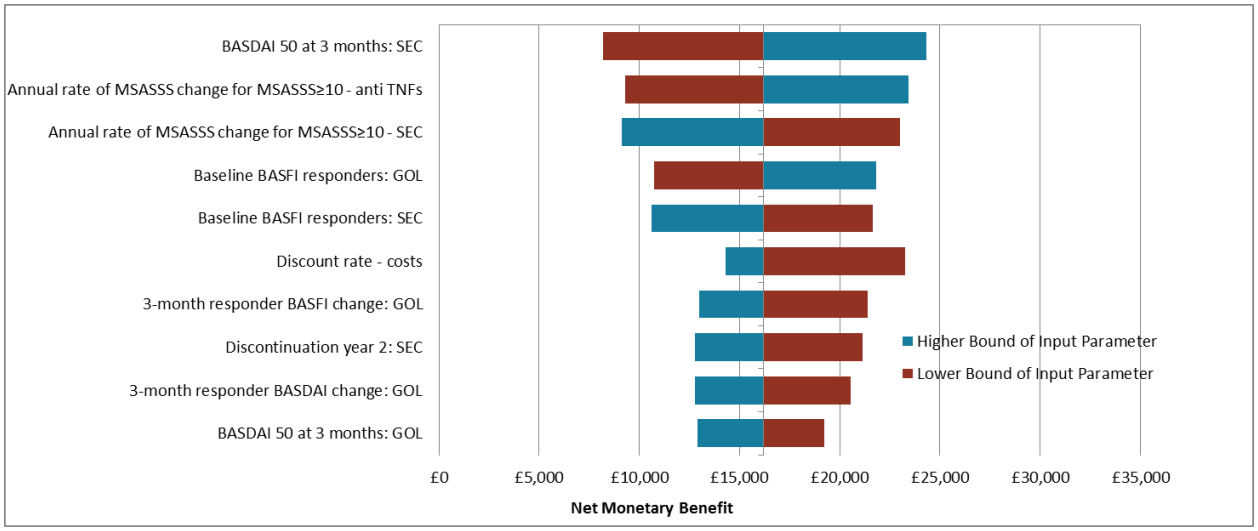


Figure 30. OWSA results for secukinumab vs infliximab – biologic naïve population

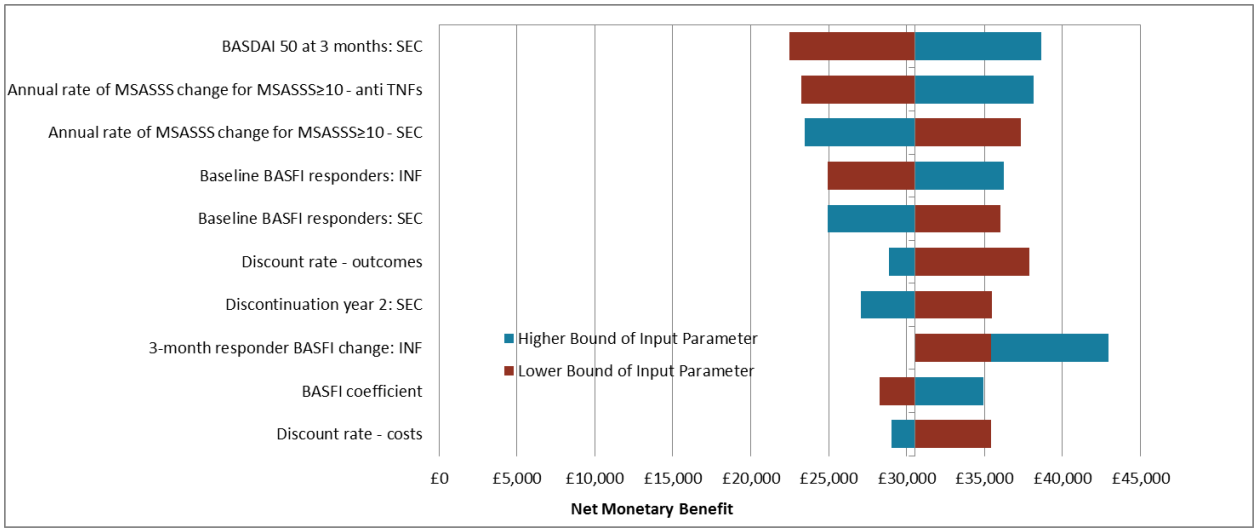


Figure 31. OWSA results for secukinumab vs infliximab biosimilar – biologic naïve population

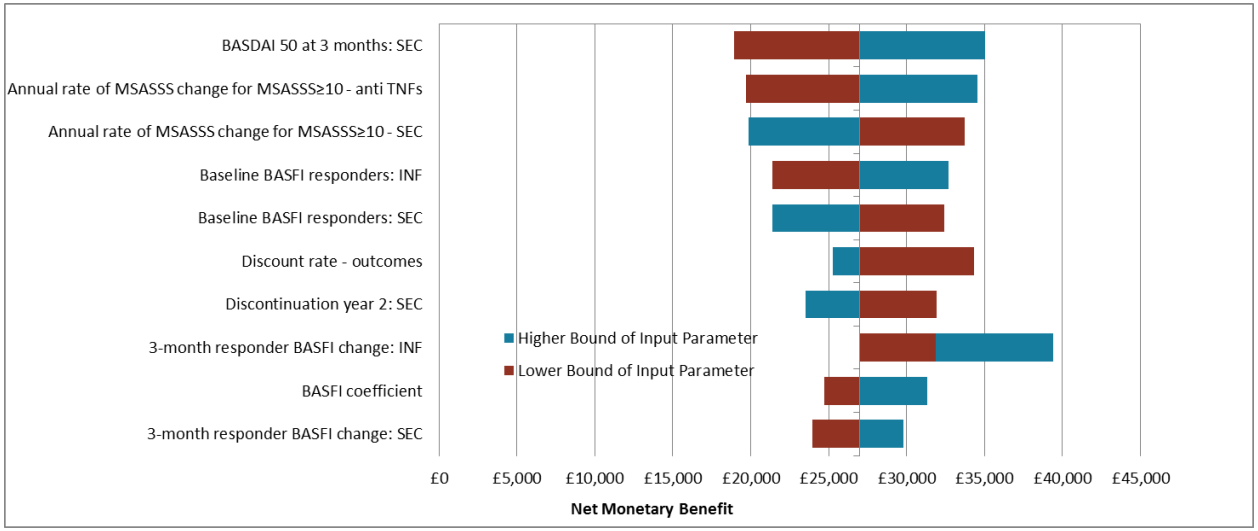
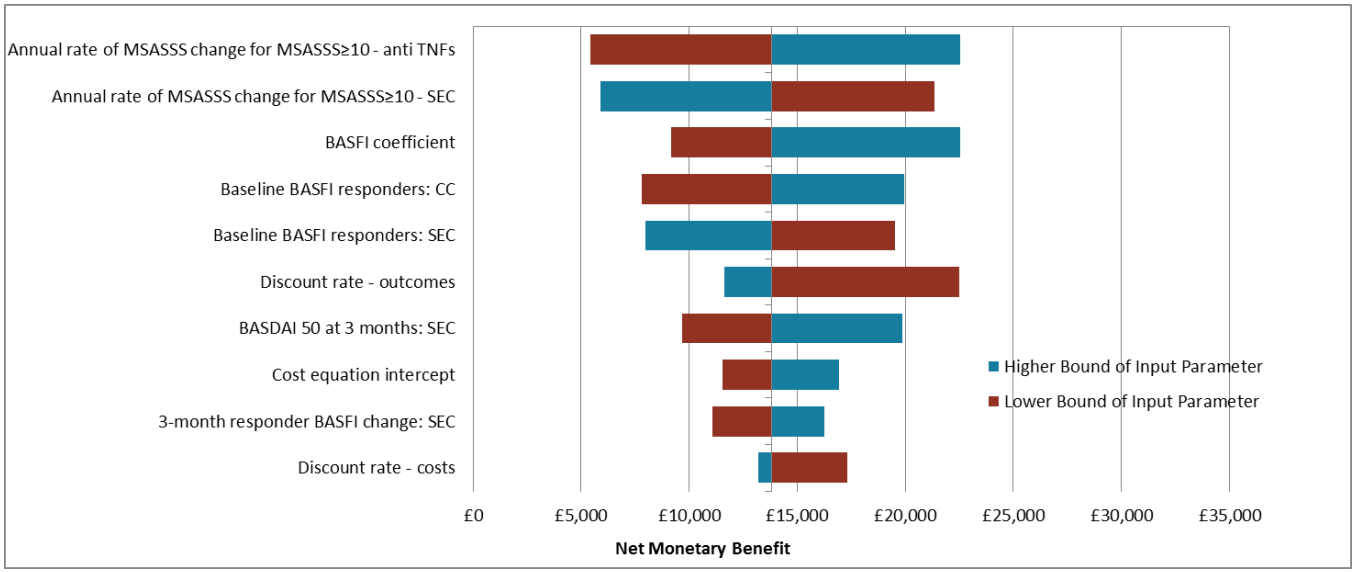


Figure 32. OWSA results for secukinumab vs conventional care – biologic experienced population



Scenario analysis

Table 88 and Table 89 below shows the results of the scenario analyses for each biologic comparator versus secukinumab in the biologic naïve population. Results are presented in this way since secukinumab is the lowest cost option in all but two scenarios (scenarios 3 and 6c, where etanercept is in the least expensive option). Table 90 presents the results of the scenario analyses in the biologic experienced population. In this case, results are expressed as ICERs for secukinumab versus conventional care.

Table 88: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part a]

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£15,300	-0.359	SEC dominates	£9,202	-0.359	SEC dominates	£16,703	0.025	£674,914

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Scenario 1a	£15,217	-0.354	SEC dominates	£9,092	-0.352	SEC dominates	£16,623	0.026	£632,894
Scenario 1b	£14,296	-0.260	SEC dominates	£8,441	-0.238	SEC dominates	£14,949	0.041	£361,558
Scenario 2	£16,025	-0.380	SEC dominates	£10,113	-0.386	SEC dominates	£16,923	0.018	£941,421
Scenario 3≠	£15,273	-0.291	SEC dominates	£9,216	-0.313	SEC dominates	£17,549	-0.063	SEC dominates
Scenario 4	£15,203	-0.120	SEC dominates	£10,671	-0.033	SEC dominates	£13,402	0.036	£374,910
Scenario 5	£23,265	-0.471	SEC dominates	£14,903	-0.474	SEC dominates	£25,783	0.029	£874,073
Scenario 6a	£17,762	-0.095	SEC dominates	£11,829	-0.133	SEC dominates	£19,009	0.318	£59,771
Scenario 6b	£17,318	0.086	£200,791	£10,361	0.062	£166,570	£16,205	0.358	£45,225
Scenario 6c	£11,280	-0.312	SEC dominates	£4,768	-0.367	SEC dominates	£9,880	-0.065	SEC dominates
Scenario 7a	£15,300	-0.369	SEC dominates	£9,202	-0.465	SEC dominates	£16,703	-0.065	SEC dominates
Scenario 7b	£15,300	-0.330	SEC dominates	£9,202	-0.331	SEC dominates	£16,703	0.022	£755,800
Scenario 8	£15,300	-0.359	SEC dominates	£9,202	-0.359	SEC dominates	£16,703	0.025	£674,914
Scenario 9	£16,581	-0.410	SEC dominates	£10,482	-0.409	SEC dominates	£17,984	-0.025	SEC dominates
Scenario 10	£15,344	-0.357	SEC dominates	£9,137	-0.353	SEC dominates	£16,606	0.028	£591,477

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.
≠Analysis has changed versus original approach – see response to B33

Table 89: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part b]

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,033	-1.046	SEC dominates	£1,018	-1.046	SEC dominates	£26,223	-0.216	SEC dominates	£22,649	-0.216	SEC dominates
Scenario 1a	£1,828	-1.037	SEC dominates	£813	-1.037	SEC dominates	£26,104	-0.208	SEC dominates	£22,529	-0.208	SEC dominates
Scenario 1b	£1,171	-0.867	SEC dominates	£157	-0.867	SEC dominates	£25,658	-0.069	SEC dominates	£22,129	-0.069	SEC dominates
Scenario 2	£3,185	-1.086	SEC dominates	£2,171	-1.086	SEC dominates	£27,402	-0.250	SEC dominates	£23,827	-0.250	SEC dominates
Scenario 3≠	£1,227	-0.730	SEC dominates	£212	-0.730	SEC dominates	£22,643	-0.134	SEC dominates	£26,218	-0.134	SEC dominates
Scenario 4	£10,228	-0.367	SEC dominates	£8,344	-0.367	SEC dominates	£29,192	0.167	£174,456	£25,394	0.167	£151,759
Scenario 5	£1,792	-1.378	SEC dominates	£325	-1.378	SEC dominates	£37,686	-0.122	SEC dominates	£32,454	-0.122	SEC dominates
Scenario 6a	£4,029	-0.877	SEC dominates	£2,948	-0.877	SEC dominates	£30,252	-0.072	SEC dominates	£26,472	-0.072	SEC dominates
Scenario 6b	£3,265	-0.618	SEC dominates	£2,186	-0.618	SEC dominates	£27,711	0.231	£119,703	£24,046	0.231	£103,872

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Scenario 6c	-£834	-1.056	£790*	-£1,796	-1.056	£1,701*	£20,730	-0.293	SEC dominates	£17,450	-0.293	SEC dominates
Scenario 7a	£2,033	-1.084	SEC dominates	£1,018	-1.084	SEC dominates	£26,223	-0.421	SEC dominates	£22,649	-0.421	SEC dominates
Scenario 7b	£2,033	-0.956	SEC dominates	£1,018	-0.956	SEC dominates	£22,649	-0.197	SEC dominates	£26,223	-0.197	SEC dominates
Scenario 8	£2,033	-1.046	SEC dominates	£1,018	-1.046	SEC dominates	£47,993	-0.216	SEC dominates	£44,419	-0.216	SEC dominates
Scenario 9	£3,313	-1.097	SEC dominates	£2,299	-1.097	SEC dominates	£27,504	-0.266	SEC dominates	£23,930	-0.266	SEC dominates
Scenario 10	£1,701	-1.028	SEC dominates	£686	-1.028	SEC dominates	£26,303	-0.214	SEC dominates	£22,729	-0.214	SEC dominates

*Indicates an ICER in the south-west quadrant i.e. less costly and less effective vs secukinumab
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY; quality-adjusted life years.
≠Analysis has changed versus original approach – see response to B33

Table 90. Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population

	Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
Base case	£1,747	0.778	£2,245
Scenario 1a	£3,358	0.643	£5,223
Scenario 1b	£1,979	0.769	£2,574
Scenario 2	£8,556	0.601	£14,248
Scenario 3*	N/A	N/A	N/A
Scenario 4	£1,363	0.654	£2,083
Scenario 5	£3,704	1.036	£3,574
Scenario 6a	N/A	N/A	N/A
Scenario 6b	N/A	N/A	N/A
Scenario 6c	N/A	N/A	N/A
Scenario 7a	£1,747	0.882	£1,979
Scenario 7b	£1,747	0.711	£2,455
Scenario 8	N/A	N/A	N/A
Scenario 9	£1,238	0.798	£1,551
Scenario 10	£2,173	0.762	£2,853

Note: Scenarios 3, 6a, 6b & 6c are not relevant to comparison versus conventional care since the ratio of BASDAI / BASFI change from baseline amongst responders versus non-responders and the network meta-analysis results only affect comparisons versus the TNFα inhibitors. Scenario 8 is not relevant to comparison versus conventional care since it only affects comparison with infliximab and infliximab biosimilar.

REFERENCES

1. Braun J, Sieper J. Building consensus on nomenclature and disease classification for ankylosing spondylitis: results and discussion of a questionnaire prepared for the International Workshop on New Treatment Strategies in Ankylosing Spondylitis, Berlin, Germany, 18-19 January 2002. Ann Rheum Dis 2002;61 Suppl 3:iii61-7.

2. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 2014;48-49:128-33.

3. Novartis Data on File: MEASURE 2 Clinical Study Report – Week 52 Analysis.

4. Novartis Data on File: MEASURE 1 Clinical Study Report – Week 52 Analysis.

5. Keat A, Barkham N, Bhalla A, et al. BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. Rheumatology (Oxford) 2004;44:939-47.

6. Committee for Medicinal Products for Human Use. Draft Guideline on CLinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis. June 2005.

7. van der Heijde D, Kivitz A, Schiff MH, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136-46.

8. Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.

9. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 2014;73:587-94.

10. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39-47.

11. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 2010;30:1437-40.

12. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.

13. Inman RD, Davis JC, Jr., Heijde D, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008b;58:3402-12.

14. Department of Health. The Musculoskeletal Services Framework. 2006.

15. Office of National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland. Mid-2006. Available at http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland. Last accessed 08/03/2016.

16. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. Rheumatology (Oxford) 2014;53:650-7.

17. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. New England Journal of Medicine 2015;373:2534-2548.

18. Ciurea A *et al.* The Reason of Discontinuation of a First TNF Inhibitor Affects Drug Retention of a Second Anti-TNF Agent in Axial Spondyloarthritis. 2015 ACR/ARHP Annual Meeting. 29th September 2015. Abstract No. 976

19. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64:1568-75.

20. Dias S, Sutton AJ, Welton NJ, et al. Evidence synthesis for decision making 3: heterogeneity--subgroups, meta-regression, bias, and bias-adjustment. Medical Decision Making 2013;33:618-640.

21. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 5: Evidence synthesis in the baseline natural history model [Internet]. Sheffield: 2011 [accessed 24.2.16].

22. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: inconsistency in networks of evidence based on randomised controlled trials [Internet]. Sheffield: 2014 [accessed 24.2.16].

23. National Institute for Health and Care Excellence. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance TA383 [Internet], 2016 [accessed 24.2.16]:70.

24. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. Available at https://www.nice.org.uk/article/pmg9/chapter/Foreword. Last accessed 10.3.16. 2013.

25. National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233): Assessment Report. 2014. Available at https://www.nice.org.uk/guidance/gid-tag355/documents/ankylosing-spondylitis-and-

axial-spondyloarthritis-nonradiographic-adalimumab-etanercept-infliximab-and-golimumab-inc-rev-ta143-and-ta233-assessment-report-2. Last accessed 13th January 2016.

26. Corbett M, Soares M, Jhuti G, et al. TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233. York: CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, 2014:371.

27. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA383]. Multiple Technology Appraisal (MTA): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis - Addendum. 2016. Available at https://www.nice.org.uk/guidance/TA383/documents/ankylosing-spondylitis-and-axial-spondyloarthritis-nonradiographic-adalimumab-etanercept-infliximab-and-golimumab-inc-rev-ta143-and-ta233-id694-committee-papers4. Last accessed 2nd February 2016.

28. National Institute for Health and Care Excellence (NICE). Technology Appraisal Guidance [TA383]. Multiple Technology Appraisal (MTA): TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. 2016. Available at https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077. Last accessed 2nd February 2016.

29. Ramiro S, van Tubergen A, van der Heijde D, et al. How to deal with missing items in BASDAI and BASFI. "RHEUMATOLOGY (OXFORD, ENGLAND)" 2014;53:374-6.

30. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645-54.

31. Ramiro S, Stolwijk C, van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. Annals of the Rheumatic Diseases 2013.

32. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-158, iii-iv.

33. Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. Value Health 2015;18:425-31.

34. McLeod C, Bagust A, Boland A, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. HEALTH TECHNOLOGY ASSESSMENT 2007;11:1-158, iii-iv.

35. Wailoo A, Hernandez M, Philips C, et al. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. VALUE IN HEALTH 2015;18:425-31.

36. Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. ANNALS OF THE RHEUMATIC DISEASES 2003;62:732-40.

37. BMJ Group and Pharmaceutical Press. British National Formulary (BNF). Available at: https://www.medicinescomplete.com/mc/bnf/current/. Last accessed 08/03/2016.

38. Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. Ann Rheum Dis 2003;62:732-40.

39. van der Heijde D, Schiff MH, Sieper J, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis 2009;68:922-9.

40. van der Heijde D, Breban M, Halter D, et al. Maintenance of improvement in spinal mobility, physical function and quality of life in patients with ankylosing spondylitis after 5 years in a clinical trial of adalimumab. Rheumatology (Oxford) 2015;54:1210-9.

41. Hu Z, Xu M, Li Q, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. Int J Rheum Dis 2012;15:358-65.

42. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. Ann Rheum Dis 2014;73:587-94.

43. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Annals of the Rheumatic Diseases 2013.

44. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Supplementary Data. Annals of the Rheumatic Diseases 2013.

45. Sieper J, Landewe R, Rudwaleit M, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. Arthritis Rheumatol 2015;67:668-77.

46. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. Rheumatol Int 2010;30:1437-40.

47. Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). Ann Rheum Dis 2011;70:799-804.

48. Dougados M, Braun J, Szanto S, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. Rheumatology (Oxford) 2012;51:1687-96.

49. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.

50. Braun J, Deodhar A, Dijkmans B, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. Arthritis Rheum 2008;59:1270-8.

Appendices

Appendix A: A21 diagrams

Figure 33: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case)

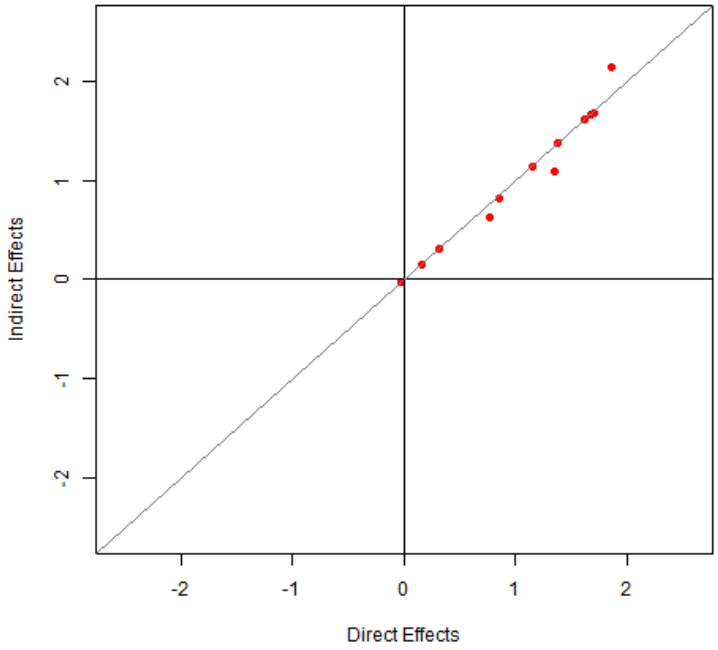


Figure 34: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case)

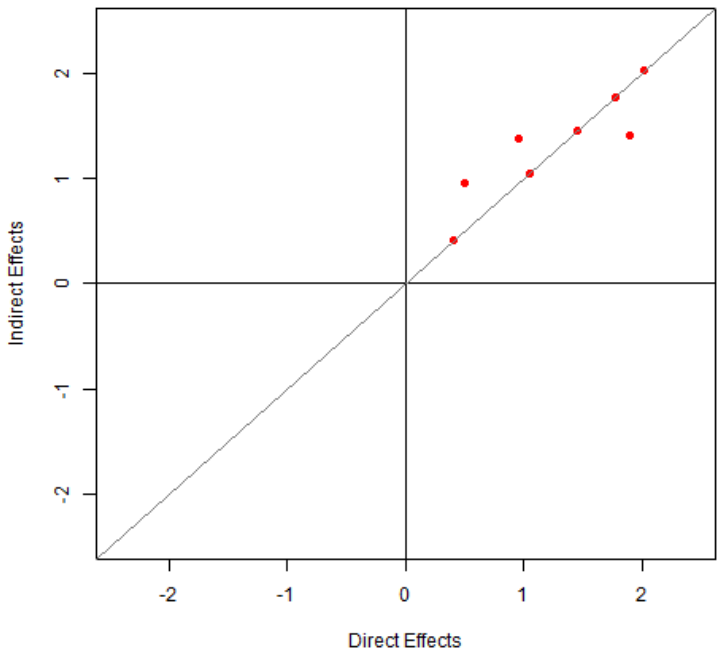


Figure 35: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 excluded (Sensitivity analysis 1)

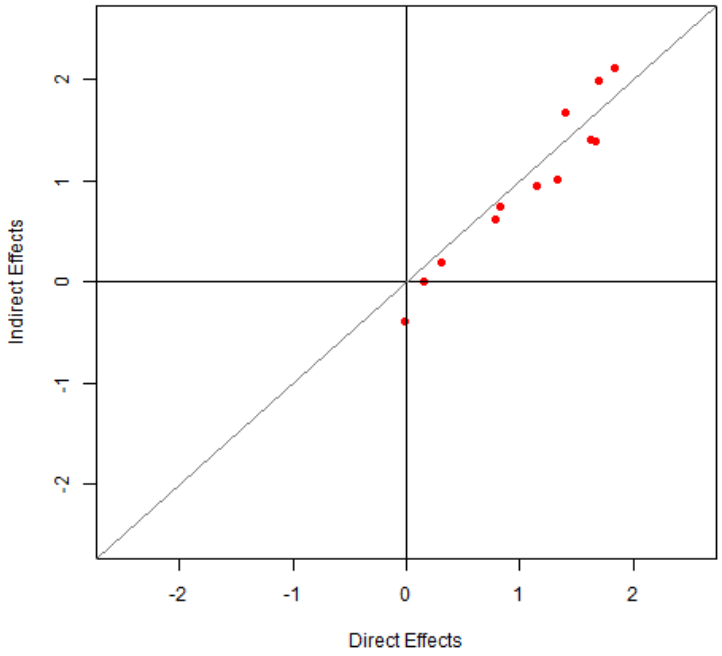


Figure 36: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 excluded (Sensitivity analysis 1)

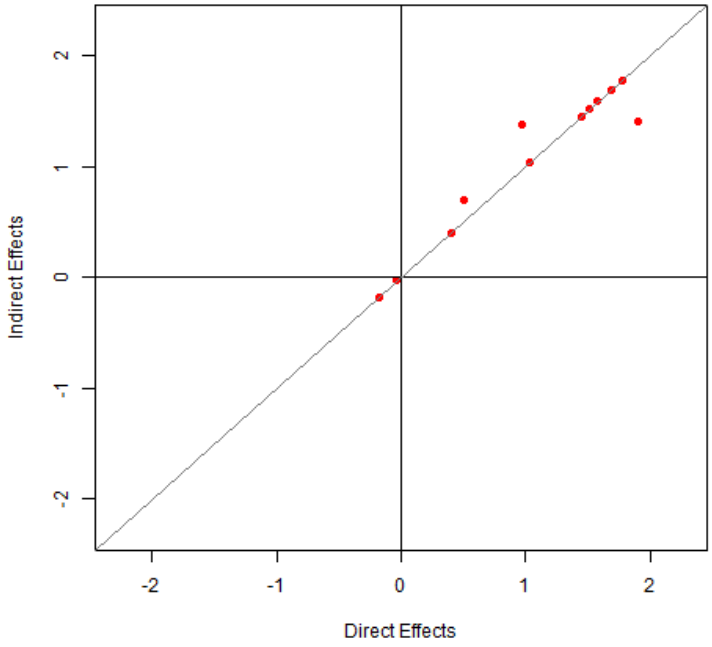


Figure 37: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2)

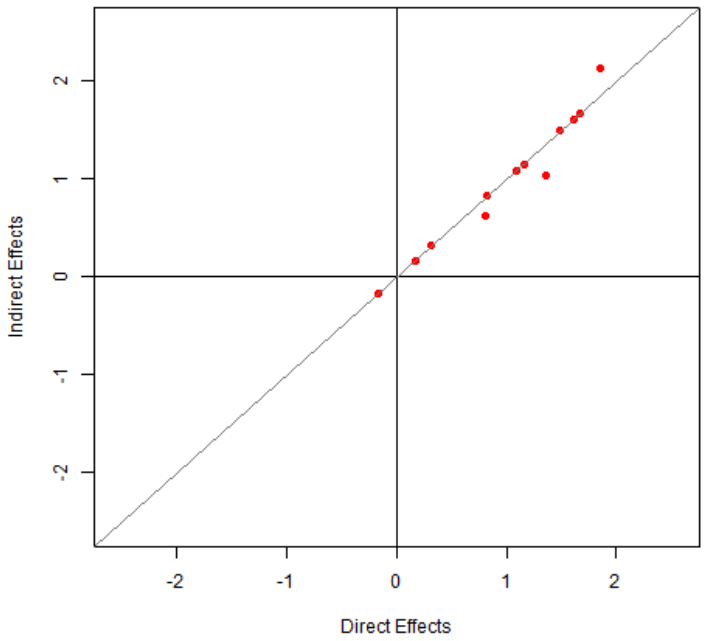


Figure 38: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2)

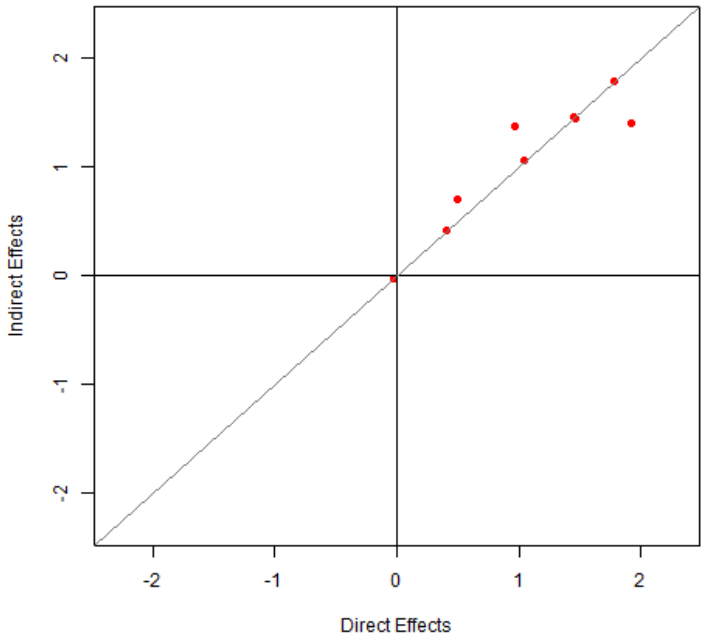


Figure 39: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3)

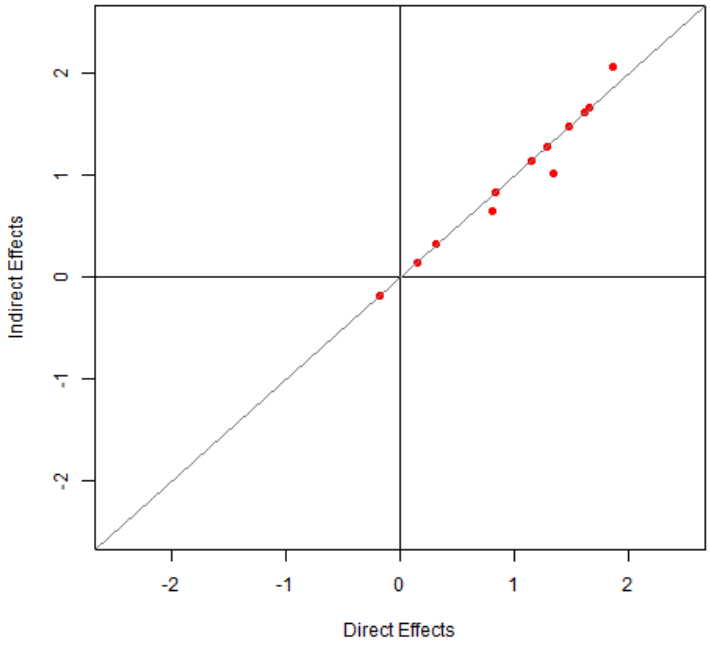


Figure 40: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3)

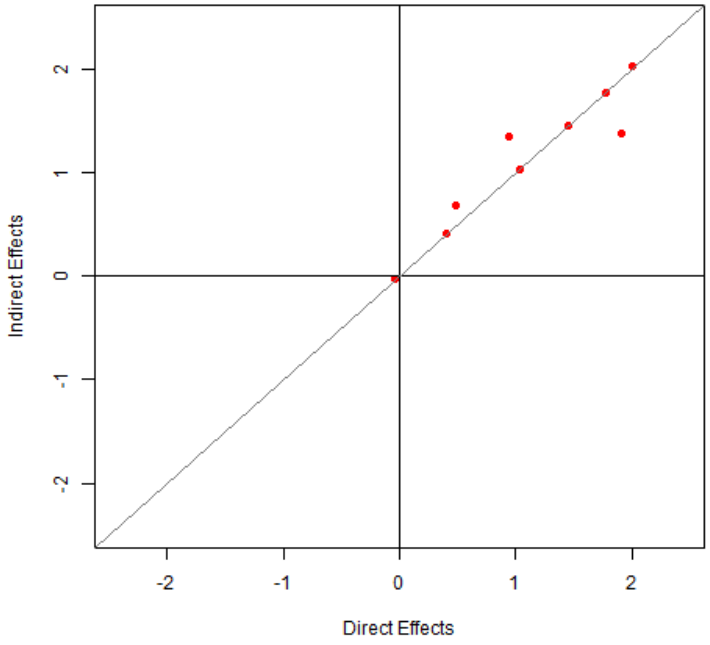


Figure 41: Comparison of estimated relative risk in ASAS20 response from fixed- NMA at 12 to 16 weeks with Measure 1 and 2 (Base case) among biologics-naïve

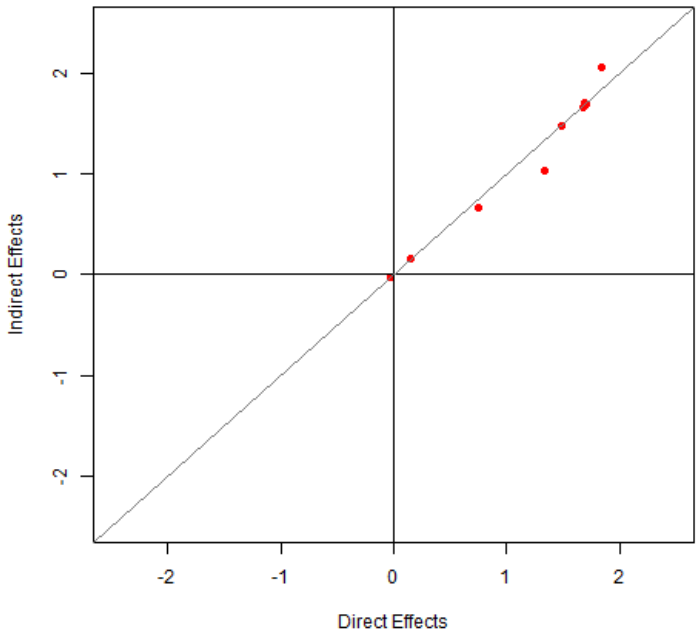


Figure 42: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 and 2 (Base case) among biologics-naïve

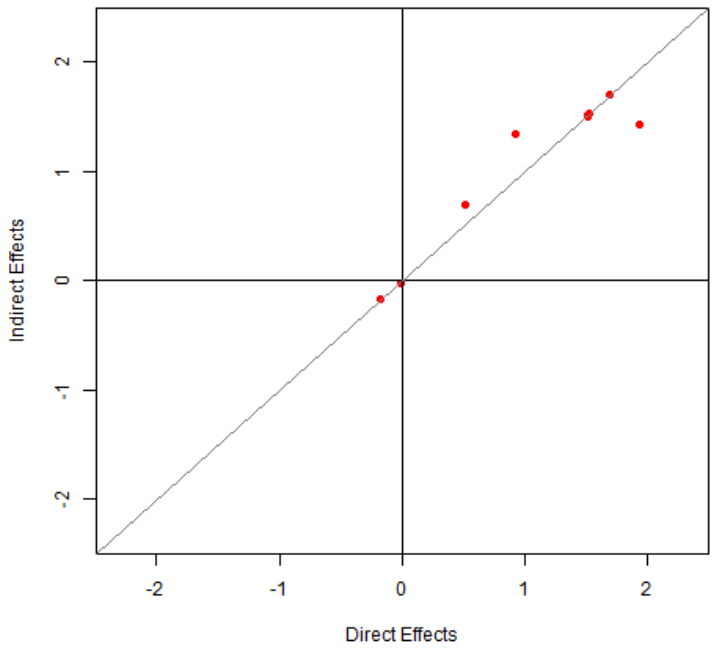


Figure 43: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 removed (Sensitivity analysis 1) among biologics-naïve

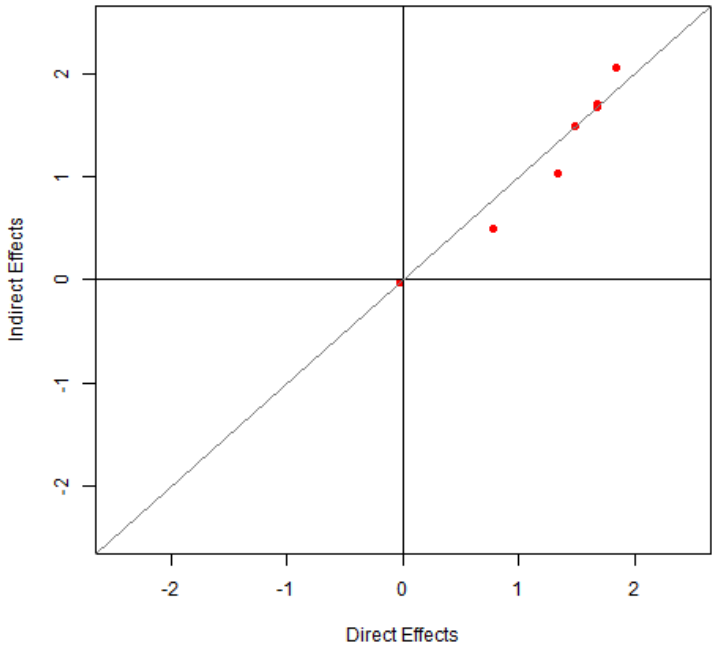


Figure 44: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 to 16 weeks with Measure 1 removed (Sensitivity analysis 1) among biologics-naïve

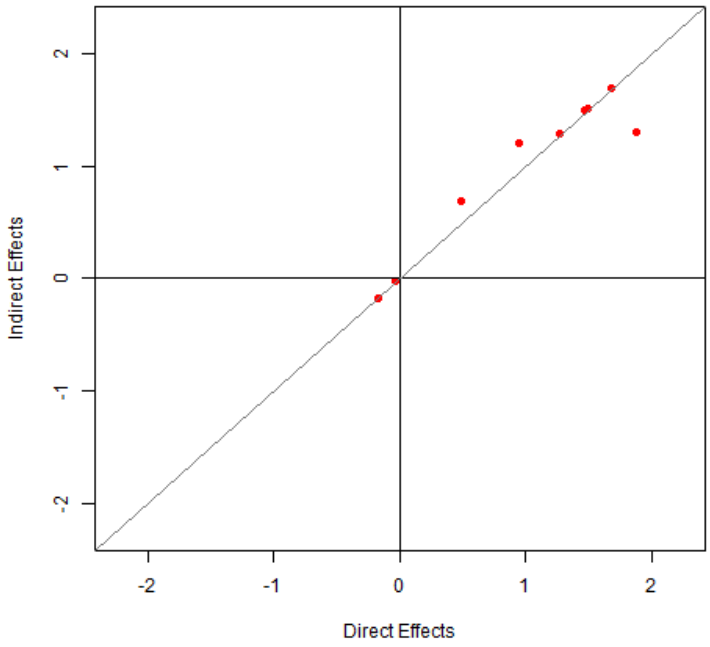


Figure 45: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2) among biologics-naïve

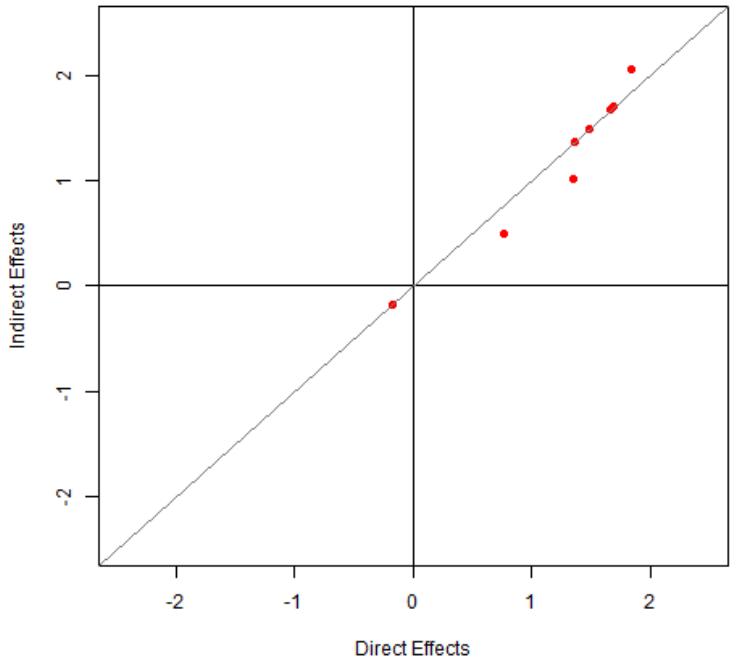


Figure 46: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 and 2 (Sensitivity analysis 2) among biologics-naïve

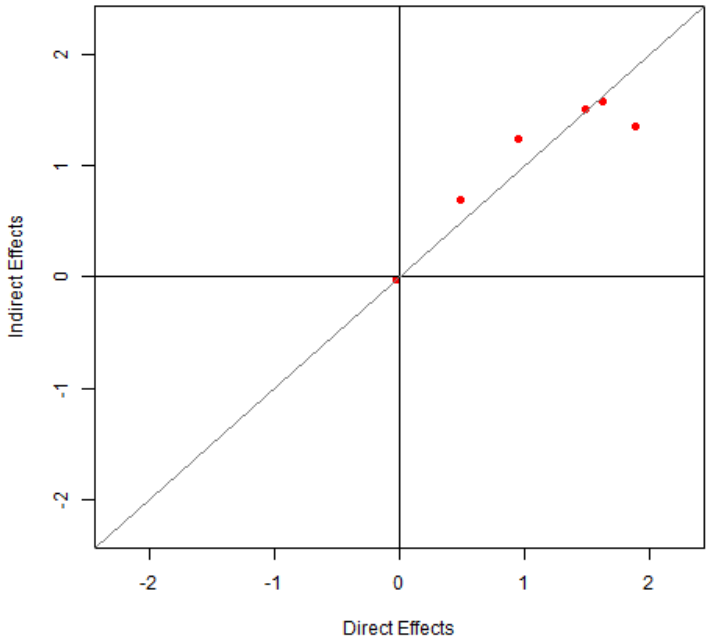


Figure 47: Comparison of estimated relative risk in ASAS20 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3) among biologics-naïve

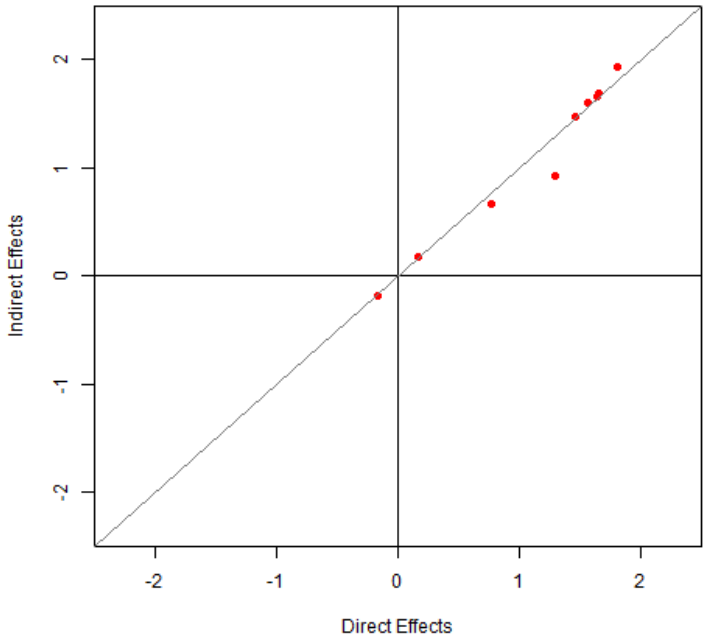
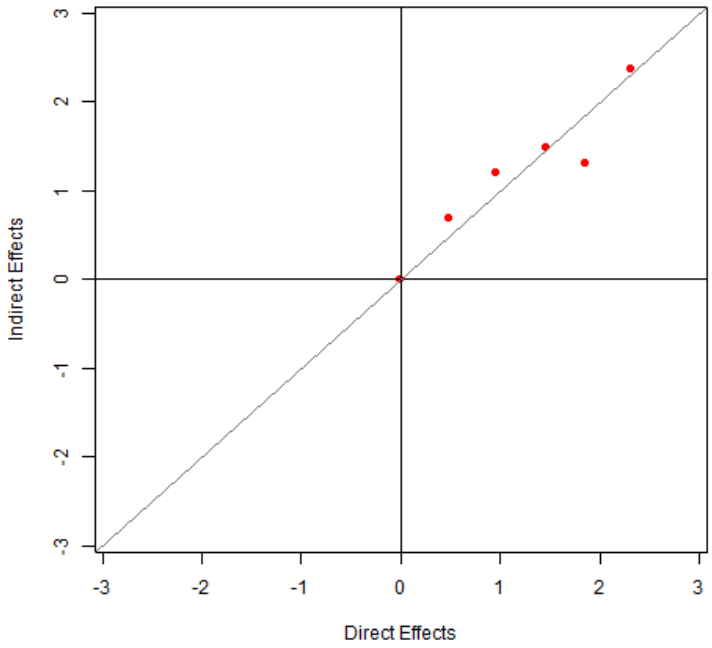


Figure 48: Comparison of estimated relative risk in ASAS40 response from fixed-effects NMA at 12 weeks with Measure 1 excluded (Sensitivity analysis 3) among biologics-naïve



Appendix B: B7 WinBugs code

Model B: Code from Assessment Group Report Appendix 9 which did not run

```
model{
for (i in 1:10) {
y[i] ~ dnorm(theta[i], y.prec[i]) #change in score
theta[i] <- mu[s[i]] + d[t[i]]
}
for (i in 11:18) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
theta[i] <- mu[s[i]] + d[t[i]]
}
for (i in 19:28) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
theta[i] <- mu[s[i]] + d[t[i]]
}
for (j in 1:14) {
mu[j] ~ dnorm(0,0.001)
}
d[1] <- 0
for (k in 2:6) {
d[k] ~ dnorm(re,intau)
}
re ~ dnorm(0, 0.01)
intau <- 1/tau
tau <- pow(sd,2)
sd ~ dunif(0,2)
re.pred ~ dnorm(re,intau)
rho[1] ~ dunif(-1,1)
rho[2] ~ dunif(-1,1)
}
```

Comment [GS1]: Incorrect specification of standard deviation. Changed this to incorporate correct specification as per winBUGS

Comment [GS2]: Probit function in winBUGS caused error. This has also been noticed in other situations. Used the standard normal function which is the same as using probit(p[i]).

Comment [GS3]: The reciprocal of the square root of standard deviation was used, where just the standard deviation needs to be given as per statistical model B

Comment [GS4]: Similar comment on sd as per comment 1

Comment [GS5]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i].

Comment [GS6]: Same as comment 2.

Model B: Modified code used to generate results:

```
model{
  for (i in 1:10) {
    y[i] ~ dnorm(theta[i], y.prec.n[i])
    y.prec.n[i]<-1/pow(y.prec[i],2)#change in score
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (i in 11:18) {
    r[i] ~ dbin(p[i], n[i])
    aux[i] <- equals(t[i],1)+1
    p[i] <- phi(-(b[i]*0.5 + theta[i])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (i in 19:28) {
    r[i] ~ dbin(p[i], n[i])
    y[i] ~ dnorm(theta[i], y.prec.n[i]) #change in score
    y.prec.n[i]<-1/pow(y.prec[i],2)
    aux[i] <- equals(t[i],1)+1
    p[i] <- phi(-(b[i]*0.5 + theta[i])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
    theta[i] <- mu[s[i]] + d[t[i]]
  }
  for (j in 1:14) {
    mu[j] ~ dnorm(0,0.001)
  }
```

```
  d[1] <- 0
  for (k in 2:6) {
    d[k] ~ dnorm(re,intau)
  }
  re ~ dnorm(0, 0.01)
  intau <- 1/tau
  tau <- pow(sd,2)
  sd ~ dunif(0,2)
  re.pred ~ dnorm(re,intau)
  rho[1] ~ dunif(-1,1)
  rho[2] ~ dunif(-1,1)
}
```

Model C: Code from Assessment Group Report Appendix 9 which did not run:

```
model{
for (i in 1:10) {
y[i] ~ dnorm(theta[i,1], y.prec[i]) #change in score
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 11:14) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 15:16) {
r[i] ~ dbin(p[i], n[i])
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
}
for (i in 17:26) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i,1], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 27:28) {
y.f[i] ~ dnorm(theta[i,2], y.prec.f[i]) #change in score BASF1
}
for (i in 29:30) {
r[i] ~ dbin(p[i], n[i])
y[i] ~ dnorm(theta[i,1], prec[i]) #change in score
aux[i] <- equals(t[i],1)+1
probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(pow(prec[i],-0.5)*pow(5/4+rho[aux[i]],0.5))
}
for (i in 1:30) {
theta[i,1:2] ~ dmnorm(delta[i,1:2],B[1:2,1:2])
delta[i,1] <- mu1[s[i]] + d1[t[i]]
delta[i,2] <- mu2[s[i]] + d2[t[i]]
}
d1[1] <- 0
d2[1] <- 0
for (k in 2:6) {
d1[k] ~ dnorm(re1,intau)
d2[k] ~ dnorm(re2,intau)
}
B[1,1]<- 1/(pow(sd[1],2)*(1-pow(cor,2)))
B[2,2]<- 1/(pow(sd[2],2)*(1-pow(cor,2)))
B[1,2]<- -cor/(sd[1]*sd[2]*(1-pow(cor,2)))
B[2,1]<- B[1,2]
sd[1] ~ dunif(0,5)
sd[2] ~ dunif(0,5)
cor~dunif(0,1)
for (i in 1:15) {
mu1[i] ~ dnorm(0,0.01)I(-5,5)
mu2[i] ~ dnorm(0,0.01)I(-5,5)
}
re1 ~ dnorm(0, 0.01)I(-10,10)
re.pred1 ~ dnorm(re1,intau)
re2 ~ dnorm(0, 0.01)I(-10,10)
re.pred2 ~ dnorm(re2,intau)
intau <- 1/tau
tau <- pow(sd.re,2)
sd.re ~ dunif(0,2)
rho[1] ~ dunif(0,1)
rho[2] ~ dunif(0,1)
for (k in 2:6) {
d1.pred[k] ~ dnorm(re1,intau)
}
}
```

Comment [GS1]: Correct standard deviation specification, refer to comment 1.

Comment [GS2]: Correct standard deviation specification, refer to comment 1.

Comment [GS3]: Refer to comments 2 & 3

Comment [GS4]: Correct standard deviation specification, refer to comment 1.

Comment [GS5]: Refer to comments 2 & 3

Comment [GS6]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i] (same as comment 5)

Comment [GS7]: Refer to comments 2 & 3

Comment [GS8]: Refer to comments 2 & 3

Comment [GS9]: Refer to comments 2 & 3

Comment [GS10]: Incorrect standard deviation used (Refer to the line in comment) prec[i] used instead of y.prec[i] (same as comment 5)

Comment [GS11]: Refer to comments 2 & 3

Model C: Modified code used to generate results:

```
model{
  for (i in 1:10) {
```

```
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 11:14) {
  r[i] ~ dbin(p[i], n[i])
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 15:16) {
  r[i] ~ dbin(p[i], n[i])
  aux[i] <- equals(t[i],1)+1
  probit(p[i]) <- -(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5))
}
for (i in 17:26) {
  r[i] ~ dbin(p[i], n[i])
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 27:28) {
  y.f[i] ~ dnorm(theta[i,2], y.prec.f.n[i]) #change in score BASFI
  y.prec.f.n[i]<-1/pow(y.prec.f[i],2)
}
for (i in 29:30) {
  r[i] ~ dbin(p[i], n[i])
  y[i] ~ dnorm(theta[i,1], y.prec.n[i]) #change in score
  y.prec.n[i]<-1/pow(y.prec[i],2)
  aux[i] <- equals(t[i],1)+1
  p[i] <- phi(-(b[i]*0.5 + theta[i,1])/(prec[i]*pow(5/4+rho[aux[i]],0.5)))
}
for (i in 1:30) {
  theta[i,1:2] ~ dmnorm(delta[i,1:2],B[1:2,1:2])
  delta[i,1] <- mu1[s[i]] + d1[t[i]]
  delta[i,2] <- mu2[s[i]] + d2[t[i]]
}
d1[1] <- 0
d2[1] <- 0
for (k in 2:6) {
  d1[k] ~ dnorm(re1,intau)
  d2[k] ~ dnorm(re2,intau)
}
B[1     ,1]<- 1/(pow(sd[1],2)*(1-pow(cor,2)))
B[2,2]<- 1/(pow(sd[2],2)*(1-pow(cor,2)))
B[1,2]<- -cor/(sd[1]*sd[2]*(1-pow(cor,2)))
B[2,1]<- B[1,2]
sd[1] ~ dunif(0,5)
```

```
  sd[2] ~ dunif(0,5)
  cor~dunif(0,1)
  for (j in 1:15) {
    mu1[j] ~ dnorm(0,0.01)I(-5,5)
    mu2[j] ~ dnorm(0,0.01)I(-5,5)
  }
  re1 ~ dnorm(0, 0.01)I(-10,10)
  re.pred1 ~ dnorm(re1,intau)
  re2 ~ dnorm(0, 0.01)I(-10,10)
  re.pred2 ~ dnorm(re2,intau)
  intau <- 1/tau
  tau <- pow(sd.re,2)
  sd.re ~ dunif(0,2)
  rho[1] ~ dunif(0,1)
  rho[2] ~ dunif(0,1)
  for (k in 2:6) {
    d1.pred[k] ~ dnorm(re1,intau)
  }
}
```

Appendix C: B8 JAGS Code

```
# Binomial likelihood, logit link
model{                                          # *** PROGRAM STARTS

for(i in 1:ns){
mu[i] ~ dnorm(0,.0001)
    for (k in 1:na[i])  {
        r[i,k] ~ dbin(p[i,k],n[i,k])
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
        rhat[i,k] <- p[i,k] * n[i,k]
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
           +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

       }
    resdev[i] <- sum(dev[i,1:na[i]])
    }

totresdev <- sum(resdev[])
d[1]<-0
d[2] ~ dnorm(0,.0001)
for (k in 3:nt){  d[k] ~ dnorm(classmu,.0001) }
classmu ~ dnorm(0,.0001) }

for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
```

```
        RR[c,k] <-T[k]/T[c]
        RD[c,k] <-T[k]-T[c]
        }
    }
for (c in 1:(nt)) {
     for (k in 1:(c)) {
          OR[c,k] <- 0
           lor[c,k] <- 0
           RR[c,k] <-0
          RD[c,k] <-0
          }
    }

for (i in 1: ns){
                    mu1[i] <- mu[i]*equals(t[i,1],1)}
                    A<- sum(mu1[])/nt1
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

}                                                   # *** PROGRAM ENDS

# Continuous outcomes, identity link
model{                                              # *** PROGRAM STARTS
for(i in 1:ns){
   mu[i] ~ dnorm(0,.0001)

   for (k in 1:na[i]) {
      vr[i,k] <- pow(se[i,k],2)

          prec[i,k] <- 1/vr[i,k]
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k
     }
   resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])
for(i in 1:ns){
    for (k in (na[i]):(maxn + 1)){
        dev[i,k+1] <- 0
            theta[i,k+1] <- 0
      }
    }

d[1]<-0
d[2] ~ dnorm(0,.0001)
```

```
for (k in 3:nt){   d[k] ~ dnorm(classmu, classtau) }  # class specific priors for antiTNF treatment effects
classmu ~ dnorm(0,0.001)              # hyperprior for antiTNF class mean
classtau <- 1/(clsd*clsd)
clsd~dunif(0,5)              # hyperprior for antiTNF class sd

for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        D[c,k] <- (d[k]-d[c])
       }
  }

for (c in 1:(nt)) {
     for (k in 1:(c)) {
        D[c,k] <- 0
                  }
    }

for (i in 1: ns){
                  mu1[i] <- mu[i]*equals(t[i,1],1)}
                  A<- sum(mu1[])/nt1

for (k in 1:nt) { T[k] <- A + d[k]  }

}                                                  # *** PROGRAM ENDS
```

Appendix D: Update to Appendix J in the original submission (matching-adjusted indirect comparison of secukinumab and adalimumab)

With MEASURE 2

A matching-adjusted indirect comparison (MAIC) was conducted between secukinumab and adalimumab by matching the pooled secukinumab dose arms in MEASURE 2 to the adalimumab arm in the ATLAS trial, and the placebo arm from MEASURE 2 to the placebo arm in the ATLAS trial.

The base case scenario matched patients from both trials according to age, gender, CRP, prior TNFα inhibitor treatment and baseline BASFI score (see Table 93) Two further scenarios were performed, which matched patients according to the same characteristics, with the exception that in the second scenario baseline BASDAI score was matched instead of baseline BASFI score, and in the third scenario, both BASDAI and BASFI baseline scores were matched (see Table 96 and Table 99).

Results for ASAS20 and ASAS40 for secukinumab 150 mg and adalimumab in the base case scenario at Week 12, Week 16, Week 24 and Week 52 are shown in Table 91 and Table 92, respectively. At Week 24, the MAIC demonstrated that secukinumab 150 mg was associated with statistically significantly better results than adalimumab 40 mg with regards to ASAS20 and ASAS40 response relative to placebo. This was also the case at Week 52 for the ASAS20 response, demonstrating the significant sustained effects of secukinumab 150 mg in comparison to an active biologic comparator (adalimumab).

Statistically significantly better results for secukinumab 150 mg compared to adalimumab at Week 24 for both ASAS20 and ASAS40 relative to placebo were seen consistently across both alternative scenarios. At Week 52, ASAS20 and ASAS40 results for secukinumab 150 mg were numerically higher than adalimumab relative to placebo across all both alternative scenarios, though the results were not statistically significant. However this lack of statistical significance should be interpreted taking into account the fact that the adalimumab data at Week 52 used LOCF analysis and did include placebo switchers, thus not following the intention-to-treat principle. Results for secukinumab 150 mg were based on the more conservative non-responder imputation and also followed the intention-to-treat principle.

MEASURE 2 Base Case (Scenario 1):

Table 91: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 92. ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 93: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in the base case scenario

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=34)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	42.0 (12.48)	42.4 (9.1)

Female, n (%)	51 (24.5%)	26 (36.1%)	28.8%
Disease characteristics			
BASFI, mean (SD)	5.2 (2.2)	6.2 (2.1)	5.5 (1.7)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.3 (2.9)
TNF-naïve, n (%)	100%	44 (61.6%)	100.0%

ESS: Effective Sample Size

MEASURE 2 Scenario 2:

Table 94. ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]							
Adalimumab 40 mg								

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 95: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]							
Adalimumab 40 mg								

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 96: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in scenario 2

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=39)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	41.9 (12.5)	41.7 (9.5)
Female, n (%)	51 (24.5%)	26 (36.1%)	29.5%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.6 (1.5)	6.4 (1.0)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.2 (3.1)
TNF-naïve, n (%)	100%	43 (60.6%)	100.0%

ESS: Effective Sample Size

MEASURE 2 Scenario 3:

Table 97: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 98: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; Abbreviations: NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 99: Baseline characteristics for ATLAS and MEASURE 2 before and after matching in scenario 3

Baseline characteristics	ATLAS	MEASURE 2 (before matching)	MEASURE 2 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=72)	SEC 150mg (ESS=34)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	41.9 (12.5)	42.7 (8.9)
Female, n (%)	51 (24.5%)	26 (36.1%)	28.5%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.6 (1.5)	6.3 (1.0)
BASFI, mean (SD)	5.2 (2.2)	6.2 (2.1)	5.6 (1.6)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.6 (5.0)	2.4 (2.9)
TNF-naïve, n (%)	100%	43 (61.1%)	100.0%

ESS: Effective Sample Size

With MEASURE 1

In addition to the matching-adjusted indirect comparison (MAIC) using MEASURE 2, another MAIC was conducted between secukinumab and adalimumab by matching secukinumab arms of MEASURE 2 to the adalimumab arm in the ATLAS trial.

The base case scenario matched patients from both trials according to age, gender, CRP, prior TNFα inhibitor treatment and baseline BASFI score (see Table 102) Two further scenarios were performed, which matched patients according to the same covariates, with the exception that in the second scenario baseline BASDAI score was matched instead of baseline BASFI score, and in the third scenario, both BASDAI and BASFI baseline scores were matched (see Table 105 and Table 108).

Results for ASAS20 and ASAS40 response relative to placebo for secukinumab 150 mg and adalimumab in the base case scenario at Week 12, Week 16, Week 24 and Week 52 are shown in Table 10 and Table 11, respectively. At Week 16 the MACI demonstrated that secukinumab 150mg was associated with statistically significantly better results than adalimumab with regards to ASAS20. ASAS40 was not reported for adalimumab at week 16. At week 24, secukinumab 150 mg was associated with statistically significantly better results than adalimumab 40 mg with regards to ASAS20 and ASAS40 responses.

Statistically significantly better results for secukinumab 150 mg compared to adalimumab at Week 24 for both ASAS20 and ASAS40 were seen consistently across both alternative scenarios. In some of the comparisons, statistically significant results were also observed at week 16 and week 52.

At Week 52, ASAS20 and ASAS40 results for secukinumab 150 mg were numerically higher than adalimumab across all scenarios, though the results were not statistically significant. However this lack of statistical significance should be interpreted taking into account the fact that the adalimumab data at Week 52 used LOCF analysis and did include placebo switchers, thus not following the intention-to-treat principle. Results for secukinumab 150 mg were based on the more conservative non-responder imputation and also followed the intention-to-treat principle.

MEASURE 1 Base Case (scenario 1):

Table 100: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (base case scenario)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 101: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (base case scenario)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 102: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in the base case scenario

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=88)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.1 (10.0)
Female, n (%)	51 (24.5%)	41 (32.8%)	25.4%
Disease characteristics			
BASFI, mean (SD)	5.2 (2.2)	5.6 (2.2)	5.3 (1.8)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (2.1)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

MEASURE 1 Scenario 2:

Table 103: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]		[redacted]		[redacted]		[redacted]	
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 104: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 2)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]		[redacted]		[redacted]		[redacted]	
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 105: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in Scenario 2

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=88)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.8 (9.9)
Female, n (%)	51 (24.5%)	41 (32.8%)	27.1%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.3 (1.6)	6.4 (1.3)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (2.1)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

MEASURE 1 Scenario 3:

Table 106: ASAS20 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations**: NR, not reported.
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 107: ASAS40 response for secukinumab vs. adalimumab in the matching-adjusted indirect comparison (Scenario 3)

Treatment	Week 12		Week 16		Week 24		Week 52**	
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab 40 mg	[redacted]		[redacted]		[redacted]		[redacted]	

*p<0.05; **Abbreviations:** NR, not reported
** Week 52 data for ADA is LOCF and contains placebo switchers as other data were not available.

Table 108: Baseline characteristics for ATLAS and MEASURE 1 before and after matching in Scenario 3

Baseline characteristics	ATLAS	MEASURE 1 (before matching)	MEASURE 1 (after matching)
	ADA 40mg (N=208)	SEC 150mg (N=125)	SEC 150mg (ESS=83)
Demographics			
Age (years), mean (SD)	41.7 (11.7)	40.1 (11.6)	40.8 (9.8)
Female, n (%)	51 (24.5%)	41 (32.8%)	26.4%
Disease characteristics			
BASDAI, mean (SD)	6.3 (1.7)	6.3 (1.6)	6.4 (1.2)
BASFI, mean (SD)	5.2 (2.2)	5.6 (2.2)	5.3 (1.8)
CRP (mg/dL), mean (SD)	1.8 (2.2)	1.7 (2.2)	1.8 (1.9)
TNF-naïve, n (%)	100%	92 (73.6%)	100.0%

ESS: Effective Sample Size

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

Your name: [redacted]

Name of your organisation:

1. **British Society for Rheumatology (BSR)**
    a. **BSR's Nominee**
    b. **Consultant Rheumatologist, Clinical Director & Research Lead,** [redacted]
    c. **Chair, BRS Guidelines Group for biologics in the treatment of axial spondyloarthritis**
    d. **Medical Advisor & Trustee, National Ankylosing Spondylitis Society**
    e. **Treasurer & Trustee, British Society for Spondyloarthritis**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? √

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology?

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

What is the expected place of the technology in current practice?

Initial treatment for Axial Spondyloarthritis (axSpA; including Ankylosing Spondylitis [AS]) comprises anti-inflammatory drugs and physiotherapy. Approximately 40% patients will need escalation of treatment to biological therapies. TNF–inhibitors are the only biological therapies currently available to treat severe AS and non-radiographic axial spondyloarthritis (NICE technology appraisal guidance [TA383] Published date: February 2016) Despite this, approximately 20-30% of AS patients do not respond to their first TNF inhibitor and only 50% respond if switched to a second. In addition, data from registries show that between 25% and 30% of patients with active SpA lose their response to anti-TNF treatment over the first year, while up to 40% don't respond in the first 2 years of treatment (Glintborg et al. 2013) This means that between 10 and 20% of biologics eligible AS patients have no other effective treatment option.

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A antibody of the IgG1/κ-class which represents a novel approach to targeting the chronic inflammatory process by selectively targeting the predominant cytokine of the unique subset of helper Th17 cells, as well as other cells that play a role in SpA. An extensive Phase 2/3 program demonstrated that secukinumab is effective in managing signs and symptoms of AS in TNF inadequate responders and is well tolerated (Baeten et al 2015). IL-17 inhibition therefore represents a unique and effective approach for managing AS patients who have not responded to TNF inhibitors.

References

1.Glintborg B et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013 May;65(5)

2. Baeten D et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. NEJM 2015; 373: 2534-48.

The technology is for use in a secondary care setting. The treatment is a self-administered sub-cutaneous monthly injection. The technology is already used in the NHS by Dermatologists for patients with severe psoriasis.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

The advantages and disadvantages of the technology

UK healthcare for the provision of biological treatments is appropriately established for the treatment of axSpA. This technology will add to the treatment options for patients through the current treatment pathway. We see no additional practical requirements being necessary in order to make this technology available.

AxSpA patients are required to have appropriate baseline screening prior to commencing biologic therapies. This screening will be similar for patients commencing this new technology.

The phase 3 trials of this technology accurately reflect UK practise. The treatment was given to patients who have evidence of high disease activity (BASDAI and back pain score>4) and are refractory to NSAID therapy.

The side-effect profile in randomised controlled trials is favourable.

Any additional sources of evidence

Not applicable.

Implementation issues

No additional NHS resources/departmental infrastructure would be necessary in order to implement this technology. We envisage that clinician training and patient education materials will be made available by the pharmaceutical company prior to launch.

As previously mentioned, the technology is already in use in the NHS by dermatologists for the treatment of severe psoriasis.

Equality

Existing guidelines for the use of biologics in AxSpA address patients with disabilities and these will be applicable to any new technologies.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: National Ankylosing Spondylitis Society (NASS)

Your position in the organisation: Information and Communications Manager

Brief description of the organisation:

The National Ankylosing Spondylitis Society (NASS) was founded in 1976 by a group of patients, doctors and physiotherapists at the Royal National Hospital for Rheumatic Diseases in Bath.

The 3 main aims of NASS are:

- To seek a cure for ankylosing spondylitis (AS) and related conditions, and improve their treatment in the UK;
- To promote awareness of these conditions in the UK; and
- To provide guidance, advice and information for people affected by these conditions including their families, their carers and their employers.

NASS is the only registered charity in the UK dedicated to the needs of people with ankylosing spondylitis (including axial spondyloarthritis) in the UK.

NASS is a membership organisation, with around 5,000 members and receive no government or statutory funding. We are funded by membership subscriptions, donations and grants.

The NASS head office is based in West London where we currently have 6 full time members of staff. However we have a network of 91 local branches spread throughout the UK, of which 77 are based in England.

The branches provide regular physiotherapy, hydrotherapy and gym sessions that are supervised by physiotherapists with an interest in AS. Most branches meet weekly on weekday evenings. Although the main aim of meeting is for exercise, most branches also have an educational and social aspect.

NASS wanted to represent the views of people living with ankylosing spondylitis in our submission. We emailed a link to a survey on the issues to all members and supporters in England for whom we have an email address (4,136). We additionally posted a link to the survey on the NASS website, advertised the survey in our monthly E-Newsletter and asked all our branch contacts to ensure branch members were aware of the research.

The survey was set up to allow only one entry per IP address. The survey was only for people with a diagnosis of ankylosing spondylitis who were living in England. The survey opened on Thursday 7 January 2016 and was closed at 09:00 on Tuesday 19 January 2016.

The introduction to the survey explained that NICE was reviewing secukinumab and had asked NASS to get involved as a patient organisation. It explained NASS would use the views given in the survey to write our submission. We additionally explained there was a page of information on secukinumab within the survey. Respondents were assured all their replies would be completely anonymous.

642 completed the survey. We screened out people who did not have AS and who did not live in England. This left 520 respondents living in England with a diagnosis of AS who were included in our analysis.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Ankylosing spondylitis (AS) is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage.

The key symptom in early disease is inflammatory back pain (IBP). The onset of back pain and stiffness is usually gradual, being especially severe at night and following immobility. For many people sleep is disturbed, often causing them to get out of bed in the night to move around so as to improve their back pain and stiffness. Pain and stiffness in AS are commonly at their worst first thing in the morning and may improve with stretching and light exercise.

Persistence of the disease leads to progressive spinal stiffness which may be accompanied by deformity. Up to 25% of people with AS eventually develop complete fusion of the spine which leads to substantial disability and restriction.

50% of people with AS also suffer from associated disorders at sites distant from the spine. In particular, 40% experience episodic eye inflammation (iritis), 16% develop psoriasis and 10% inflammatory bowel disease.

Symptoms of AS usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships.

Symptoms are often present for a long time (7-10 years) before the diagnosis is made. The evidence suggests the delay to diagnosis is currently 8.5 years.

Although most people with AS live a normal lifespan, there is an increased risk of premature death from cardiovascular disease in particular.

Since many people with AS are neither deformed nor have peripheral joint abnormalities, much of the burden of living with AS is invisible. The spectrum of severity means that although many people with AS live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment.

Work disability is a major problem with more than 50% of people who are affected suffering work instability. The average age of diagnosis is 24, a prime time for establishing a career. In addition, one-third of people with AS give up work before normal retirement age and another 15% reduce or change their work because of axial SpA. The work capacity of people with AS in the middle decades of life is similar to that of people with rheumatoid arthritis.

Being unable to work has important consequences for the individual and his/her family through both loss of earnings and the loss of self-esteem that a career and income provide.

People with AS are more likely to be divorced or never to have married and women with AS are less likely to have children. Many people with AS suffer with issues including depression, fatigue and poor sleep during their lives. All of these problems exert a profound influence on their quality of life.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

When speaking to people with AS, they are clear that they want their symptoms to be improved by treatment. In particular they hope to have significantly less pain and stiffness. This would mean that they could enjoy a better quality of life including an improved family life, social life and an increased ability to be economically active.

People with AS often suffer a great deal with fatigue and they often hope that their fatigue will be reduced through treatment. Where fatigue is exacerbated by disturbed sleep due to pain and stiffness, the improvement in fatigue is often a secondary affect.

In summer 2012 we conducted a quick poll via the NASS website. We asked:

'If there was a new treatment for your AS what single thing would you most like it to do for you?'

A total of 277 people took part and the responses were as follows:

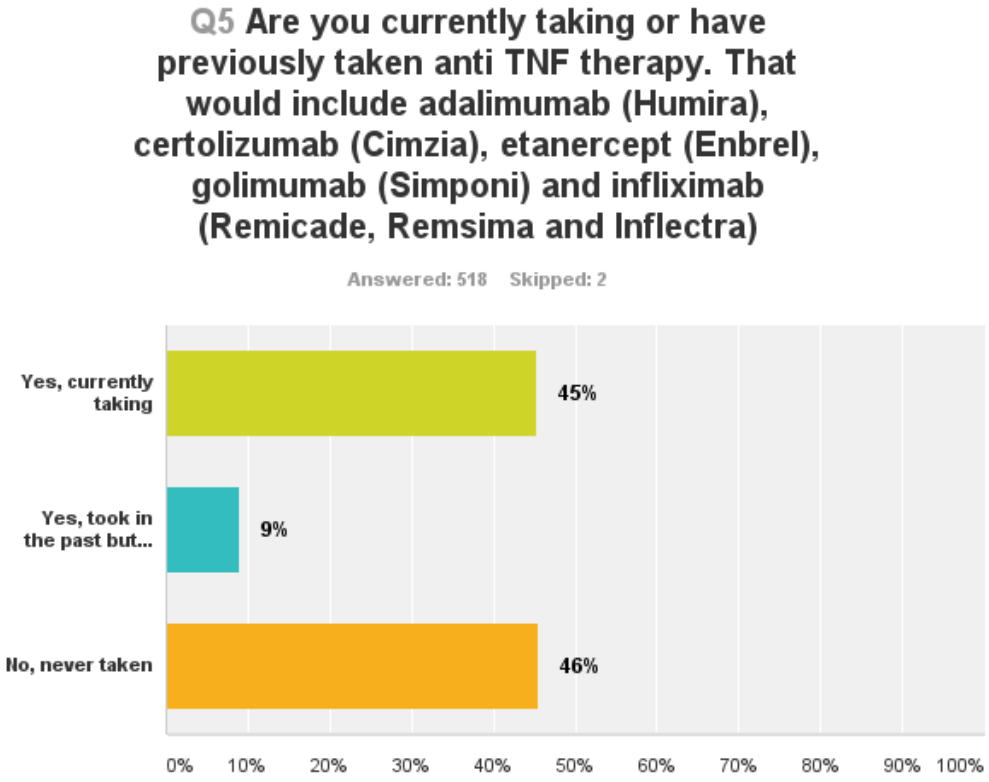
Prevent further damage to your spine and joints	**44%**
Relieve your pain	**27%**
Reduce fatigue	**19%**
Give you a sense of being well	**6%**
Improve your social life and give you the ability to interact normally with your family and friends	**4%**

This indicates that, once people's symptoms are controlled, they hope to avoid further progression of disease.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Many people with mild to moderate AS can often be managed effectively with a combination of anti inflammatory medications and physiotherapy. However, people with more severe AS may well find these medications ineffective at controlling symptoms or may have side effects which means they can no longer tolerate anti inflammatory medication.

The main option for people with severe AS who have failed on anti inflammatory medication is anti TNF therapy. In our survey we asked about use of anti TNF therapy. As the chart below shows, 45% of the sample were currently taking anti TNF therapy, 9% had taken it in the past but it was no longer being prescribed and 46% had never taken anti TNF therapy.



From the research we conducted for the NICE multiple technology appraisal of TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233), we know that people on anti TNF therapy reported that it had made a big difference to their life. They noted it had significantly reduced symptoms of pain and stiffness and had led to improvements in mobility. It had also reduced extra-articular symptoms such as uveitis. The result of these improved symptoms was a significantly improved quality of life.

The benefits of anti TNF therapy were seen as being reduced pain and stiffness, improved mobility, reduction in attacks of uveitis and reduced levels of fatigue. Again, these improvements in symptoms lead directly to an improved quality of life. People reported that they were able to independently manage activities of daily living that were previously problematic and be economically active. They were also better able to carry out the exercises that are vital for optimising outcome in AS. A number noted they had been able to significantly cut down on their use of other painkilling medications.

The perceived downsides of anti TNF therapy centred around the fact that it is an injection rather than an oral medication, the impact of the medication on the immune system and concerns over the potential long term side effects and risks.

In this current survey we asked those currently taking anti TNF therapy (235), to indicate, using a 1 to 5 scale where 5 is very effective and 1 is not very effective at all, how effective their anti TNF therapy had been overall in improving their AS symptoms. On average people scored their anti TNF 4.16 out of a possible 5, with 44% scoring 5 and 34% scoring 4. Just 3% scored their anti TNF a 1 or 2, indicating it was not very or not at all effective.

NASS is aware that data shows anti TNF therapy is efficacious in around 80% of AS patients. This leaves 20% in whom anti TNF therapy is ineffective and who are left struggling with severe symptoms. We asked the 9% of people in our survey who had taken anti TNF in the past but were no longer taking it, why they had stopped. Around half had stopped due to either initial lack of efficacy or a reduction in efficacy over time, while another half had stopped due to side effects. Smaller numbers had stopped due to events including pregnancy, surgery and development of conditions which would contraindicate the use of anti TNF therapy, such as cancer.

There are currently no alternative treatments for AS and thus it is likely that this group of patients will have had to go back to anti inflammatory medication and / or codeine based medications. This emphasises the need for an alternative therapy to be made available.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

The 520 people in England with AS taking part in the survey were shown a short page of information about secukinumab, covering the mode of action, how it has been tested, efficacy, side effects and risks, mode of administration and indication.

Based on this information, respondents were asked, how important, if at all, it would be for rheumatologists to be able to prescribe secukinumab to suitable AS patients. Respondents were asked to use a 1 to 5 scale where 1 meant not at all important and 5 meant very important.

The average score was 4.59 out of a possible 5. Just over seven in ten (72%), scored 5, indicating it would be very important to make secukinumab available, while another 16% scored 4.

The main reason for believing it would be important to make secukinumab available was to widen the options and choices for rheumatologists and AS patients. AS patients felt it was important to have another option which could be chosen either after anti inflammatory failure or anti TNF therapy failure. Those on anti TNF therapy and doing well still often worry about the future and have concerns about what would happen if efficacy started to decline or they developed side effects. These patients want the reassurance that another class of drugs is available if needed. Having an alternative class of drugs in the armamentarium could ultimately help AS patients stay economically active and live independent lives.

AS can be a debilitating disease and drugs like secukinumab being available mean that patients have more options open to them that potentially allow them to lead a near normal life. Not all drugs suit everyone, so choices are very important.

My understanding of anti TNF is that it is unlikely to be effective for the rest of my working life for me, which means that in 10 years I may be unable to work and have little to no quality of life..... Another option would extend my working life and quality of life - good for me, good for society.

Every treatment I've had thus far has either been totally or largely ineffective, or given me severe side effects. Any new treatment, and in particular a treatment such as this which targets a completely different immunological pathway offers tremendous hope for those of us who have either had limited success with existing treatments or been forced to abandon treatments due to severe side effects.

I have benefitted immeasurably myself from Humira but I am aware that not all drugs are suitable for all patients. It is therefore vital that a range of treatments are available to offer hope to those suffering AS symptoms.

At the moment it feels like if anti TNF does not work for you there are no further options. This would give an additional option and further hope to patients.

Another drug in the arsenal. As it has a different mechanism of action this may prove to be a better choice than an anti TNF. I'm taking etanercept and over time I feel that the effect is not as great than when I first started using.

Just 2% scored a 1 or a 2 out of 5, believing it was not very or not at all important for secukinumab to be made available. The reasons behind the low scores were concerns over the likely levels of efficacy, side effects and long term risks. Some of the people who had suffered severe side effects on anti TNF therapy were understandably reticent about trying another new therapy.

I am somewhat cautious about a new drug. I was informed Humira would be like a 'magic bullet' by the doctor. It might as well have been a real bullet. Taking this drug proved catastrophic.

The key benefit of secukinumab was perceived as being its novel mode of action. In AS treatment options are currently limited and people with AS want to see another option made available. This would offer real hope for those in whom anti TNF therapy has failed and for those who fear anti TNF failure in the future.

The main benefit is that it is another option in the fight against this condition. It also gives another avenue for relief and keeps the hope alive.

I know that traditional medication does not work for my aggressive AS. Anti TNF has been an absolute life changer. Should my current anti TNF fail, this gives me the hope to have an effective alternative which can ensure that I have a life without constant pain and all the other devastating symptoms associated with AS.

For people who anti TNF hasn't worked, or no longer works, this is another possible option. There are few things worse than having a treatment no longer work and being told there is nothing else. The more treatment options available, the more people will benefit from more normal lives without the continual daily struggle.

When you're in that dark place it's good to know there's new drugs available.

Secukinumab was perceived to offer the benefits of reducing the pain of AS and improving movement and mobility. Thus it would improve quality of life. The hope of AS patients was that secukinumab could keep them independent and economically active.

Primarily for me it's quality of life, I am a father to a 10 month old and my biggest fear is not being able to play with her. I struggle to lift her some days already.

Overall improvement in quality of life and to enable people to be able to live a normal life style and not be all fused up like myself after 40+ years of AS.

If I had a 20% improvement in my own symptoms I'd be fitter, stronger, be able to work harder, earn more money and overall be happier.

The efficacy has been shown to be good and most importantly, seems to provide sustained relief of symptoms.

This looks like a very effective treatment. Also after the initial injections, it only needs to be repeated at monthly intervals, so less invasive and more user friendly than current weekly/fortnightly treatments.

Anything that can help alleviate some, if not all, of the constant, constant pain and assist in winning back even a little of the joint movement lost, can't be a bad thing.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As outlined above, secukinumab, is a novel treatment for AS which would offer an alternative to the current, limited options.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not aware.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Please list any concerns patients or carers have about current NHS treatments in England.

Please note we have covered this in **section 3.**

Please list any concerns patients or carers have about the treatment being appraised.

Secukinumab is a novel treatment for AS and this means it is an unknown treatment to AS patients. They would want to know more about the effectiveness and side effects from a range of sources including their own rheumatology team.

In particular, people with AS express concerns about short and long term side effects and risks. They were wary about immunosuppression leading to infections and about the possibility of allergic reactions. The fact that secukinumab was a self injection, as opposed to an oral formulation was perceived as a drawback. A number of people were concerned about the possible cost of secukinumab to the NHS.

Any possible side effects that may occur in the future with prolonged use.

New drugs so the effects of long term treatment are not known.

Side effects. I am 84 years old and live on my own. I like to keep my independence and do a lot of exercises every day. I would not like to develop any side effects.

Upper respiratory tract infections. I have asthma and frequent bronchitis and may be even more susceptible than I am now.

Probably infections of the chest would be the biggest disadvantage. AS sufferers already have a problem expanding their lungs.

Like any treatment there will be side effects. This can't be helped. I take Humira and suffer the side effects because it does help. I just hope they can do something about the lowering of the immune system. The cost will be a main disadvantage.

It's currently going to be expensive, being a new medication, and not as widely trialled as existing medications.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not aware

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not aware

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not aware

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes ☐ **No**

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not aware

9. Other issues

Do you consider the treatment to be innovative?

☐ **Yes** ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Secukinumab has a different mode of action to anti TNF therapy. It is a fully human monoclonal antibody that works on a different part of the immunological pathway targeting a cytokine called IL 17A. We are aware that research shows IL 17A plays an important role in driving the body's immune response in psoriasis and the spondyloarthritides, including psoriatic arthritis and AS.

Are there any other issues that you would like the Appraisal Committee to consider?

No

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Current treatment of AS is limited to anti inflammatory medications and anti TNF therapy
- Research shows anti TNF therapy is effective for approximately 80% of people with AS. This means 20% of people with severe AS which was not managed effectively by anti inflammatories do not respond to anti TNF therapy. As there are no alternative treatments, these patients currently have to go back to anti inflammatories or codeine based medication.
- There is a real unmet need for a novel medication in AS. Secukinumab works on a different part of the immunological pathway, thus offering an alternative to current therapeutic options.
- Symptoms of AS usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships. It is vital for young patients to feel confident that there are a range of treatments which their rheumatologist can access to help them live an active and satisfying life.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]
Name of your organisation: Royal College of Nursing
Are you (tick all that apply):

a specialist in the treatment of people with the condition for which NICE is considering this technology?

a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

✓ other? **Member of the RCN and specialist nurse in biologics for patients with ankylosing spondylitis**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

What is the expected place of the technology in current practice?

The condition is currently treated in the initial stages with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics. Patients with more severe disease will be considered for and treated with anti TNFα biologic therapy if they meet the criteria. There is still significant variability in the availability of anti TNFα across the country although this does seem less than previously. Most specialists in the management of ankylosing spondylitis appear to agree that the use of anti TNF is an appropriate option for the treatment of this patient group.

The disadvantage of current treatments is that not all patients are able to tolerate NSAIDs or they are contraindicated. Although anti TNFα is effective for the majority of patients, there is a small group who does not respond adequately to the treatment and it is thought that there may be another part of the immune system that is having a significant impact on the disease progression.

Another group to be considered are those who have non-radiographic axial spondyloarthropathy. They have the symptoms but no x-ray changes and their disease can be just as debilitating.

The technology should be used in secondary care and managed within specialist teams. This technology would be used in place of existing technologies in most cases so there would not be any significant impact on the current services.

The technology is not licenced in the United Kingdom (UK) for use with ankylosing spondylitis at present and is not in regular use.

NICE TA 143, TA 233 – Etanercept, Adalimumab, Infliximab, Golimumab
These guidelines have been used for a number of years and there appear to be agreement that that the methodology used would be appropriate. Some of the evidence in these guidelines has been superseded and is being addressed at present in NICE Technology appraisal of Ankylosing spondylitis and axial spondyloarthritis (non-radiographic) - adalimumab, etanercept infliximab and golimumab (inc rev TA143 and TA233) ID694 which is due to be published in February 2016. This will allow for further options for technologies already licensed and also for treatment of individuals who have non-radiographic axial spondyloarthropathy.

The advantages and disadvantages of the technology

At present if an individual fails an anti TNFα, use of a second or third one is at the discretion of the Clinical Commissioning Group (CCG), if allowed there is evidence that there is loss of effect of 10% for each further attempt. It is important that there is an alternative to anti TNFα that can provide the same benefit.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

The technology is given by subcutaneous route and after the loading dose it is delivered by a monthly injection which is more convenient for the majority of patients. It seems to be available in both needle and syringe and pen versions which allow patient choice as one device does not suit all patients.

It is assumed that the rules on the use of this technology would be the same as the existing ones in TA143 and 233 which have been demonstrated to be effective.

Papers published seem to be using standard research protocols that appear to be similar to those used for technologies currently in use. The tools and outcome measures, such as the Bath Indices follow current UK and international practice. They appear to show the technology achieves the current improvement levels expected of anti TNFα technologies currently in use.

Reported side effects appear similar to currently used technologies.

Any additional sources of evidence

No comment

Implementation issues

The introduction of this technology should have a minimal impact on NHS staff as it would be for individuals who are already under the care of the specialist and have failed anti TNFα treatment. Staff would require education about the technology and its devices to enable them to provide appropriate education and monitoring to individuals starting the treatment and know when it should be discontinued.

Equality

There are no comments to submit at this stage.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by ~~[insert name of nominating organisation]~~British Society for Rheumatology and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: 16/6/2016

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
[redacted]

Name of your organisation
Leeds Teaching Hospitals Trust and University of Leeds

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **X Clinical Lead for the Leeds SpA service, currently overseeing in excess of 1000 patients with SpA**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **X**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? [redacted] **and trustee of the British Society for SpA**
- other? (please specify) [redacted] **board to the National Ankylosing Spondylitis Society (NASS**)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Management of people with axial SpA including ankylosing spondylitis in the UK is underpinned by the recently published NICE TA383 (1 February 2016) which allows for the use of TNF inhibitors (adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi) and infliximab (Remicade, Remsima, Inflectra) in cases of severe active ankylosing spondylitis or severe non-radiographic axial spondyloarthritis who have previously been unsuccessfully exposed to non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, there are 30-40% of people with AS who do not respond or have a partial response to TNFi, yet they still suffer from active AS leading to pain, stiffness leading to significant impairment of their quality of life. The new technology, Secukinumab offers an alternative with a new mechanism of action (inhibition of IL17-A), a cytokine pathway known to be particularly relevant in SpA. In addition, data from phase III clinical trials with Secukinumab show supreme response from skin psoriasis, higher to that achieved by TNFi. This would make Secukinumab a particularly attractive option in those cases of AS with associated skin psoriasis.

It is expected that Secukinumab would be used alongside TNFi in general practice as available data from the Measure 1 and 2 programmes suggests equal efficacy in biologic naïve and previous TNFi exposed patients. In the absence of any clinical

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

biomarkers of disease geno/phenotype both treatments strategies (TNFi and IL-17Ai) should be equally available.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Secukinumab efficacy data shows that it is in line with currently available TNF inhibitors. The studies did include a significant proportion of TNFi exposed individuals (nearly 40%) showing equal levels of activity. As such it represents a valuable alternative both as first liner and in previous TNF exposed cases. Effect on skin psoriasis would also be of benefit. An obvious advantage of the new technology would be the monthly dose which tends to be favoured over twice monthly or weekly injections.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable. There is no reason to believe that Secukinumab use would impact equality and diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

I am not aware of any additional evidence that may be submitted in support beyond what has been published or may be available from ongoing clinical trials in axial spondyloarthritis, psoriasis and/or psoriatic arthritis.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not envisage any way by which NICE guidance on this technology may affect the delivery of care. The administration route and clinical characteristics of the drug are similar to other technologies and as such clinicians and patients are well familiar with them.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by [National Ankylosing Spondylitis Society] and consequently I will not be submitting a personal statement.

Name:

Signed:

Date: 15/06/16

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Secukinumab for ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

Produced by	Kleijnen Systematic Reviews (KSR) Ltd., United Kingdom (UK) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University, The Netherlands (NL)
Authors	Robert Wolff, Reviews Manager, KSR Ltd. Nasuh Büyükkaramikli, Health Economics Researcher, EUR Maiwenn Al, Health Economics Researcher, EUR Steve Ryder, Health Economist, KSR Ltd. Richard Birnie, Reviews Manager, KSR Ltd. Nigel Armstrong, Health Economist, KSR Ltd. Gill Worthy, Statistician, KSR Ltd. Janine Ross, Information Specialist, KSR Ltd. Johan L. Severens, Professor of Evaluation in Health Care, EUR Jos Kleijnen, Director, KSR Ltd.; Professor of Systematic Reviews in Health Care, Maastricht University
Correspondence to	Robert Wolff, Kleijnen Systematic Reviews Ltd. Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	15 April 2016 (version including corrections following factual error check)
Source of funding	This report was commissioned by the NIHR HTA Programme as project number STA 15/06/02.

Declared competing interests of the authors
None

Acknowledgements
None

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Wolff R, Büyükkaramikli N, Al M, Ryder S, Birnie R, Armstrong N, Worthy G, Ross J, Severens JL, Kleijnen J. Secukinumab for ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2016.

Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Nasuh Büyükkaramikli and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Steve Ryder and Richard Birnie acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Janine Ross critiqued the search methods in the submission and contributed to the writing of the report. Johan L Severens critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

ADA40	Adalimumab 40 mg
AE	Adverse event
AiC	Academic in confidence
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BIM	Budget impact model
BMD	Bone mineral density
BNF	British National Formulary
BSC	Best supportive care
BSR	British Society for Rheumatology
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Conventional care
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness Acceptability Curve
CER P	Certolizomab Pegol
cfb	Change from baseline
CI	Confidence Interval
CiC	Commercial in confidence
CMA	Cost minimisation analysis
COX	Cyclooxygenase
CrI	Credible interval
CRP	c-reactive protein
CS	Company submission
CSR	Clinical study report
CUA	Cost-utility analysis
CZP	Certolizumab pegol
CZP 200	Certolizumab pegol 200 mg
CZP 400	Certolizumab pegol 400 mg
DANBIO	Danish registry for biological treatment in rheumatology
DMARD	Disease modifying anti-rheumatic drug
DNA	Deoxyribonucleic acid
EAM	Extra-articular manifestations
EES	Economic Evaluation Database
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
ETN50	Etanercept 50 mg
EULAR	European League Against Rheumatism
EUR	Erasmus University Rotterdam
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Final analysis set
FE	Fixed effects
GOL	Golimumab
GOL50	Golimumab 50 mg
GOL100	Golimumab 100 mg

GP	General practitioner
HCHS	Hospital and community health services
HLA	Human leukocyte antigen
HRG	Healthcare Resource Group
HrQoL	Health-related Quality of Life
hs	High sensitivity
HTA	Health Technology Assessment
HUI	Health Utilities Index
i.a.	intra-articular
ICER	Incremental cost-effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IL	Interleukin
INF	Infliximab
INF5	Infliximab 5 mg
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen English: Institute for Quality and Efficiency in Health Care
IR	Inadequate responder
IRT	Interactive response technology
ISPOR	International Society for Pharmacoecomics and Outcomes Research
ITT	Intention to Treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	Kilogram
KSR	Kleijnen Systematic Reviews
LOCF	Last observation carried forward
LRiG	Liverpool Reviews and Implementation Group
LY	Life year
MAR	Missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCMC	Markov Chain Monte Carlo
MCS	Mental component score
MD	Mean difference
mg	Milligram
MIMS	Monthly Index of Medical Specialities
MMRM	Mixed-effect model repeated measures
MRI	Magnetic resonance imaging
mSASS	modified Stoke Ankylosing Spondylitis Spine Score
MTA	Multiple Technology Appraisal
MTC	Mixed treatment comparison
MTX	Methotrexate
NA	Not applicable
NA	Not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
OASIS	Outcomes in Ankylosing Spondylitis International Study
ONS	Office for National Statistics
OR	Odds Ratio
ORR	Objective response rate

OS	Overall survival
OWSA	One way sensitivity analysis
PAS	Patient Access Scheme
PBO	Placebo
PCS	Physical component score
PD	Pharmacodynamic
PFS	Pre-filled syringe
PFS	Progression-free survival
PK	Pharmacokinetic
PRESS	Peer Review of Electronic Search Strategies
PRN	Pro re nata (when necessary)
PsA	Psoriatic arthritis
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year
QoL	Quality of life
QW	Once weekly
RA	Rheumatoid arthritis
RCC	Renal cell carcinoma
RCT	Randomised Controlled Trial
RE	Random effects
RR	Relative Risk
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC150	Secukinumab 150 mg
SF-36	Short form 36
SF-6D	Short form-6 dimension
SHI	Statutory health insurance
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SSZ	Sulfasalazine
TA	Technology Appraisal
TB	Tuberculosis
TNF	Tumour Necrosis Factor
TTP	Time to progression
Tx	Treatment
UK	United Kingdom
VAS	Visual analogue scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health
WTP	Willingness to pay

Table of Contents

Table of Tables

Table of Figures

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The decision problem addressed in the company submission was the same as the final scope issued by NICE. The company submission report presented data which were representative of the patient population, intervention, comparators and outcomes as described in the decision problem.

The searches in the company submission (CS) were well documented and easily reproducible; searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.

There is a degree of uncertainty regarding the prevalence of disease due to the considerable variation in estimates (dependent on which evidence source is used). Whilst this will have no direct bearing on clinical or cost effectiveness, the degree of uncertainty will be important for policy decisions incorporating budget impact analysis.

1.2 Summary of clinical effectiveness evidence submitted by the company

The evidence base for the clinical efficacy of secukinumab 150 mg in the treatment of ankylosing spondylitis (AS) in adults with an inadequate response to conventional care consists of three randomised controlled trials, as identified by a systematic literature review: MEASURE 2, MEASURE 1 and A2209. MEASURE 2 and MEASURE 1 are Phase III randomised controlled trials (RCTs) and comprise the main evidence base for the clinical efficacy and safety of secukinumab presented in this submission.

MEASURE 1 was a two year study with an initiation date of October 2011 which randomised 371 adult patients with moderate to severe disease from 64 centres. In MEASURE 1, treatment of interest comprised secukinumab i.v. (10 mg/kg intravenous) at baseline, week 2 and week 4 then secukinumab 150 mg s.c. starting at week 8 and injected subcutaneously every four weeks. At 16 weeks there were 247 patients with data for analysis (placebo plus intervention of interest).

MEASURE 2 was a five year trial with an initiation date of October 2012 which randomised 222 adult patients with moderate to severe disease from 52 centres. In MEASURE 2, treatment of interest comprised secukinumab 150 mg s.c. plus placebo 75 mg once weekly at baseline, weeks 1, 2, 3 and 4, followed by dosing every four weeks starting at Week 4. At 16 weeks there were 146 patients with data for analysis (placebo plus intervention of interest).

The A2209 study was considered to be an unreliable source of evidence on account of its small size, short duration as well as inconsistencies in study time endpoints and an absence of licensed dose being administered. Table I presents outcomes reported in MEASURE 1 and MEASURE 2 some of which have comparable outcomes in trials included in the MTC.

Secukinumab showed benefit over placebo at both 12 and 16 weeks in MEASURE 2 and at 16 weeks in MEASURE 1 for ASAS 20, ASAS 40, BASDAI 50 and BASDAI change from baseline. In all instances the relative performance of secukinumab at 16 weeks is broadly similar to that achieved at 12 weeks (MEASURE 2). Data at 12 weeks were not reported for BASFI change from baseline, ASAS 5/6 response or SF-36 PCS, but at 16 weeks, secukinumab also showed benefit over placebo in both MEASURE 1 and MEASURE 2 for these outcomes. For most other outcomes (where no results from mixed treatment comparison are available, i.e. comparisons with other trials were not made)

secukinumab showed benefit over placebo at 16 weeks in both MEASURE 1 and MEASURE 2. One exception was ASAS partial remission where there was no significant difference between secukinumab and placebo in MEASURE 2, whereas there was in MEASURE 1. [redacted]

Table I: Outcomes from MEASURE 1 and MEASURE 2 at 16 weeks

Outcomes	**MEASURE 1**		**MEASURE 2**	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
Analysed for MEASURE 1, MEASURE 2 and other trials in MTC				
ASAS 20	60.8% (OR 3.89; 95% CI 2.28 to 6.65)	28.7%	61.1% (OR 4.38; 95% CI 2.14 to 8.96)	28.4%
ASAS 40	41.6% (p<0.0001)	13.1%	36.1% (p<0.001)	10.8%
BASDAI 50	37.6% (p<0.0001)	8.2%	30.6% (p<0.01)	10.8%
BASDAI change from baseline	-2.32, SE 0.172 [n=121]	-0.59, SE 0.180 [n=108]	-2.19, SE 0.248 [n=67]	-0.85, SE 0.252 [n=64]
BASFI change from baseline	-1.84, SE 0.17 [n=121]	-0.37, SE 0.17 [n=108]	-2.15, SE 0.23 [n=67]	-0.68, SE 0.24 [n=64]
ASAS 5/6 response	48.8% (p<0.01)	13.1%	43.1% (p<0.001)	8.1%
SF-36 PCS	5.57, SE 0.59 [n=122]	0.96, SE 0.61 [n=111]	6.06, SE 0.78 [n=67]	1.92, SE 0.79 [n=66]
Analysed for MEASURE 1 and MEASURE 2 only				
ASAS partial remission	15.2% (p<0.01)	3.3%	13.9% (p=0.0941)	4.1%
ASDAS-CRP [major improvement]	[redacted]	[redacted]	[redacted]	[redacted]
Patient's global assessment of disease activity	-27.98, SE 2.030 [n=121]	-6.64, SE 2.130 [n=108]	-27.69, SE 2.83 [n=67]	-12.87, SE 2.89 [n=64]
BASMI	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	**MEASURE 1**		**MEASURE 2**	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
linear change from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral symptoms measured via MASES score change	[redacted]	[redacted]	[redacted]	[redacted]
Health-related quality of life (ASQoL) – using MMRM	-3.58, SE 0.424 [n=121]	-1.04, SE 0.437 [n=111]	-4.00, SE 0.528 [n=66]	-1.37, SE 0.53 [n=66]
Health-related quality of life (FACIT-Fatigue)	[redacted]	[redacted]	[redacted]	[redacted]
Health-related quality of life (MCS)	[redacted]	[redacted]	[redacted]	[redacted]
Hs-CRP change from baseline	0.40, SE 1.090 [n=121]	0.97, SE 1.095 [n=107]	0.55; SE 1.104 [n=68]	1.13, SE 1.105 [n=66]
Percent work time missed due to health (WPAI-GH)	[redacted]	[redacted]	[redacted]	[redacted]
Percent impairment while working due to	[redacted]	[redacted]	[redacted]	[redacted]

Outcomes	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
health (WPAI GH)				
Percent overall work impairment due to health (WPAI-GH)	[redacted]	[redacted]	[redacted]	[redacted]

ASAS = Assessment of Spondyloarthritis; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; CI = confidence interval; CRP = c-reactive protein; FACIT = Functional Assessment of Chronic Illness Therapy; hs = high sensitivity; i.v. = intravenous; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MCS = mental component score; mg = milligram; MMRM = Mixed-effect model repeated measures; MTC = Mixed treatment comparison; OR = Odds ratio; PCS = Physical component score; s.c. = subcutaneous; SD = standard deviation; SE = standard error; SF-36 = Short form 36; WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health

Mixed treatment comparison was used to compare the effectiveness of secukinumab 150 mg s.c. against other treatments for ankylosing spondylitis. The proportion of patients who achieved an ASAS 20 response was modelled as a binomial endpoint based on a network including nine studies comparing nine treatments pooling data reported at 12-16 weeks in the whole population. [redacted]

The proportion of patients who achieved an ASAS 40 response was modelled as a binomial endpoint based on a network including nine studies comparing nine treatments pooling data reported at 12-16 weeks in the whole population. [redacted]

[redacted]

The proportion of patients who achieved a BASDAI 50 response was modelled as a binomial endpoint based on a network including seven studies comparing eight treatments pooling data reported at 12-16 weeks in the whole population[redacted]

The change from baseline in the BASDAI score was modelled as a continuous endpoint based on a network of nine studies comparing nine treatments pooling data reported at 12-16 weeks in the whole population.

[redacted]

The change from baseline in the BASFI score was modelled as a continuous endpoint based on a network of nine studies comparing nine treatments pooling data reported at 12-16 weeks in the whole population.

[redacted]

[redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The evidence presented is relevant to the scope of the decision problem.

It is not clear how mild or early AS has been identified nor why mild or early AS has been excluded from literature searches since *"there is no agreed consensus on the terms used to classify the severity of AS"* according to the response to request for clarification. Therefore, the only legitimate severity-based exclusion should have been non-active AS.

The screening phases of study selection were compliant with recognised guidelines but data extraction methods were not. The processes outlined in the CS fall short of this standard in two regards. Firstly only one reviewer was used in the process and secondly abstracts or posters were only used when these were the terminal source, which is not advised since they may still include relevant and unique outcomes even when they are not the terminal source. Therefore, there is a chance that relevant data might have been missed or extracted incorrectly.

There is no comment within the CS as to how quality assessment was undertaken. Best practice would have been for more than one person extract data from every report to minimise errors and reduce potential biases. However, the ERG has reviewed the quality assessment of MEASURE 1 and MEASURE 2 and is in agreement with the company's assessment.

The ERG notes that MEASURE 1 is based on intravenous administration of secukinumab, whereas MEASURE 2 is based on subcutaneous administration. This is recognised by the company as being a potential limitation of the evidence, with MEASURE 1 loading dosage not being reflective of the subcutaneous loading schedule. The ERG agrees with the company, that, although not ideal, inclusion of MEASURE 1 seems reasonable in the light of limited evidence for subcutaneous administration.

The company did not provide comparable 12 week effectiveness data for all outcomes specified in the scope. This means that comparisons at 16 weeks for MEASURE 1 and MEASURE 2 with trials reporting outcomes after 12 weeks should be viewed with a degree of scepticism. This being said, the performance of secukinumab in relation to placebo seems relatively stable between 12 and 16 weeks for the main outcomes the ERG has been able to assess from MEASURE 2.

The selection of studies for inclusion in the MTC appears to be appropriate and the application of the MTC methodology seems to be correct. There are some potential limitations which may lead to bias in the results. The quality assessment of the studies included in the MTC highlighted a potential imbalance between treatment arms at study onset in three studies. In two of these three studies patients in the placebo arm had less severe disease than those patients randomised to active treatment.

The effect of this imbalance is difficult to predict. The base case MTC analysis pooled data from time points between 12 and 16 weeks based on the primary endpoint of the individual studies. This creates a potential bias in favour of those treatments in studies with longer endpoints. The sensitivity analysis reported in the CS which limited analysis to only data reported at 12 weeks showed reduced effectiveness for secukinumab for most outcomes.

The base case MTC analysis reported results from a fixed effect model based on the justification that there was no difference in the DIC statistic between fixed or random effects models and that a random effects model was not mathematically feasible in some cases. The difficulty in obtaining results from random effects is likely to be a result of the small number of studies for each treatment comparison in the evidence networks. This means that the variation between studies is estimated based on a small number of data points. Although the estimation of the variability in the treatment effects is difficult due to the lack of data it is unlikely that the variability is zero as defined in a fixed effect model. The use of a fixed effect model is likely to underestimate the true variation in the treatment effects.

1.4 Summary of cost effectiveness evidence submitted by the company

The population of the cost effectiveness analysis was the adult population of patients with active AS, for whom conventional therapy (i.e. non-steroidal anti-inflammatory drugs alongside physiotherapy), or prior biologic therapy, has been inadequately effective or not tolerated.

For the biologic naïve population, all anti TNF-alphas were considered as secukinumab's comparators, including available biosimilars of infliximab and etanercept. For the biologic experienced population, conventional care was the only comparator. A National Health Service (NHS) and Personal and Social Services (PSS) perspective is adopted with a lifetime time horizon. Discount rates used for costs and quality-adjusted life years (QALYs) were 3.5%

The cost effectiveness model was a decision tree representing the induction period embedded to a Markov model representing the post induction period. If a patient responds to a treatment s/he enters maintenance therapy, otherwise s/he receives conventional care. While the structure was similar for the biologic naïve and experienced populations, the input parameters were different.

Treatment effectiveness was modelled via short/long term changes in BASDAI and BASFI scores and treatment response at the end of the induction period. Response conditional BASDAI and BASFI short term changes were applied on the response conditional baseline scores. It was assumed that after initial improvement, the BASDAI score remains constant whereas the BASFI score increases slowly. For patients on biologics, it is assumed that the annual rate of BASFI progression was smaller. After biologic discontinuation, it is assumed that patients lost all the initial BASFI improvements. The BASDAI and BASFI score per cycle are instrumental in calculating that cycle's state costs and QALY estimates.

Regression models (a utility mapping model derived from MEASURE 1 and MEASURE 2 as the base case) and other published models in the literature were used to translate BASFI/ BASDAI to cost/ QALY estimates

Data from MEASURE 1 and 2 trials were used for secukinumab effectiveness. Comparative effectiveness estimates of secukinumab with other biologics in terms of BASDAI 50 and BASDAI/BASFI change from baseline were obtained via separate MTCs. In these MTCs, two possible options were available for selecting response assessment time points (strictly week 12 or

between weeks 12-16). In addition to these, some conversion factors were derived from MEASURE 1 and 2 trials to transform the response probability and the change from baseline estimates from one response definition to another.

In the company base case, the response definition was chosen as "BASDAI 50", the base case used MTC inputs synthesised data from time points between weeks 12-16, and used secukinumab data from both MEASURE 1 and MEASURE 2. The company base case used withdrawal rates that were separately derived for each comparator.

In the company base case for the biologic naïve population, secukinumab dominated all anti Tumour Necrosis Factor (TNF) alpha agents except for golimumab (which had an ICER of £674,914 per QALY). For the biologic experienced population, the ICER estimate was around £2,200 per QALY gained

Next to the base case scenarios, two exploratory analyses were conducted. The first one was to estimate the impact of allowing for a second line biologic treatment for biologic naïve patients. The second analysis focused on the comparison of secukinumab with other anti TNF-alpha agents for the biologic experienced population. Both of the analyses resulted in similar ICERs as in the base case. After exploratory analyses, probabilistic sensitivity and scenario analyses were conducted. In most of the scenarios secukinumab was either dominant or demonstrated lower costs and lower QALYs compared to other biologics, where the ICER for the other biologics would be higher than £20,000/QALYs.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG deemed that the revised model (provided by the response to the clarification letter) was generally well reported. The major errors identified by the ERG in the original CS model had already been corrected in the revised model. However, the ERG still identified additional programming errors in the revised model, which were minor and mostly concerned the outcomes of the exploratory/scenario and probabilistic sensitivity analyses. These errors did not impact the estimates of the deterministic ICERs for the base case scenarios.

The population of the cost effectiveness analysis seems to be broadly in line with the scope. Some of the biologic comparators of secukinumab were licensed only for severely active AS, which may potentially create a bias if their effectiveness is based on populations which include non severely active AS patients.

For the treatment naïve population, all anti TNF-alphas were considered as secukinumab's comparators, including available biosimilars of infliximab and etanercept. For the biologic experienced population, conventional care was the only comparator. The ERG considers that other biologics should be also considered as comparators to secukinumab in the biologic experienced population.

The model structure represents clinical practice for first line biologic treatment, but the model did not allow for comparing biologic treatment sequences, which is a limitation considering the increasing number of biologics available for this indication.

Regression models (utility mapping model derived from MEASURE 1 and MEASURE 2 trials as the base case) were used to translate BASFI/ BASDAI to QALY estimates. Unfortunately, the details of

the utility mapping model and the model selection procedure were not provided by the company despite the request from the ERG.

Data from MEASURE 1 and 2 trials were used for secukinumab effectiveness. In MEASURE 1, loading doses of secukinumab were administered intravenously whereas it was licensed to be administered subcutaneously.

In the modelling of the BASFI and BASDAI progression, response conditional baseline scores were used. In many of the baseline scores, it was observed that the responders had lower (better) baseline scores than non-responders. This might imply that patients with a better condition (with lower BASDAI/BASFI scores) would benefit more from the treatment than the patients at a worse condition (with higher BASDAI/BASFI scores). This implication was criticised by the appraisal committee of the National Institute for Health and Care Excellence (NICE) Technology Appraisal (TA) 383.

In addition, the response conditional baseline values and the conversion factors used in transforming effectiveness parameters (e.g. in between different response definitions) were all calculated based on MEASURE 1 and 2 trial data collected from a fixed time point (week 12 or week 16). Hence, these values remain unchanged when MTC approaches with different time point assumptions were selected.

The ERG considers that the independent evidence synthesis approach for these dependent parameters (BASDAI, BASFI baseline and change from baseline estimates and BASDAI 50) are not plausible. These parameters are correlated and the independent synthesis approach followed by the company overlooks the very high correlation between these parameters. Due to this independent approach, the model generates sometimes unreasonable estimates (e.g. change from baseline estimates that are sometimes higher than the baseline scores, response conditional BASDAI change from baseline is less than 50% of the baseline BASDAI even though response was defined as "BASDAI 50" etc.).

To overcome this issue, the ERG requested results from the joint modelling approach based on the York model. However, the results provided in the response to the clarification letter used data from a mixed population (biologic naïve and experienced) and the time point(s) when the response was measured were not reported. Therefore, the ERG could not base the ERG base case analysis on the provided results from the joint evidence synthesis results. In spite of the limitations of the joint evidence synthesis results, instead the ERG conducted a scenario analysis, in which the treatment effectiveness of the biologics and secukinumab were based on these results.

In the company base case, the response definition was chosen as "BASDAI 50", MTC inputs synthesising data from time points between weeks 12-16 were selected and data from both MEASURE 1 and MEASURE 2 were used for secukinumab effectiveness. The ERG thinks using MTC inputs based on time points between week 12 and week 16 would be inconsistent with the economic model, because the induction period was strictly 12 weeks. Furthermore, this would create a bias against interventions which had effectiveness evidence coming only from week 12, as these interventions would lack the additional effectiveness benefit that the other interventions have from the extra weeks of treatment after week 12. Therefore the ERG opted for the inputs from MTCs that use data coming from strictly week 12.

The other questionable input choice was how the withdrawal rates were selected in the original CS base case. The ERG was in favour of using the same withdrawal rate derived in the York Multiple

Technology Appraisal (MTA) report for all biologics instead of using separately derived withdrawal rates for each intervention as in the CS.

A similar issue also arose for the adverse event rates, since the adverse event rates were derived separately for each intervention. However, the ERG decided not to update the CS base case rates considering the limited impact on incremental results.

Note that the MTCs do not produce results for all of the comparators in the biologic naïve population. For example treatment effectiveness of certolizumab pegol was assumed to be the average of the other anti TNF-alpha treatments, since there is no trial for certolizumab pegol that reports its effectiveness in biologic naïve patient populations. Even though this approach was approved by the clinical experts from the UK, it should be kept in mind while interpreting the cost effectiveness results.

Two exploratory analyses were conducted to estimate the impact of allowing for a second line biologic treatment for biologic naïve patients, and the comparison of secukinumab with other anti TNF-alpha agents for biologic experienced population. Both of the analyses resulted in similar ICERs as the base case ICER for biologic naïve population, because in both of the exploratory analyses, the treatment effectiveness data for the biologics used in the second line originated from the same MTC results used in the base case for the biologic naïve population. The only difference is that the efficacy reduction factors derived from the MEASURE 1 and 2 trials were applied. Therefore, these exploratory analyses were not very informative.

Another ambiguity concerning the reduction factors from MEASURE 1 and 2 is as follows: these factors may reflect the reduction in secukinumab effectiveness when secukinumab was applied after an anti-TNF-alpha. However, it is questionable to assume that anti TNF-alpha effectiveness would reduce with the same proportion after secukinumab or after another anti TNF-alpha, since these are different drug classes.

After exploratory analyses, probabilistic sensitivity analyses were conducted. The ERG found some errors in the probabilistic sensitivity analysis (PSA) code of the original model, which were causing the average PSA results to differ from base case deterministic results substantially. The ERG corrected these errors in the PSA code, which lead to more plausible average PSA results. Even though average PSA results are comparable to the deterministic base case results after corrections from the ERG, using PSA results may still be misleading, since the existing correlation in baseline BASDAI/BASFI, BASDAI/BASFI change from baseline and BASDAI 50 inputs were not reflected as they were sampled independently.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal. The company's submission and response to clarification provided sufficient details for the ERG to appraise the searches. Literature screening within the evidence review was also undertaken to reasonable standards and the ERG agrees with the company's assessment of quality for MEASURE 1 and MEASURE 2 trials. Supporting evidence used to assess quality is well documented and quality of the trials themselves suggests a low risk of bias.

Overall, the CS is well presented and in line with the final scope. The ERG consider it particularly helpful to include infliximab as a legitimate comparator, even though until prior to February 2016 the drug was not recommended for use in the population. Inclusion of this comparator is seen as conservative to secukinumab.

The model structure was based on the York model, which was clinically validated and used in previous NICE TA383. EQ-5D data were available from the clinical studies to inform the utilities used in the model, thus providing good quality evidence for the cost effectiveness analysis. Extensive sensitivity and scenario analyses were performed, showing the robustness of the results.

1.6.2 Weaknesses and areas of uncertainty

The searches employed in some of the Cochrane databases included unnecessary study design filters. The processes used to determine study quality and to extract data did not adhere to recognised international standards (Cochrane Handbook). Only one reviewer, rather than a minimum of two, was used in data extraction and quality assessment processes. Additionally, abstracts or posters were only used when no full text paper was available. Therefore, there is a chance that relevant data might have been missed or extracted incorrectly.

The company did not provide 12 week data but the company had previously provided details after 12 weeks for ASAS 20, ASAS 40, BASDAI 50, and BASDAI change from baseline for MEASURE 2 only as appendices to the MEASURE 2 clinical study report. This means that comparisons with other trials reporting outcomes after 12 weeks should be viewed with a degree of scepticism. This being said, the performance of secukinumab in relation to placebo seems relatively stable between 12 and 16 weeks for the main outcomes the ERG has been able to assess from MEASURE 2. Lack of evidence from MEASURE 1 at 12 weeks further weakens the evidence base.

The ERG feels there is considerable uncertainty surrounding prevalence estimates and that this is an area for future research.

Uncertainty surrounds the severity of patients between trials and within trials, which brings into question their comparability. The company suggested in its response to clarification that "*there is currently no consensus on the definitions of mild, moderate or severe ankylosing spondylitis (AS). The classification of AS continues to be a topic of debate and the absence of agreed terminology means that the relevance and importance of this classification is unclear"*. Aside from issues surrounding evidence comparability, the issue is problematic in two further regards. Firstly, screening of title and abstracts was undertaken with instructions to exclude evidence relating to mild or early AS. If there is inherent uncertainty over severity definitions then one cannot be certain that such exclusion is appropriate. The ERG is sympathetic to the approach taken by the company but perhaps this uncertainty should have been acknowledged. The ERG notes that the Equality Impact Assessment for TA383 mentions, as part of the appraisal scoping process, that "*people with severe disease are currently not allowed to switch to second TNF-alpha inhibitor if their disease does not respond to their first TNF-alpha inhibitor"*. However, the ERG is not aware that this applies to patients with non-severe forms of the condition.

The evidence synthesis approach that was followed in the CS synthesised BASDAI, BASFI and BASDAI 50 separately. This approach may overlook the correlations between the treatment effectiveness parameters and may contribute to implausible outcomes such as having a BASDAI decline from the baseline higher than the baseline itself.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG defined a new base case analysis. This new ERG base case included the following adjustments:

- Biologic naïve population:
  - Errors confirmed and corrected by the company
  - Programming/coding errors relating to the conversion factor estimates and other errors (these do not have an impact on the base case cost effectiveness analyses)
  - Using MTC#3 for BASDAI 50 response rate and change from baseline estimates (MEASURE 1 and MEASURE 2, using week 12 data)
  - Choice of MTC withdrawal rates from York model
- Biologic experienced population:
  - Errors confirmed and corrected by the company
  - Programming/coding errors relating to the conversion factor estimates (do not have an impact on the base case cost effectiveness analyses)
  - Using week 12 response data instead of week 16 from MEASURE 1 and MEASURE 2. (14/61 for secukinumab and 5/62 for conventional care)
  - Choice of MTC withdrawal rates from York model

The ERG decided to keep the other assumptions of the base case analyses from the updated model sent in the response to the clarification letter. Even though the ERG has reservations especially around the assumptions concerning how the treatment effectiveness is modelled, it was considered best to follow the base case and show the impact of the questionable assumptions in the scenario analyses.

We observe that the ERG base case leads to substantially different results than the company base case, without materially changing the acceptability of secukinumab given the common threshold of £20,000 to £30,000 per QALY gained. Overall, secukinumab remains cost-saving, as was observed in the company base case. However, for some of the comparators, secukinumab no longer yields higher QALYs, meaning that a trade-off needs to be made between cost-saving and loss of QALYs.

Additional scenario analyses were conducted by the ERG to explore the structural uncertainties in the assumptions taken in the base case.

The scenario analysis results show that etanercept (both original and biosimilar version) is associated with lower QALYs and higher costs versus secukinumab in all scenarios.

Infliximab (both original and biosimilar version) is associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for infliximab versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained.

Adalimumab, golimumab and certolizumab pegol are mostly associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for comparator versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained. For the scenarios in which different treatment effectiveness inputs were used (e.g. from different MTCs), secukinumab dominates these treatments (i.e. secukinumab provides higher QALYs with lower costs). Results are generally robust in terms of the value for money of secukinumab.

2 BACKGROUND

2.1 Introduction

This Chapter presents an overview of ankylosing spondylitis (AS) and its management. The content is based on information presented in Section 3 of the company submission (CS) "Health condition and position of the technology in the treatment pathway".[1] Further information on prevalence, signs and symptoms, disease burden, eligible population and life expectancy can be found on pages 35 to 38 of the CS while additional information on treatment pathways and existing NICE guidance can be found on pages 38 to 41.[1]

2.2 Critique of company's description of underlying health problem

The CS describes AS as *"...a progressive arthritic disease that afflicts patients of working age, causing pain and severe physical impairments that negatively impact on quality of life and social functioning".*

Clinical features associated with AS include inflammatory back pain, inflammation of spinal joints (sacroiliitis and enthesitis), peripheral arthritis and restricted spinal flexibility as a result of joint fusion (ankylosis). The large peripheral joints (hips, shoulders and knees) may also be involved, and the eyes and cardiovascular system can also be affected. [CS reference 58-60] The disease is further characterised by inflammation of the sacroiliac joint at the base of the spine (sacroiliitis). [CS reference 54] Chronic inflammation along the spine leads to back pain and stiffness which places a considerable burden on patients in terms of physical impairment, pain, quality of life and social functioning. [CS reference 69]

Age of onset is typically between the ages of 17–35 years, with 90-95% of cases diagnosed before the age of 45 years but symptoms often present years before a formal diagnosis - which requires radiographic evidence of sacroiliitis. [CS reference 55-57] AS is three times more common in men than in women, and men are also more likely to have more severe disease. [CS reference 76]

The CS suggests that the cause of AS remains unknown.[2] A recent systematic review undertaken by Maxwell et al. suggested that the aetiology of the disease has a strong association with the gene HLA-B27 and that is about 2% in those of those positive for HLA-B27.[3] No validated molecular biomarkers have been identified as being associated with AS diagnosis or disease activity, but there is evidence to suggest a key role for pro-inflammatory cytokines such as IL-17A in AS pathophysiology. [CS reference 70-71]

The CS suggests that exact prevalence of AS in the UK is not known and estimates are found to vary considerably. In Europe the prevalence is estimated to be 23.8 cases per 10,000 (18.6 per 10,000 when weighted for study design). [CS reference 51] According to data from the Department of Health in 2006, the number of patients diagnosed with AS was 200,000. [CS reference 72] An alternative estimate from the NICE Biologics Commissioning Guide (2012) estimates 70,000 cases of AS in England, based on AS prevalence estimates provided by the British Society for Rheumatology (BSR) guidelines in 2004 – from 500 to 1,000 cases in a community of 500,000 adults.[4] The CS suggests that figures are an underestimate of the real prevalence of AS, in part due to a mean diagnostic delay of 8.57 years [CS reference 73-74] and that approaches to earlier diagnosis offer the opportunity of improving estimates.

ERG comment: The definition of AS is consistent with that used in other NICE appraisals, i.e. *"Ankylosing spondylitis is a progressive and irreversible condition causing a great deal of pain and discomfort and impacting on an individual's ability to go about their daily life"*.[5]

The ERG believes that the company's description of the underlying health problem is appropriate and relevant to the decision problem under consideration. Further thought could have been given to defining what is meant by inadequate responses to conventional therapy (including a focus on defining what is meant by "intolerant" and the proportion of patients who might be described as such).

The ERG feels that more detailed discussion of prevalence estimates would have been appropriate in the background section, given the huge variation found in estimates and the potential budget impact of such variation. On the one hand, based on figures quoted in the CS, the ERG (and the company) estimates prevalence for the UK of 42.1 per 10,000 (200,000 cases and ONS population estimates of 47.5 million adults resident in the UK in 2006). On the other hand, the ERG also calculates a prevalence estimate of 16.6 per 10,000 for England (based on ONS estimate of population for England of 42.1 million in 2012 and 70,000 cases estimated in NICE Biologics Commissioning Guide 2012). Additionally, in response to clarification questions, the company has suggested that an estimate of 42,1 cases per 10,000 is a similar order of magnitude to alternative European prevalence estimates of 23.8 cases per 10,000.[6] Whilst the ERG agrees with the company that this is the case, it should be noted that, on those prevalence estimates, the UK would have had 870,000 more cases than might be expected at the European prevalence level (equivalent to 77% more than expected). The estimate for England is also of a similar order of magnitude to the European estimate but, in this instance, England would have had 302,000 less cases than might be expected at the European prevalence level (equivalent to 30.1% less than expected).

The CS includes a statement *"The Commissioning Guide estimates that there are approximately 20,000 patients with AS in England eligible for treatment with biologic treatment"*. [CS reference 39] However, on review, the ERG found that the cited reference was not the Commissioning Guide and does not refer to 20,000 patients. The only reference to a Commissioning Guide was a high level link with no reference to a figure of 20,000. [CS reference 84] In the absence of further information, the ERG was unable to check these numbers.

2.3 Critique of company's overview of current service provision

The CS states that conventional care in the UK for patients with AS is treatment with non-steroidal anti-inflammatory drugs (NSAIDs) alongside non-pharmacological pain relieving interventions like physiotherapy. The CS suggests clinical concerns about side effects associated with long term use of NSAIDs, particularly with mean delays from onset of symptoms to diagnosis of 8.57 years during which time patients may have been regularly using NSAIDs. In the case of adults whose disease has responded inadequately to or who cannot tolerate NSAIDs, the CS reports on a recent Multiple Technology Appraisal (MTA; TA 383), which recommends, in such circumstances, the use of TNFα inhibitor biologic therapies (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), within their marketing authorisations, for the treatment of severe active AS in adults.[7] This recommendation can be viewed in the context of other treatment guidelines including those issued by the BSR in 2005. [CS reference 39] These guidelines recommend the use of TNFα inhibitor therapy when patients have failed conventional treatment (two or more NSAIDs each taken sequentially at maximum tolerated/recommended dosage for four weeks) in patients who have a diagnosis of AS according to the modified New York criteria, where AS is active (Bath Ankylosing Spondylitis

Disease Activity Index (BASDAI) ≥4 cm and spinal pain visual analogue scale (VAS; last week) ≥4 cm noted on two occasions at least four weeks apart without any change of treatment) .

ERG comment: The ERG believes that the company's overview of current service provision is largely appropriate and relevant to the decision problem under consideration. A point regarding the inclusion of infliximab is discussed below.

However, one concern is that switching between TNF inhibitors has not been considered as part of current service provision. Emery et al. 2012 suggest *"inadequate response to one TNF inhibitor does not preclude response to another"* and consequently that *"...the prescribing physicians of a large proportion of patients who achieve only a partial response are likely to try other therapeutic options, such as switching to another TNF inhibitor or a new class of agent in an effort to help patients gain a better response"*.[8]

Although comments by Emery et al. refer to patients with rheumatoid arthritis, the company should have discussed whether the same behaviour reflects current service provision for adults with active ankylosing spondylitis for whom NSAIDs or TNFα inhibitors have been inadequately effective or not tolerated. Interestingly, Section 5.2.2 of the CS suggests that, as part of the assessment of cost effectiveness, expert clinical feedback was gathered during model development which suggested that 75% of patients might be expected to use an alternative biologic therapy after failure of a first.[6] Perhaps this information should have been cross-referenced in the overview of clinical effectiveness.

3 Critique of company's definition of decision problem

Table 3.1: Summary of the decision problem
(Based on table 1 of the CS[1])

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active ankylosing spondylitis for whom non-steroidal anti-inflammatory drugs, or TNFα inhibitors have been inadequately effective or not tolerated.	This submission considers the population of adult patients with active AS for whom conventional care has not been effective (biologic naïve population) or for whom conventional care and TNFα inhibitors have not been effective (biologic inadequate responder [IR] population)	NA
Intervention	Secukinumab	Secukinumab 150 mg	NA
Comparator(s)	TNFα inhibitors For people whose disease has responded inadequately to, or who are intolerant to TNFα inhibitors: • Established clinical management without secukinumab	Biologic naïve population: TNFα inhibitors Biologic experienced population: • Conventional care (base case): i.e. having discontinued their first biologic, patients move to conventional care • TNFα inhibitors and conventional care (exploratory analysis): i.e. having discontinued their first biologic, patients can move to either conventional care or a TNFα inhibitor	There are no formal guidelines on sequencing of biologics (i.e. administering a second biologic following discontinuation of an initial biologic therapy), and there is a lack of robust clinical data to support use of the TNFα inhibitors in the biologic experienced population, as acknowledged by the Assessment Group as part of the NICE MTA in AS and supported by the systematic literature review in Section **Error! Reference ource not found.** of the CS.[7, 9] Therefore, for the biologic experienced population conventional care is considered to represent established clinical management. Comparison to biologics in this population is included as an exploratory analysis.
Outcomes	• Disease activity • Functional capacity	• Disease activity (ASAS20; ASAS40; BASDAI 50; BASDAI change from baseline; ASAS 5/6; ASAS partial remission; ASDAS-CRP [major	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Disease progression • Pain • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • Symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • Adverse effects of treatment • Health-related quality of life.	improvement]; hsCRP change from baseline; patient's global assessment of disease activity) • Functional capacity (BASFI change from baseline; BASMI linear change from baseline) • Disease progression (mSASS; MRI outcomes) • Pain (as captured by ASAS and BASDAI criteria) • Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) (MASES) • Symptoms of extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis (captured under safety reporting) • Adverse effects of treatment • Health-related quality of life (ASQoL, EQ-5D, SF-36 PCS and MCS, FACIT-Fatigue) • Impairment in work and activities (WPAI-GH)	
Economic analysis	• Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). • The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	• Cost effectiveness analysis results expressed as incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY • Lifetime time horizon: a lifetime time horizon is consistent with previous models in AS, including the recent MTA of biologic therapies.[7] AS is a chronic, progressive life-long condition for which there is no cure. The mean age of patients entering the model is 42.37; a 58-year time horizon is therefore appropriate to capture the lifetime of patients, as all patients within the model are assumed to die by age 101. This assumption is consistent with the fact that only 0.02% of the overall UK population survive to reach centenarian status. [CS reference 21]	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• NHS and Personal Social Services (PSS) perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	• The perspective of the NHS and PSS is used. • Patient access schemes for secukinumab, certolizumab pegol and golimumab 100 mg are taken into account.	
Other considerations	If evidence allows, the appraisal should consider people who have or have not had TNFα inhibitors	The decision problem addressed by the economic analysis considers both the population of patients who are biologic naïve and the population of patients who are biologic experienced	NA

AS = Ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; EQ-5D = EuroQol 5D questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; (hs)CRP = (high sensitivity) C-reactive protein; ICER = incremental cost-effectiveness ratio; IR = inadequate responder; SF-36 PCS = Short Form 36 Physical Component Summary; MCS = Mental Component Summary; mg = Milligram; MRI = magnetic resonance imaging; mSASSS = Modified Stoke Ankylosing Spondylitis Spinal Score; MTA = Multiple Technology Appraisal; NA = not applicable; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; TNFα = Tumour necrosis factor alpha; WPAI-GH = Work Productivity and Activity Impairment Questionnaire – General Health

3.1 Population

The company submission considers the population of adult patients with active AS for whom conventional care has not been effective (biologic naïve population) or for whom conventional care and TNFα inhibitors have not been effective (biologic inadequate responder [IR] population).

ERG comment: Whilst the ERG feels that the clinical evidence submitted by the company broadly matches the final scope[10], there are three concerns. One concern relates to the way severity is handled, another to lack of distinction between non-response and intolerance, and the third to a possible mismatch between the company's summary of the decision problem (Table 1 of the CS) and the eligibility criteria for title and abstract screening for generation of evidence (Table 6 of the CS).

There are references throughout the CS to mild (see Table 6 – lists of criteria for inclusion and exclusion of studies), moderate and severe forms (see Table 8 – summary of literature references) of AS but these terms are not clearly defined nor is current service provision considered in respect of these different forms of AS. With regard to the *"mild or early form of AS"*, it is not clear why this group is incompatible with *"adults with active ankylosing spondylitis for whom NSAID or TNF-alpha inhibitors have been inadequately effective or not tolerated"*. It is not known whether papers were excluded according to this criterion, but if this was the case then potentially important evidence might have been missed.

In response to clarification, the company suggested that there is no agreed consensus on terminology used to clarify the severity of AS.[6] Lack of information on the severity of patients, using universally recognised methods, means there must be a degree of uncertainty on the comparability of trials.

On page 23 of the CS, the populations in MEASURE 1 and MEASURE 2 are described: *"Both trials included pre-specified sub-groups; firstly, patients naïve to prior TNFα inhibitor treatment and secondly patients who had either experienced an inadequate response to prior TNFα inhibitor treatment or who had been intolerant to at least one administration of a TNFα inhibitor agent: referred to hereafter as the TNFα inadequate responder (IR) population"*.[1] This suggests that the TNFα IR population comprises two separate groups, namely "inadequate responders" and "those who had been intolerant". There is no consideration as to whether these two groups are clinically different or whether they might respond differently. There is also no opportunity to explore whether the proportions of those who are intolerant within trials reflects the characteristics of the patient population in England and Wales eligible for treatment.

3.2 Intervention

The CS states that secukinumab is a first-in-class, recombinant, high-affinity, fully human monoclonal anti-human antibody of the IgG1/kappa isotype. Secukinumab holds a marketing authorisation with the European Medicines Agency (EMA) and is therefore licensed for marketing in the European Union.

Table 2 of the CS states that marketing authorisation for secukinumab is for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

ERG comment: The intervention described in the CS matches the intervention described in the final scope. It should be noted that a fixed dose (secukinumab 150 mg) was defined in the summary of the decision problem.

3.3 Comparators

In regard of the biologic naïve population, the CS lists comparators as TNFα inhibitors, i.e. adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®), and infliximab (Remicade®) including any licensed biosimilar products.

In the biologic experienced population, the CS comparators as conventional care, i.e. NSAIDs and physiotherapy. The CS further suggests a lack of data on currently licensed alternative biologics as the reason for not including this as a comparator in this population.

ERG comment: The ERG believes that the company's overview of comparators is appropriate and relevant to the decision problem under consideration. However it notes that, in May 2008, NICE issued guidance that *"Infliximab is not recommended for people with AS"*.[5] However, in a report published in 2016, NICE re-assessed the evidence and have allowed rheumatologists to prescribe infliximab *"if treatment is started with the least expensive infliximab product"*.[7] Given the recentness of latest guidance on infliximab, it is appropriate for it to be included in an overview of current service provision. The ERG believes that inclusion of infliximab as a comparator is conservative to secukinumab and therefore more appropriate than had it been excluded.

The ERG notes that the Equality Impact Assessment for TA383 mentions, as part of the appraisal scoping process, that *"people with severe disease are currently not allowed to switch to second TNF-alpha inhibitor if their disease does not respond to their first TNF-alpha inhibitor"*.[11] However, the ERG is not aware that this applies to patients with non-severe forms of the condition. Lack of evidence on the proportions of patients with moderate and severe forms of the disease means it is difficult to assess the impact of omitting switching. The CS suggests that a lack of data on currently licensed alternative biologics was a reason why this form of treatment was not considered as a comparator. However, there is little evidence of attempts being made to elicit clinical opinion on this which, at least, might have helped with scoping such treatment scenarios.

3.4 Outcomes

The company has assessed the following outcomes:

- Disease activity (Assessment of Spondyloarthritis (ASAS)-20; ASAS40; BASDAI 50; BASDAI change from baseline; ASAS 5/6; ASAS partial remission; ASDAS- c-reactive protein (CRP) [major improvement]; hsCRP change from baseline; patient's global assessment of disease activity)
- Functional capacity (Bath Ankylosing Spondylitis Functional Index (BASFI) change from baseline; Bath Ankylosing Spondylitis Metrology Index (BASMI) linear change from baseline)
- Disease progression (modified Stoke Ankylosing Spondylitis Spine Score (mSASSS; magnetic resonance imaging (MRI) outcomes)
- Pain (as captured by ASAS and BASDAI criteria)
- Peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) (Maastricht Ankylosing Spondylitis Enthesitis Score (MASES))
- Symptoms of extra-articular manifestations including uveitis, inflammatory bowel disease and psoriasis (captured under safety reporting)
- Adverse effects of treatment

- Health-related quality of life (Ankylosing Spondylitis Quality of Life (ASQoL), European Quality of Life-5 Dimensions (EQ-5D), short form 36 (SF-36) physical (PCS) and mental component score (MCS), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue)
- Impairment in work and activities (Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH))

ERG comment: This matches the outcomes described in the final scope and is a comprehensive list of appropriate outcomes.

3.5 Economic analysis

ERG comment: As can be seen in Table 3.1 above, the decision problem addressed by the company matches the final scope.

3.6 Other relevant factors

Two potential equity considerations were explored in this submission, one relating to patient assessments and the other potential needle phobia.

In the case of patient assessments, guidance in TA143 was cited and followed namely *"...there are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease (...) In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances"*. [CS reference 37]

In the case of needle phobia, the company suggest that the SensoReady® pen has features that may aid injection in patients with needle phobia, thereby avoiding any inequity. The SensoReady® pen has been shown to result in high patient acceptability in studies evaluating secukinumab in patients with psoriasis.

ERG comment: The section relating to patient assessments is difficult to follow. The ERG assumes that the issue is the same as that referred to in a recent equality impact assessment (TA 383)[11], namely that for people with physical, sensory or learning disabilities or communication difficulties, it may not always be easy to BASDAI and spinal pain VAS scores. These scores are the usual way of defining whether response is adequate or not. In such circumstances, it is acknowledged that clinicians can use a wider judgement than just "scores" when interpreting concepts like response. This means that access to the drug for such patients will not be unfairly restricted. This is the ERG's interpretation of the issue within the CS.

[redacted]

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Description of company's search strategies and critique

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[12] The submission was checked against the Single Technology Appraisal (STA) specification for company/ sponsor submission of evidence.[13] The ERG has presented only the major limitations of each search strategy in the main report.

Clinical effectiveness

The company submission states that a systematic literature review (SLR) was conducted to identify relevant clinical evidence for the use of secukinumab and relevant comparators in the treatment of active AS. Searches were initially undertaken in January 2015 and updated in September 2015. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, BIOSIS and the Cochrane Library. In addition online congress abstracts for the European League Against Rheumatism, National Ankylosing Spondylitis Society, American College Rheumatology and British society of Rheumatology were searched for the last three years (2013-2015). Searches of the EMA European Public Assessment Reports, ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) were also undertaken. These meet the requirements specified in current best practice guidance as detailed in NICE guide to the methods of technology appraisal.[14] Search strategies for the database searches were provided in Appendix C of the company submission and are well reported and reproducible. Strategies for the congress searches and trials searches were not included in the CS, however the strategies for ClinicalTrials.gov and ICTRP were provided following a clarification request.

The database hosts for each database and the date search conducted were listed, however a specific date span for each database was not provided. In response to a clarification request, the company stated that the databases were searched from inception to the search dates above; database inception dates for PubMed, EMBASE and BIOSIS were provided. These details are important in the search methodology for reproducibility purposes as different databases have different date spans and time segments, for example the Cochrane Library Database of Abstracts of Reviews of Effectiveness ceased to be updated from March 2015 and so searching it for the update is unlikely to have retrieved further results.

The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a large number of synonyms for the interventions and comparators. Terms were used to limit results to randomised controlled trials (RCTs) only; a validated filter does not appear to have been used or referenced but a wide range of relevant terms were used in the limit. The EMBASE strategy included some terms for additional study designs such as cohort analysis and comparative studies. Different platforms were used for the Embase and BIOSIS searches in the initial searches and the update searches, adequate translation of indexing and field tags for those searches were used.

The search strategy for the Cochrane databases contained a study design filter limiting the results to trials. The ERG considered that this could be unnecessarily overly restrictive as the Cochrane

databases are ready filtered resources, i.e. CENTRAL is predominately trials, the use of such a filter could therefore compromise the sensitivity of the search.

Indirect and mixed treatment comparisons

The clinical effectiveness searches reported in Section 4.1 and Appendix C were used to inform the indirect and mixed treatment comparisons. As the searches included a facet of relevant comparators the ERG considered the searches fit for purpose.

Non-randomised and non-controlled evidence

The company states that there is no relevant non-randomised and non-controlled evidence for presentation in this submission

Adverse events

No specific AE searches were performed; data appear to have been taken from MEASURE 2 and MEASURE 1 trials and from the safety of secukinumab in another similar indication (psoriasis).

Cost effectiveness

The CS states that a SLR was conducted to identify evidence from economic analyses relating to the use of secukinumab and relevant biologic comparators in the treatment of adult patients with AS. Studies which included cost, resource utilisation or utility data were also identified. Searches were initially undertaken in January 2015 and updated in September 2015. Searches were reported for MEDLINE, MEDLINE In-Process, Embase, EconLit, BIOSIS and the Cochrane Library (CENTRAL, NHS EED and HTA). The database searches were limited from 1999 to January 2015 and the update searches limited to 1 January 2014 to January 2015. In addition the following resources were searched: NICE, Scottish Medicines Consortium (SMC), International Society for Pharmaco-economics and Outcomes Research (ISPOR), CADTH and Institute for Quality and Efficiency in Healthcare (IQWiG) websites. Section 5.1.2 of the CS also mentions congress abstracts searching but no information regarding which congresses were searched were provided. Search strategies for the database searches were provided in the Appendix L of the company submission and are well reported and reproducible.

In response to a clarification request, the company stated that the databases were searched from inception to the search dates above; database inception dates for PubMed, EMBASE and BIOSIS were provided. These details are important in the search methodology for reproducibility purposes as different databases have different date spans and time segments, for example the National Health Service's Economic Evaluation Database (NHS EED) ceased to be updated from March 2015 and so searching it for the update is unlikely to have retrieved further results. The database searches were clearly structured and used combinations of index terms appropriate to the resource searched, free text and a large number of synonyms for the interventions and comparators.

As with the clinical effectiveness SLR, different platforms were used for the Embase and BIOSIS searches in the initial searches and the update searches, adequate translation of indexing and field tags for those searches were used.

Economics and cost terms were included in the Cochrane Library search, particularly when searching NHS EED. As this is an economics database the ERG believes it is not necessary to include this facet for this database.

Measurement and value of health effects

The same SLR used in the cost effectiveness section above, and therefore the same comments regarding the search methods apply here.

Cost and healthcare resource use identification, measurement and valuation

The same SLR used in the cost effectiveness section above, and therefore the same comments regarding the search methods apply here.

4.1.2 Inclusion criteria

Inclusion and exclusion criteria used to screen for relevant studies in the CS are set out in Tables 4.1 and 4.2 below. Table 4.1 includes the eligibility criteria that were applied on review of titles and abstracts whereas Table 4.2 focuses on eligibility criteria applied at full paper review.

Table 4.1: Eligibility criteria of studies at level 1 (title and abstract) screening
(Based on Table 6 of the CS[1])

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult (≥18 years) patients with active or severe active AS • TNFα inhibitor-naïve patients as long as they had demonstrated prior intolerance or inadequate response to conventional treatments • Second-line patients who had inadequate response to prior treatments (e.g., conventional treatment with DMARDs, NSAIDs, and/or TNFα inhibitors) • Second-line patients who were intolerant to prior treatments (e.g., conventional treatment with DMARDs, NSAIDs, and/or TNFα inhibitor)	• Children • Patients with mild or early AS; if population was mixed (i.e., mild to severe), the studies were excluded if data for active or severe active AS were not reported separately • Non-radiographic axial spondyloarthritis • Treatment-naïve patients
Intervention	• Secukinumab	• Non-biologic treatments for AS (e.g., DMARDs, NSAIDs)
Comparators	• Certolizumab pegol (Cimzia®) • Etanercept (Enbrel® [biosimilars: Avent, BX2922, CHS-0214, ENIA11, Etacept, Etanar, GP2013, GP2015, HD203, LBEC0101, PRX-106, SB4, TuNEX, Yisaipu]) • Adalimumab (Humira®, Trudexa [biosimilars: ABP 501, BI695501, CHS-1420, GP2017, M923, PF-06410293]) • Infliximab (Remicade® [biosimilars: CT-P13, Remsima, Inflectra]) • Golimumab (Simponi®)	• Non-biologic treatments for AS (e.g., DMARDs, NSAIDs) • Combinations of the therapies of interest
Outcomes	Any	None

Criteria	Inclusion criteria	Exclusion criteria
Study design	• Randomised, controlled, prospective clinical trials • Long-term follow-up studies (e.g. open-label follow-up studies with continuation of treatments in their respective randomised group) • Systematic reviews, including meta-analyses[a]	• Non-randomised clinical trials • Preclinical studies • Phase I studies • Prognostic studies • Retrospective studies • Prospective observational studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews
Language	All languages	None
Date	No limit	None

AS = ankylosing spondylitis; DMARD = disease modifying anti-rheumatic drug; NSAID = non-steroidal anti-inflammatory drug; TNFα = tumour necrosis factor alpha.
Note: The inclusion criteria encompassed studies evaluating biosimilar products for etanercept, adalimumab and infliximab; The interventions of interest in this review consist of all therapy versions of the listed treatments at labelled doses.
[a]Only used for identification of primary studies that were missed in the electronic searches. Systematic reviews and meta-analyses were only included during the initial screening process and were excluded during the full-text review process (see table 4.3)

ERG comment: All of the ERGs comments relate to population as defined set out in the Table 4.1 above. Firstly, it is not clear how mild or early AS has been identified. Secondly, it is not clear why mild or early AS has been excluded since according to page 70 of the company's response to clarification questions *"there is no agreed consensus on the terms used to classify the severity of AS"*.[6] Therefore, the only legitimate severity-based exclusion should have been non-active AS. Finally, the ERG notes exclusion of non-radiographic axial spondyloarthritis and therefore assumes that this group should be excluded from any recommendations in regard of secukinumab. All other aspects of the CS seem to be compatible with the NICE scope.

Table 4.2: List of criteria for the inclusion and exclusion of studies at level 2 (full-text) screening (Based on table 7 of the CS[1])

Criteria	Inclusion criteria	Exclusion criteria
Population	As level 1	As level 1
Intervention	As level 1	As level 1
Comparators	As level 1	As level 1
Outcomes	To be included in the review, a study must report at least one of the outcomes of interest. *Efficacy measurements:* • ASAS score • Proportion of patients achieving ASAS20 response, ASAS40 response, ASAS70 response or ASAS 5/6 response	None

Criteria	Inclusion criteria	Exclusion criteria
	• Proportion of patients achieving ASAS20 or ASAS40 response in the subgroup of patients who are TNFα inhibitor-naïve, have inadequate response to TNFα or who are TNFα intolerant • ASAS partial remission • Patient's global assessment of disease activity • Proportion of patients with inactive disease (ASDAS<1.3) • Proportion of patients with clinically important change (defined as ASDAS improvement of ≥1.1) • Proportion of patients with major improvement (defined as ASDAS improvement of ≥2.0) • BASDAI score • Spinal mobility assessed by BASMI (cervical rotation, maximal intermalleolar distance, lateral spinal flexion, lumbar flexion [modified Schober], tragus-to-wall distance), chest expansion and occiput-to-wall distance • BASFI score • 44 tender and swollen joint count • Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) • Serum high-sensitivity C-reactive protein • modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS): proportion of patients with a relapse • Patient assessment spinal pain *QoL measurements:* • ASQoL • EQ-5D • SF-36 • HAQ • FACIT-fatigue *Safety outcomes:* • Overall AEs • Overall serious AEs • Mortality • Treatment-related mortality • Discontinuations due to AEs • Individual safety outcomes (may include serious viral upper respiratory infections, dyslipidemia, headache, gastrointestinal symptoms [nausea/pain], serious infections; TB; malignancies (including lymphoma, melanoma, and NMSC); injection site reactions; immunogenicity, uveitis flair, uveitis de novo, major adverse cardiac event, and leukopenia)	
Study design	• Randomised, controlled, prospective clinical trials • Long-term follow-up studies (e.g. open-label follow-up studies if patients continued in the group to which they were	As level 1, Systematic reviews and

Criteria	Inclusion criteria	Exclusion criteria
	randomised)	meta-analyses
Language	As level 1	As level 1
Date	As level 1	As level 1

AE = adverse event; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; EQ-5D = EuroQol 5D questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; HAQ = Health Assessment Questionnaire; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; QoL = quality of life; SF-36 = Short Form Health Survey; NMSC = non-melanoma skin cancer; TNFα = tumour necrosis factor alpha

ERG comment: All aspects of the inclusion and exclusion criteria for full text screening as outlined in Table 4.2 of the CS seem to be compatible with the NICE scope.

4.1.3 Critique of data extraction

Page 44 of the CS describes the methods for study selection in terms of two stage screening and resulting data extraction of eligible studies.[1] Titles and abstracts were retrieved for all identified records and then independently screened by two researchers against the predefined PICOS inclusion and exclusion criteria (Table 4.1) with differences resolved by a third reviewer where consensus could not be reached. A second round of screening was performed on full papers with a closer focus on admissible outcome criteria (see Table 4.2 above). The same methods were employed in both screening phases for resolving differences between reviewers.

In respect of data extraction, the CS commented *"Data for included articles were extracted from full-text versions of studies, when these were available, by one reviewer. Abstracts or posters were only used for extraction when these were the terminal source document. The data extracted from the relevant RCTs included the trial characteristics, patient demographics, treatment history, disease severity and interventions. Data were extracted for the following time-points, where available: Week 12, 16, 24, 52 and outcomes reported after Week 52"*.[1]

ERG comment: The screening phases of study selection were compliant with recognised guidelines[15, 16] but data extraction methods were not. In the Cochrane Handbook it is strongly recommended that more than one person extract data from every report to minimise errors and reduce potential biases.[15] The processes outlined in the CS fall short of this standard in two regards. Firstly only one reviewer was used in the process and secondly abstracts or posters were only used when no full text paper was available ('terminal source'), which is not advised since they may still include relevant and unique outcomes even when they are not the most comprehensive outcome. Therefore, there is a chance that relevant data might have been missed or extracted incorrectly.

4.1.4 Quality assessment

Quality assessment for MEASURE 1, MEASURE 2 and trials in the mixed treatment comparison (MTC) was undertaken using key questions from NICE Process and methods guides Single technology appraisal: User guide for company evidence submission template (January 2015), see page 21.[17]Results for MEASURE 1 and MEASURE 2 are reported in Appendix C (page 39) of the CS appendices and replicated below (Tables 4.3 and 4.4).[18]

Table 4.3: Quality assessment of MEASURE 2
(Based on Table 125 of [18])

Study Question	How Is the Question Addressed in the Study?	Grade*	ERG comment
Was randomisation carried out appropriately?	The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased. A subject randomisation list was produced by the IRT provider, using a validated system that automated the random assignment of subject numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management, using a validated system that automated the random assignment of medication numbers to packs containing the investigational drugs.	Yes	Agree
Was the concealment of treatment allocation adequate?	At baseline, all eligible subjects were randomised via IRT to one of the treatment arms. The investigator or his or her delegate contacted the IRT after confirming that the patient fulfilled all the inclusion and exclusion criteria. The IRT assigned a randomisation number to the subject, which was used to link the subject to a treatment arm and specified a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomisation number was not to be communicated to the caller.	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically meaningful differences in demographic and other background characteristics across the treatment groups. There were slightly more females in the 150 mg group (36.1%) than the placebo group (24.3%). Disease history and baseline characteristics were well balanced across the treatment groups and reflected a study population with moderate-to-severe, active AS.	Yes	Agree
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until the week-52 analysis, using the following methods: randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone else involved in the study, with the exception of the bioanalyst; the identity of the treatments was concealed by the use of study treatments in form of prefilled	Yes	Agree

Study Question	How Is the Question Addressed in the Study?	Grade*	ERG comment
	syringes for s.c. injection, filled with secukinumab or placebo that were identical in appearance. A double-dummy design was used because the identity of the study treatments cannot be disguised due to their different volume forms (0.5 ml vs. 1.0 ml).		
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in dropouts between the groups. No patients were lost to follow-up in any of the treatment arms.	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results were reported for primary, secondary, and exploratory efficacy endpoints. Safety data, quality-of-life, and utility data also were reported.	No	Agree
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set was composed of all patients from the randomised set to whom study treatment was assigned. Following the ITT principle, patients were evaluated according to the treatment assigned to at randomisation. Missing data for ASAS20/40 response and other binary efficacy variables for data up to 1-year were handled as follows: patients who dropped out of the trial for any reason were considered non-responders from the time they dropped out through Week 52; patients who did not have the required data to compute response at baseline and at the specific timepoint were classified as non-responders. Patients who were unblinded prior to the scheduled time point were considered non-responders from the time of unblinding up to Week 16. The primary analysis used the non-responder imputation. Continuous variables were analysed using a mixed-effects model repeated measures, which was valid under the missing at random assumption. For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed, and the subject was removed from the analysis of the corresponding variable.	Yes	Agree

AS = Ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis; IRT = Interactive response technology; ITT = Intention to treat; mg = Milligram; ml = Millilitre; s.c. = subcutaneous

* Grades rated as Yes/No/Not Clear/NA

Table 4.4: Quality assessment of MEASURE 1
(Based on Table 126 in CS appendices [18])

Study Question	How Is the Question Addressed in the Study?	Grade*	ERG comment
Was randomisation carried out appropriately?	The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased. A subject randomisation list was produced by the IRT provider, using a validated system that automated the random assignment of subject numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management, using a validated system that automated the sequential assignment of medication numbers to study drug packs containing each of the study drugs.	Yes	Agree
Was the concealment of treatment allocation adequate?	At the baseline, all eligible subjects were randomised via IRT to one of the treatment arms. The investigator or his or her delegate contacted the IRT after confirming that the patient fulfilled all the inclusion and exclusion criteria. The IRT assigned a randomisation number to the subject, which was used to link the subject to a treatment arm and specified a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomisation number was not communicated to any of the site staff including the unblinded pharmacist or unblinded qualified site personnel.	Yes	Agree
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no clinically meaningful differences in demographic and other background characteristics across the treatment groups. Most (95.4%) patients were < 65 years of age, with a median age ranging from 39.0 (secukinumab 150 mg group) to 41.0 years (secukinumab 75 mg and placebo groups). More than two-thirds (69.3%) of the patients were male, and 60.9% were Caucasian (white). Disease history and baseline characteristics were well-balanced across the treatment groups and reflected a study population with moderate to severe active AS. The median time since the first diagnosis of AS was 4.1 to 5.8 years. Mean baseline BASDAI scores were similar across all treatment groups. Mean hsCRP level was approximately 17 mg/l in all treatment groups. Baseline values for other variables, including the BASMI linear score and individual components and the erythrocyte sedimentation rate (ESR), were also similar across the treatment groups.	Yes	Agree

Study Question	How Is the Question Addressed in the Study?	Grade*	ERG comment
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, investigator staff (with the exception of the unblinded pharmacist), persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until the Week 52 analysis, using the following methods: • Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study with the exception of the bioanalyst, the Novartis unblinded monitors and for the preparation of the study medication, an independent, unblinded pharmacist/nurse/physician or authorised personnel at the investigator's site who prepared the study medication for patients. • The identity of treatments were concealed by the use of study drugs in the form of syringes (for s.c.) and infusion bags (for i.v.) filled with reconstituted secukinumab/placebo solutions that were identical in appearance, but the actual secukinumab or placebo vials with lyophilisate were supplied "open-label".	Yes	Agree
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in dropouts between the groups.	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results were reported for primary, secondary, and exploratory efficacy endpoints. Safety data, quality-of-life, and utility data also were reported.	No	Agree
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The full analysis set was composed of all patients from the randomised set to whom study treatment was assigned. Following the ITT principle, patients were evaluated according to the treatment assigned to at randomisation. Missing data for ASAS20/40 response and other binary efficacy variables (e.g. ASAS 5/6, etc.) for data up to 1-year (Week 52) were handled as follows: Patients who drop out of the trial for any reason were considered non-responders from the time they drop out through Week 52. Patients who do not have the required data to compute response (e.g. ASAS components) at baseline and at the specific time point were	Yes	Agree

Study Question	How Is the Question Addressed in the Study?	Grade*	ERG comment
	classified as non-responders. Patients who were unblinded prior to the scheduled time point were considered non-responders from the time of unblinding up to placebo-controlled period (Week 24). The primary analysis used the non-responder imputation. Continuous variables (e.g. ASAS components) were analysed using a MMRM which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data was not performed (e.g., last observation carried forward (LOCF)). For analyses of these parameters, if all post-baseline values were missing then these missing values were not imputed and this patient was removed from the analysis of the corresponding variable, i.e. it might be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS. Data collected after Week 52 was generally presented as 'observed case'; i.e. all available data for each time point was included in the analyses.		

AS = Ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = c-reactive protein; ESR = erythrocyte sedimentation rate; FAS = Final analysis set; hs = high sensitivity; IRT = Interactive response technology; ITT = Intention to treat; i.v. = intravenous; LOCF = last observation carried forward; MAR = missing at random; mg = Milligram; MMRM = Mixed-effect model repeated measures; s.c. = subcutaneous

* Grades rated as Yes/No/Not Clear/NA

ERG comment: There is no comment within the CS as to how quality assessment was undertaken. Best practice would have been for more than one person extract data from every report to minimise errors and reduce potential biases.[15] The ERG has reviewed the quality assessment of MEASURE 1 and MEASURE 2 and is in agreement with the company's assessment.

The company identified some methodological deficiencies in other trials in the MTC. Full quality assessment tables for all studies included in the MTC are reported in Appendix K of the CS on page 86.[1] In the study by Huang et al. 2014 there was some evidence that the study groups were not similar at the outset of the study.[19] The group randomised to ADA treatment had 5.5% more patients in the very high ASDAS category compared to the placebo group (65.5% vs. 60%).

A similar imbalance between treatment groups was reported for the RAPID-ax SpA study. Specifically, 40% of patients in the CZP 200 mg arm had disease duration of <5 years compared to only 28.1% in the placebo arm. The median CRP level was 16.6 mg/ml in the placebo arm compared to 12.9 mg/ml in the CZP 400 mg arm. The exposure to prior TNFα was also higher in the placebo group compared to the CZP groups.

The SPINE study also showed some imbalance between treatment groups at the outset of the study. There were 7% of patients that were spinal radiological stage II in the placebo group compared to

18% in the ETN group. In addition, the mean BASDAI score at baseline was 58 in the placebo group and 64 in the ETN group.

ERG comment: If treatment groups within studies are unbalanced at baseline then this may introduce bias in the treatment effects reported by those studies. This may in turn influence any treatment effects calculated in the MTC based on those studies. In general, patients with more severe disease are less likely to respond to treatment. In both RAPID-ax SpA and SPINE the patients in the respective placebo groups may have had more severe disease than those randomised to active treatment. This creates a potential bias in favour of the active treatment groups, CZP (RAPID-ax SpA) and ETN (SPINE) respectively. A series of sensitivity analyses to explore the impact of this potential bias where data allow would have been informative.

4.1.5 Evidence synthesis

The main synthesis of evidence provided by the company took the form of separate MTCs for both the entire population and separately for the biologic-naïve population. Comparisons varied depending upon whether or not outcome data was produced for specific effects. Specific effects considered in the MTC were measured in terms of ASAS20, ASAS40, BASDAI 50, BASDAI change form baseline and BASFI change from baseline. Analysis of ASAS 5/6 response and SF-36 PCS were analysed by the company but results were only available on request.[20] These are presented below.

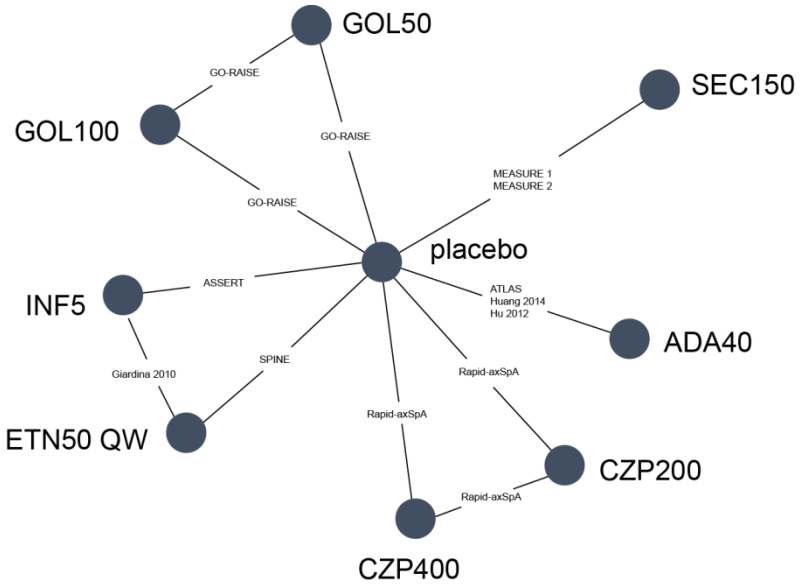
Other effectiveness outcomes were presented for MEASURE 1 and MEASURE 2 (in appendices) but these were not assessed for other studies in the MTC. These were; ASAS partial remission; ASDAS-CRP [major improvement]; hs-CRP change from baseline; patient's global assessment of disease activity; BASMI linear change from baseline; radiographic outcomes e.g. MSASSS (MEASURE 1 only); pain (as captured by ASAS and BASDAI criteria); peripheral symptoms measured with MASES; adverse effects of treatment; health-related quality of life (ASQoL, EQ-5D, and MCS, FACIT-Fatigue) or impairment in work and activities (WPAI-GH).

No effectiveness outcomes were presented for symptoms of extra-articular manifestations (EAMs) which formed part of the original scope. However, these were assessed under safety reporting and the company identified a lack of new cases in either MEASURE 1 or MEASURE 2 suggesting that secukinumab is not associated with a worsening of EAMs.

Analysis of MTC is discussed in greater detail in Section 4.2 below.

The complete network of RCTs among AS patients was provided in Figure 20 of the CS[1] follows:

Figure 4.1: Complete treatment network of RCTs among AS patients
(Based on Figure 20 of the CS[1])



Nodes represent each treatment included in the network. Trial names along each edge indicate the trials with head-to-head comparisons for the corresponding treatments.
ADA40 = adalimumab 40 mg; AS = ankylosing spondylitis; CS = company submission; CZP200 = certolizumab pegol 200 mg weeks 0, 2 and 4 then every 2 weeks; CZP400 = certolizumab pegol 400 mg weeks 0, 2 and 4 then every 4 weeks; ETN50QW = etanercept 50 mg once weekly; GOL50 = golimumab 50 mg; GOL100 = golimumab 100 mg; INF5 = infliximab 5 mg/kg; SEC150 = secukinumab 150 mg

ERG comment: The methods of synthesising evidence seem reasonable. Outcomes that were considered relevant for MTC appear to be selected on the basis that they were primary rather than secondary endpoints in RCTs. However, some trials do report secondary outcomes which were both included in the NICE scoping document and also reported in the company submission for MEASURE 1 and MEASURE 2. For example, Huang et al. 2014[19] reports on MASES, hs-CRP change and WPAI-GH at week 12 and Dougados et al. 2012[21] reports on major improvement in ASDAS-CRP score and BASMI change. It would have been helpful if the company could have considered the possible implications of selecting only a subset of outcomes from those identified in the scope, particularly since data existed to populate more networks with these "secondary" outcomes.

It is also noteworthy that data for adverse effects are only reported for MEASURE 1 and MEASURE 2 which makes it difficult to assess the relative safety of comparator drugs. The company suggest this results from *"no active comparator safety data in the AS indication"* [page 152 of CS[1]]. The company point out that the safety profile for secukinumab is largely comparable to placebo: *"In MEASURE 2, the overall incidence of treatment-emergent AEs up to Week 16 in the secukinumab 150 mg group was comparable to the placebo group (65.3% vs. 63.5%, respectively). In MEASURE 1 there was a slightly higher rate of treatment emergent AEs up to Week 16 in the secukinumab 150 mg group compared with placebo (69.6% vs. 55.7%)"* [page 153/4 of CS[1]]. Furthermore they suggest *"the majority of adverse events were mild or moderate in severity, with the most commonly reported adverse event in both trials being nasopharyngitis"*.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Included trials

The evidence base for the clinical efficacy of secukinumab 150 mg in the treatment of AS in adults with an inadequate response to conventional care consists of three randomised controlled trials (RCTs), as identified by a systematic literature review (SLR): MEASURE 2, MEASURE 1 and A2209. MEASURE 2 and MEASURE 1 are Phase III RCTs comprise the main evidence base for the clinical efficacy and safety of secukinumab presented in this submission; the A2209 trial is a small, phase II proof-of-concept study that provides supportive data, including radiographic outcomes. The A2209 study was considered to be an unreliable source of evidence on account of its small size, short duration as well as inconsistencies in study time endpoints and an absence of licensed dose being administered. The main methodological features of MEASURE 1 and MEASURE 2 have been summarised in Table 10 of the CS[1] replicated here in Table 4.5. Definitions of outcomes were summarised in Tables 12 and 13 of the CS and replicated here in Tables 4.6 and 4.7.

Table 4.5: Summary of methodology of the relevant randomised-controlled trials
(Based on table 10 of the CS[1])

Trial Name	MEASURE 2	MEASURE 1
Location	International, multi-centre trial across 52 locations in the following countries: Austria, Canada, Czech Republic, Finland, Germany, Italy, Netherlands, Russian Federation, Singapore, Spain, Switzerland, United Kingdom, United States [redacted]/219 patients were from UK study sites.	International, multi-centre trial across 67 locations in the following countries: Belgium, Bulgaria, Canada, France, Germany, Italy, Mexico, Netherlands, Peru, Russian Federation, Taiwan, Turkey, United Kingdom, United States [redacted]/371 patients were from UK study sites.
Trial design	Randomised, double-blinded, double-dummy, parallel-group, placebo-controlled Phase III trial	Randomised, double-blinded, parallel-group, placebo-controlled Phase III trial
Inclusion and exclusion criteria for participants	Key eligibility criteria are shared across both MEASURE 2 and MEASURE 1 trials and are provided below. Patients must have fulfilled the following criteria: • Male or female ≥18 years • Moderate to severe AS fulfilling the Modified New York criteria for AS, with prior documented radiological evidence • Active AS, and BASDAI ≥4 (0-10) and spinal pain as measured by VAS ≥4 cm (0-10 cm) at baseline • Report active disease despite current or previous NSAIDs, DMARDs and/or TNFα inhibitor therapy Included patients were stratified according to being TNFα inhibitor-inadequate responders (IR) or TNFα inhibitor-naïve patients. Patients were not eligible if they fulfilled exclusion criteria such as: • Chest X-ray (or MRI in MEASURE 2 only) with evidence of ongoing infectious or malignant process, obtained within 3 months of screening and evaluated by a qualified physician • Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17A receptor • Active ongoing inflammatory diseases other than AS that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis	
Method of randomisation	In both trials, all eligible patients were randomised (1:1:1) at baseline via Interactive Response Technology (IRT) to one of the treatment arms. The IRT could be contacted via the Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). Patients were stratified at randomisation according to TNFα inhibitor-naïve patients or TNFα inhibitor inadequate responder (IR)	

Trial Name	MEASURE 2	MEASURE 1
	patients:	
	• In MEASURE 2, approximately 40% of patients had to be TNFα inhibitor-IR to ensure a representative patient population for the assessment of efficacy and safety.	• In MEASURE 1, approximately 30% of patients had to be TNFα inhibitor-IR to ensure a representative patient population for the assessment of efficacy and safety.
Trial treatments	• Group 1: secukinumab 75 mg plus placebo 150 mg once weekly at Baseline, weeks 1, 2, and 3, followed by dosing every four weeks starting at week 4 (n=73) • Group 2: secukinumab 150 mg plus placebo 75 mg once weekly at Baseline, weeks 1, 2, and 3, followed by dosing every four weeks starting at week 4 (n=72) • Group 3: placebo 75 mg and placebo 150 mg once weekly at Baseline, weeks 1, 2, and 3, followed by dosing every four weeks starting at week 4 (n=74) [All treatments administered by s.c. injections in the form of pre-filled syringe (PFS)] At week 16, patients who were randomised to placebo at baseline were re-randomised to receive secukinumab 75 mg plus placebo 150 mg or secukinumab 150 mg plus placebo 75 mg (1:1) every 4 weeks up to 5 years.	• Group 1 (i.v.-75 mg): secukinumab i.v. (10 mg/kg) at Baseline, weeks 2 and week 4 then secukinumab 75 mg s.c. every 4 weeks starting at week 8 (n=124) • Group 2 (i.v.-150 mg): secukinumab i.v. (10 mg/kg) at weeks 0, 2 and 4 then secukinumab 150 mg s.c. every 4 weeks starting at week 8 (n=125) • Group 3: placebo i.v. at Baseline, week 2 and week 4 then placebo s.c. at week 8 and week 12 (n=122) At week 16, patients who had been randomised to placebo (Group 3) at baseline were re-randomised to receive double-blind treatment up to 2 years, based on treatment response as determined by ASAS20 improvement criteria: • Placebo non-responders were re-randomised to receive secukinumab 75 mg or 150 mg s.c. (1:1) dosed every 4 weeks • Placebo responders remained on placebo s.c. at weeks 16 and 20. At week 24, these patients received secukinumab 75 mg s.c. or 150 mg s.c. (1:1) dosed every 4 weeks, regardless of responder status, as dictated by the re-randomisation.
Concomitant medicines	Guidelines for the use specific medications in MEASURE 2 and MEASURE 1 are provided in full in appendix E [of the CS[1]]. The list of concomitant medicines include: • Methotrexate (MTX) (7.5-25 mg/week) – stable dose for at least 4 weeks prior to randomisation and until week 52 • Folic acid - patients on MTX had to take folic acid supplementation before randomisation and during the trial to minimise the	

Trial Name	MEASURE 2	MEASURE 1
	likelihood of MTX associated toxicity. • Sulfasalazine (≤ 3 g/day) – stable dose for at least 4 weeks prior to randomisation and until week 52 • Systemic corticosteroids – stable dose for at least 2 weeks prior to randomisation, up to a maximum daily dosage of 10 mg prednisone equivalent. • NSAIDs (including COX-1 or COX-2 inhibitors) and acetaminophen/ paracetamol - stable dose for at least 2 weeks prior to randomisation Medicines that were prohibited from both trials and required appropriate wash-out prior to randomisation, are listed in appendix E [of the CS[1]]. The list of prohibited medicines not allowed after the start of the washout period include: • Other biological therapies (etanercept, infliximab, adalimumab, golimumab, certolizumab)* • Unstable dose of MTX or sulfasalazine • Other DMARDs (except MTX or sulfasalazine) • Leflunomide (within 4 weeks of randomisation with cholestyramine washout or within 8 weeks of randomisation without cholestyramine washout) • Unstable dose of NSAIDs (COX-1 or COX-2 inhibitors) (until week 20 in MEASURE 2) • Systemic corticosteroids > 10 mg prednisone equivalent • Intra-articular steroids injections (until week 20 in MEASURE 2 and week 16 in MEASURE 1) • Any investigational treatment or participation in any interventional trial • Analgesics other than paracetamol/ acetaminophen and low strength opioids PRN • Live vaccinations (up to week 24 in MEASURE 1)	
Primary endpoint	Proportion of patients achieving ASAS20 response at week 16	
Secondary endpoint(s)	• Proportion of patients achieving ASAS40 response at week 16 • High sensitivity C-reactive protein (hsCRP) change from baseline at week 16 • Proportion of patients achieving ASAS 5/6 response criteria at week 16 • BASDAI change from baseline at week 16 • SF-36 PCS change from baseline at week 16 • ASQoL change from baseline at week 16	

Trial Name	MEASURE 2	MEASURE 1
	• Proportion of patients achieving ASAS partial remission criteria at week 16 • To evaluate the overall safety and tolerability of secukinumab compared to placebo as assessed by vital signs, clinical laboratory values, and adverse events monitoring	
Exploratory endpoints	• Primary and secondary outcome measures at time points other than week 16 • Change from baseline in ASAS components including BASFI • Change from baseline in ASDAS-CRP and ASDAS-ESR • Change from baseline in nocturnal back pain** • Change from baseline BASMI linear scores and in BASMI components • ASDAS inactive disease (<1.3), clinically important change (≥1.1) and major improvement (≥2.0) • Change from baseline in MASES • Change from baseline in swollen or tender joint count as determined by the 44-joint assessment • Change from baseline in ESR • Work productivity (WPAI-GH), quality of life (SF-36, FACIT-FATIGUE®) and utilities (EQ-5D) • BASDAI 50 defined as a 50% improvement of the initial BASDAI • Exploration of immunogenicity against secukinumab • PK/PD relationship • Pharmacogenetic assessments • Biomarker assessments • Cumulative NSAID intake during the trial (MEASURE 2 only) In MEASURE 1, the following radiologic endpoints were also assessed (changes observed from baseline): • mSASSS; radiography scoring after 2 years of treatment • MRI of spine and sacroiliac joints at week 16, 1 year and 2 years (in TNFα inhibitor-naïve patients and at selected clinical sites only) • BMD of the lumbar spine, total hip and femoral neck after 1 year and 2 years of treatment • Markers of cartilage and bone turnover over 2 years	
Pre-planned	A pre-specified subgroup analysis was performed to explore any differences in outcomes between TNFα inhibitor-IR patients and	

Trial Name	MEASURE 2	MEASURE 1
subgroup analysis	patients who were naïve to TNFα inhibitor treatment.	

[*] These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation.
[**] Specified as nocturnal pain in MEASURE 2

AS = ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; BMD = Bone mineral density; COX(-1,-2) = cyclooxygenase(-1,-2); DMARD = disease modifying anti-rheumatic drug; EQ-5D = EuroQol 5D questionnaire; ESR = Erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; (hs)CRP = (high sensitivity) C-reactive protein; IRT = interactive response technology; IL = interleukin; IR, inadequate responder; i.v. = intravenous; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; mSASSS = modified stoke ankylosing spondylitis spine score; MTX = methotrexate; NSAIDs = non-steroidal anti-inflammatory drugs; PCS = physical component summary; PFS = pre-filled syringe; PK/PD = pharmacokinetic/pharmacodynamic; PRN = pro re nata, when necessary; s.c. = subcutaneous; SF-36 = Medical Outcome Short Form Survey-36; TNFα = tumour necrosis factor alpha; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment-General Health

Table 4.6: ASAS response criteria
(Based on Table 12 of the CS[1])

Trial outcome	Definition
ASAS response criteria [CS reference 167]	
The ASAS response measures consist of four main assessment domains, the so-called ASAS components: 1. Patient's global assessment of disease activity measured on a VAS scale 2. Patient's assessment of inflammatory back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale 3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale 4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale In addition, ASAS response measures includes two additional assessment domains: 5. Spinal mobility represented by the BASMI lateral spinal flexion assessment 6. C reactive protein (acute phase reactant) For further details of specific outcomes used within the ASAS response criteria, please see below.	
Measures of ASAS response criteria	
ASAS20/40	An improvement of at least 20% or 40% and absolute improvement of at least 1 or 2 units on a 0-10 cm scale in at least 3 of the main assessment domains (1 to 4), with no worsening in the remaining domain.
ASAS 5/6	An improvement of at least 20% in at least five of all six assessment domains.
ASAS partial remission	Defined as a value not above 2 units in each of the main assessment domains (1 to 4) on a scale of 10.
ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; VAS, visual analogue scale	

Table 4.7: Additional efficacy outcomes and definitions
(Based on Table 13 of the CS[1])

Study outcome	Definition
ASDAS-ESR, ASDAS-CRP and ASDAS response [CS 168]	The ASDAS-ESR and ASDAS-CRP scores were utilised to assess AS disease activity status. Parameters used for ASDAS include: total back pain (BASDAI question 2), the patient global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 5) and C-reactive protein (CRP) in mg/litre or erythrocyte sedimentation rate (ESR). Disease activity states included: inactive disease, moderate disease activity, high disease activity and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and moderate disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cut-offs for improvement scores were a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement".
ASQoL [CS 169]	A patient reported outcome measure designed to assess QoL in adult patients with AS. It consists of an 18 item questionnaire with dichotomous yes/no

Study outcome	Definition
	response options. A single point is assigned for each 'yes' response and zero points are assigned for a 'no' response. A lower score indicates better QoL. The purpose of the ASQoL in these studies was to assess disease specific QoL.
BASDAI	Consists of a 0 through 10 scale (1 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS: 1. Fatigue 2. Spinal pain 3. Joint pain / swelling 4. Areas of localised tenderness (called enthesitis, or inflammation of tendons and ligaments) 5. Morning stiffness duration 6. Morning stiffness severity To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness was taken. The resulting 0 to 10 score was added to the score for questions 1 through 4. The resulting 0 to 50 score was divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrolment in clinical trials evaluating new drug therapies directed at AS.
BASDAI 50 - measure of BASDAI	An improvement, i.e. decrease of at least 50% in the BASDAI score, compared to baseline. [CS reference 170]
BASFI	Set of 10 questions designed (with input from patients with AS) to determine the degree of functional limitation in AS patients. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life. A 0 through 10 scale captured as a continuous VAS) is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.
BASMI	Validated instrument that uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters included were: lateral spinal flexion; tragus to wall distance; lumbar flexion (modified Schober); maximal intermalleolar distance and cervical rotation angle. Assessments were also taken of chest expansion and occiput-to-wall distance.
ESR	Changes from baseline in ESR. Helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy.
EQ-5D [CS 171]	The measure is divided into two distinct sections. The first section includes a questionnaire addressing five dimensions of quality of life (mobility, self-care, usual activity, pain/discomfort and anxiety/depression). The second section measures self-rated global health status utilising a vertically oriented visual analogue scale (VAS), where 100 represents the "best possible health state" and 0 represents the "worst possible health state". The EQ-5D is designed to assess health status in terms of a single index value, which is obtained by transforming the responses to the questionnaire into a scale utility score. Overall scores typically range from 0 to 1, with lower

Study outcome	Definition
	scores representing a higher level of dysfunction.
FACIT-Fatigue [CS 172, 173]	The FACIT-Fatigue© is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue© in these studies was to assess the impact of fatigue on patients with AS.
hs-CRP levels	hsCRP levels were measured to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Changes from baseline in hsCRP were expressed as a ratio of post-baseline to baseline values. With the ratio normalised to 1.0 at baseline, ratios less than 1.0 represent decreased post-baseline values, whereas ratios greater than 1.0 represent increased post-baseline values.
MASES (Expanded) [CS 174]	Measure of enthesitis, including assessment of 13 enthesitis sites.
mSASSS [CS 175]	Radiographic scoring method which assesses cervical, thoracic and lumbar spine regions for damage associated with AS.
Patient's global assessment of disease activity (VAS)	Patient self-assessment performed using a 100 mm VAS ranging from not severe to very severe, after the question "How active was your disease on average during the last week?"
SF-36	Widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health The purpose of the SF-36 in these studies was to assess the HRQoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, was used
WPAI-GH	The WPAI-GH questionnaire is an instrument to measure impairments in both paid work and unpaid work. It measures absenteeism, presenteeism as well as impairments in unpaid activity because of health problems during the past seven days.
44-joint count	Forty four pre-specified joints were assessed for tenderness and swelling.

AS = ankylosing spondylitis; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASQoL = Ankylosing Spondylitis Quality of Life; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; EQ-5D = EuroQol-5D; ESR = erythrocyte sedimentation rate; FACIT = Functional Assessment of Chronic Illness Therapy; (HR)QoL = (health-related) quality of life; hs-CRP = high-sensitivity C-reactive protein; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; SF-36 = Medical Outcome Short Form Survey-36; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment - General Health

On page 25 of the CS[1] the company state *"Taken together, the results of MEASURE 2 and MEASURE 1 demonstrate the clinical efficacy of secukinumab treatment when assessed across a variety of outcome measures in two large trials. These trials also show that the clinical benefit demonstrated by secukinumab, regardless of TNFα inhibitor treatment status, is maintained for up to two years"*.

Main outcomes reported in MEASURE 1 and MEASURE 2

Results for key outcome measures are considered below.

On page 110 of the CS[1], the company reports that five main outcomes were considered relevant for inclusion in the MTC and additionally identified ASAS 5/6 response and SF-36 values as additional outcomes which were analysed. Evidence from MEASURE 1 and MEASURE 2 for each of these outcomes as described in the main submission is presented below in separate tables:

- ASAS20 response (Table 4.8)
- ASAS40 response (Table 4.9)
- BASDAI 50 response (Table 4.10)
- BASDAI change from baseline (Table 4.11)
- BASFI change from baseline (Table 4.12)
- ASAS 5/6 response (Table 4.13)
- SF-36 PCS (Table 4.14)

All other outcomes, which did not form part of the MTC, are presented in a separate table (Table 4.15) and in narrative.

Table 4.8: ASAS20 response using observed data (12 weeks) and non-responder imputation (16 weeks)

(Based on Tables 17 and 29 of the CS[1], table 14.2-1.3 of CSR[22])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	60.8% (OR 3.89; 95% CI 2.28 to 6.65)	28.7%	61.1% (OR 4.38; 95% CI 2.14 to 8.96)	28.4%

ASAS = Assessment of Spondyloarthritis; CI = confidence interval; CS = company submission; CSR = Clinical Study report; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); OR = odds ratio; s.c. = subcutaneous

For ASAS20, secukinumab shows marked benefit over placebo at both 12 and 16 weeks in MEASURE 2 and at 16 weeks in MEASURE 1. The relative performance of secukinumab at 16 weeks is broadly similar to that achieved at 12 weeks (MEASURE 2).

Table 4.9: ASAS40 response using observed data (12 weeks) and non-responder imputation (16 weeks)
(Based on Tables 19 and 31 of the CS[1], Table 14.2-2.3 of CSR[22])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	41.6% (p<0.0001)	13.1%	36.1% (p<0.001)	10.8%

ASAS = Assessment of Spondyloarthritis; CS = company submission; CSR = Clinical Study report; ; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); s.c. = subcutaneous

For ASAS40, secukinumab shows marked benefit over placebo at both 12 and 16 weeks in MEASURE 2 and at 16 weeks in MEASURE 1. The relative performance of secukinumab at 16 weeks is broadly similar to that achieved at 12 weeks (MEASURE 2).

Table 4.10: BASDAI 50 response using observed data (12 weeks) and non-responder imputation (16 weeks)
(Based on Tables 23 and 35 of the CS[1], Table 14.2-31.3 of CSR[22])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	37.6% (p<0.0001)	8.2%	30.6% (p<0.01)	10.8%

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CS = company submission; CSR = Clinical Study report; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); s.c. = subcutaneous

For BASDAI 50 secukinumab shows marked benefit over placebo at both 12 and 16 weeks in MEASURE 2 and at 16 weeks in MEASURE 1. The relative performance of secukinumab at 16 weeks is broadly similar to that achieved at 12 weeks (MEASURE 2)

Table 4.11: BASDAI change from baseline using observed data (12 weeks) and MMRM (16 weeks)
(Based on Tables 21 and 33 of the CS[1], Table 14.2-3.3 of CSR[22])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	[redacted]	[redacted]
16 weeks	-2.32, SE 0.172 [n=121]	-0.59, SE 0.180 [n=108]	-2.19, SE 0.248 [n=67]	-0.85, SE 0.252 [n=64]

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CS = company submission; CSR = Clinical Study report; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; MMRM = mixed-effect model repeated measures; NA = Not available (in same format); s.c. = subcutaneous; SD = standard deviation; SE = standard error

For BASDAI change from baseline, secukinumab shows marked benefit over placebo at both 12 and 16 weeks in MEASURE 2 and at 16 weeks in MEASURE 1. The relative performance of secukinumab at 16 weeks is broadly similar to that achieved at 12 weeks (MEASURE 2).

Table 4.12: BASFI change from baseline using MMRM
(Based on Tables 25 and 37 of the CS[1])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	NA	NA
16 weeks	-1.84, SE 0.17 [n=121]	-0.37, SE 0.17 [n=108]	-2.15, SE 0.23 [n=67]	-0.68, SE 0.24 [n=64]

BASFI = Bath Ankylosing Spondylitis Functional Index; CS = company submission; CSR = Clinical Study report; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; MMRM = mixed-effect model repeated measures; NA = Not available (in same format); s.c. = subcutaneous; SE = standard error

For BASFI change from baseline, secukinumab shows marked benefit over placebo at 16 weeks in both MEASURE 2 and MEASURE 1. No evidence was provided to evaluate effectiveness at 12 weeks.

Table 4.13: ASAS 5/6 response using non-responder imputation
(Based on Tables 135 and 160 of CS appendices[18])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	NA	NA
16 weeks	48.8% (p<0.01)	13.1%	43.1% (p<0.001)	8.1%

ASAS = Assessment of Spondyloarthritis; CS = company submission; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; NA = Not available (in same format); s.c. = subcutaneous

For ASAS 5/6 response, secukinumab shows marked benefit over placebo at 16 weeks in both MEASURE 2 and MEASURE 1. No evidence was provided to evaluate effectiveness at 12 weeks. Results from other trials (using both fixed and random effects models) were provided by the company as part of response to clarification and these were largely favourable or neutral to secukinumab.[6]

Table 4.14: SF-36 PCS change from baseline using MMRM
(Based on Tables 156 and 181 of CS appendices[18])

Weeks from baseline	MEASURE 1		MEASURE 2	
	Secukinumab 150 mg i.v. (N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
12 weeks	NA	NA	NA	NA
16 weeks	5.57, SE 0.59 [n=122]	0.96, SE 0.61 [n=111]	6.06, SE 0.78 [n=67]	1.92, SE 0.79 [n=66]

CS = company submission; ERG = Evidence Review Group; i.v. = intravenous; mg = milligram; MMRM = mixed-effect model repeated measures; NA = Not available (in same format); PCS = Physical component score; s.c. = subcutaneous; SE = standard error; SF-36 = Short form 36

For SF-36 PCS, secukinumab shows marked benefit over placebo at 16 weeks in both MEASURE 2 and MEASURE 1. No evidence was provided to evaluate effectiveness at 12 weeks. Results from

other trials (using both fixed and random effects models) were provided by the company as part of response to clarification and these were largely favourable or neutral to secukinumab.[6]

Other outcomes reported in MEASURE 1 and MEASURE 2

Table 4.15: Summary of other outcomes (MEASURE 1 and MEASURE 2)
(Based on Tables 27 and 39 of the CS[1], Tables 137, 139, 143, 145, 147, 151, 154, 156, 158, 162, 164, 168, 170, 172, 176, 179, 181 and 187 of CS appendices[18])

Other Outcomes	Weeks from baseline	MEASURE 1		MEASURE 2	
		Secukinumab 150 mg i.v.(N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
Using MMRM					
BASMI linear change from baseline	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Health-related quality of life (ASQoL) – using MMRM	12 weeks	NA	NA	NA	NA
	16 weeks	-3.58, SE 0.424 [n=121]	-1.04, SE 0.437 [n=111]	-4.00, SE 0.528 [n=66]	-1.37, SE 0.53 [n=66]
Health-related quality of life (FACIT-Fatigue)	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Health-related quality of life (MCS)	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
hs-CRP change from baseline	12 weeks	NA	NA	NA	NA
	16 weeks	0.40, SE 1.090 [n=121]	0.97, SE 1.095 [n=107]	0.55; SE 1.104 [n=68]	1.13, SE 1.105 [n=66]
Patient's global assessment of disease activity	12 weeks	NA	NA	NA	NA
	16 weeks	-27.98, SE 2.030 [n=121]	-6.64, SE 2.130 [n=108]	-27.69, SE 2.83 [n=67]	-12.87, SE 2.89 [n=64]
Peripheral symptoms measured via MASES score change	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Using non-responder imputation					
ASAS partial remission	12 weeks	NA	NA	NA	NA
	16 weeks	15.2% (p<0.01)	3.3%	13.9% (p=0.0941)	4.1%
ASDAS-CRP [major improvement]	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Using observed data					

Other Outcomes	Weeks from baseline	MEASURE 1		MEASURE 2	
		Secukinumab 150 mg i.v.(N=125)	Placebo (N=122)	Secukinumab 150 mg s.c. (N=72)	Placebo (N=74)
Percent work time missed due to health (WPAI-GH)	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Percent impairment while working due to health (WPAI-GH)	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]
Percent overall work impairment due to health (WPAI-GH)	12 weeks	NA	NA	NA	NA
	16 weeks	[redacted]	[redacted]	[redacted]	[redacted]

ASAS = Assessment of Spondyloarthritis; ASQoL = Ankylosing Spondylitis Quality of Life; BASMI = Bath Ankylosing Spondylitis Metrology Index; CRP = c-reactive protein; CS = company submission; ERG = Evidence Review Group; FACIT = Functional Assessment of Chronic Illness Therapy; hs = high sensitivity; i.v. = intravenous; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MCS = mental component score; mg = milligram; MMRM = Mixed-effect model repeated measures; NA = Not available to ERG after requesting; s.c. = subcutaneous; SD = standard deviation; SE = standard error; WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health

Other outcomes with quantified measure of effectiveness are set out in Table 4.15 above. Twelve week data were not available for any of these outcomes. In both trials, [redacted] (with the exception of ASAS partial remission in MEASURE 2) when assessed at week 16 (where the difference between secukinumab and placebo was not significant). The AS quality of life measure (ASQoL) demonstrated that the secukinumab 150 mg arm experienced significant improvements in quality of life compared to placebo controls in both trials. Furthermore, statistically significant improvements could be detected as early as week 4 in MEASURE 1 and week 8 in MEASURE 2 demonstrating the rapid onset of action (page 24 of CS). The ERG was unable to verify this statement from the materials provided by the company. For most outcomes results from MEASURE 1 are confirmed by results from MEASURE 2. However, it is notable that in MEASURE 1 secukinumab has a more marked effect then in MEASURE 2 for ASDAS-CRP [major improvement], patient's global assessment of disease activity, BASMI linear change from baseline and health-related quality of life (MCS).

In the case of peripheral symptoms measured via MASES score change, the ERG note that [redacted]

Adverse effects of treatment

Adverse effects of treatment are shown in Tables 4.16 and 4.17 (MEASURE 1) and Tables 4.18 and 4.19 (MEASURE 2) below.

Table 4.16: Deaths, other serious or clinically significant adverse events or related discontinuations – up to week 16 (Safety set) – MEASURE 1
(Based on Table 12-9 of CSR[23])

Adverse Event Profile	Secukinumab 75 mg (N=124) n (%)	Secukinumab 150 mg (N=125) n (%)	Secukinumab any dose (N=249) n (%)	Placebo (N=122) n (%)
Subjects with any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with serious or other significant events				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal SAE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study treatment due to any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]
AE = adverse event; CSR = Clinical Study Report; mg = milligram; SAE = serious adverse event				

Table 4.17: Deaths, other serious or clinically significant adverse events or related discontinuations – 52 weeks (Safety set) – MEASURE 1
(Based on Table 12-10 of CSR[23])

Adverse Event Profile	Secukinumab 75 mg (N=179) n (%)	Secukinumab 150 mg (N=181) n (%)	Secukinumab any dose (N=360) n (%)	Placebo up to week 24 (N=122) n (%)
Subjects with any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Subjects with serious or other significant events				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal SAE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study treatment due to any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]
AE = adverse event; CSR = Clinical Study Report; mg = milligram; SAE = serious adverse event				

Table 4.18: Deaths, other serious or clinically significant adverse events or related discontinuations – 16 weeks (Safety set) – MEASURE 2
(Based on Table 60 of the CS[1])

Adverse Event Profile	Secukinumab 150 mg (N=72) n (%)	Secukinumab any dose (N=145) n (%)	Placebo (N=74) n (%)
Subjects with any AE(s)	47 (65.3)	89 (61.4)	47 (63.5)
Subjects with serious or other significant events			
Death	0 (0.0)	1 (0.7)	0 (0.0)
Non-fatal SAE(s)	4 (5.6)	7 (4.8)	3 (4.1)
Discontinued study treatment due to any AE(s)	5 (6.9)	8 (5.5)	4 (5.4)
AE = adverse event; CS = company submission; mg = milligram; SAE = serious adverse event			

Table 4.19: Deaths, other serious or clinically significant adverse events or related discontinuations – 52 weeks (Safety set) – MEASURE 2
(Based on Table 12-8 of CSR[4])

Adverse Event Profile	Secukinumab 75 mg ([redacted]) n (%)	Secukinumab 150 mg ([redacted]) n (%)	Secukinumab, combined ([redacted]) n (%)	Placebo ([redacted]) n (%)
Participants with any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Participants with serious or other significant events				
Death	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal SAE(s)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued study treatment due to any AE(s)	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CSR = Clinical Study Report; mg = milligram; SAE = serious adverse event

Up to week 16 (MEASURE 1) [redacted] (see Table 4.16). In MEASURE 2, any AEs were more common than placebo in participants receiving secukinumab 150 mg but not at any dose (see Table 4.18). Over the whole 52 week treatment period (MEASURE 1 and MEASURE 2, Tables 4.17 and 4.19) [redacted]

EQ-5D

Disaggregated results for EQ-5D change from baseline up to 16 weeks are provided in Tables 4.20 and 4.21 replicated below. Results at 12 weeks have not been provided by the company and so cannot be assessed by the ERG.

Table 4.20: EQ-5D answers at baseline and week 16 using observed data (full analysis set) – MEASURE 1
(Based on Table 178 of CS appendices[18])

Question	Baseline		Week 16	
	Secukinumab 150 mg (N=125)	Placebo (N=122)	Secukinumab 150 mg (N=125)	Placebo (N=122)
	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Mobility				
I have no problems in walking about	[redacted]	[redacted]	[redacted]	[redacted]
I have some problems in walking about	[redacted]	[redacted]	[redacted]	[redacted]
I am confined to bed	[redacted]	[redacted]	[redacted]	[redacted]
Self-care				
I have no problems with self-care	[redacted]	[redacted]	[redacted]	[redacted]

Question	Baseline		Week 16	
	Secukinumab 150 mg (N=125)	Placebo (N=122)	Secukinumab 150 mg (N=125)	Placebo (N=122)
	n/m (%)	n/m (%)	n/m (%)	n/m (%)
I have some problems washing or dressing myself	[redacted]	[redacted]	[redacted]	[redacted]
I am unable to wash or dress myself	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities				
I have no problems with performing my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
I have some problems with performing my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
I am unable to perform my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
Pain or discomfort				
I have no pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
I have some moderate pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
I have extreme pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety or depression				
I am not anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]
I am moderately anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]
I am extremely anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients in each category; m=number of subjects evaluable.
EQ-5D = EuroQol 5D questionnaire ; mg = milligram

Table 4.21: EQ-5D answers at baseline and week 16 using observed data (full analysis set)- MEASURE 2
(Based on Table 153 of CS appendices[18])

Question	Baseline		Week 16	
	Secukinumab 150 mg (N=125)	Placebo (N=122)	Secukinumab 150 mg (N=125)	Placebo (N=122)
	n/m (%)	n/m (%)	n/m (%)	n/m (%)

Question	Baseline		Week 16	
	Secukinumab 150 mg (N=125)	Placebo (N=122)	Secukinumab 150 mg (N=125)	Placebo (N=122)
	n/m (%)	n/m (%)	n/m (%)	n/m (%)
Mobility				
I have no problems in walking about	[redacted]	[redacted]	[redacted]	[redacted]
I have some problems in walking about	[redacted]	[redacted]	[redacted]	[redacted]
I am confined to bed	[redacted]	[redacted]	[redacted]	[redacted]
Self-care				
I have no problems with self-care	[redacted]	[redacted]	[redacted]	[redacted]
I have some problems washing or dressing myself	[redacted]	[redacted]	[redacted]	[redacted]
I am unable to wash or dress myself	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities				
I have no problems with performing my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
I have some problems with performing my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
I am unable to perform my usual activities	[redacted]	[redacted]	[redacted]	[redacted]
Pain or discomfort				
I have no pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
I have some moderate pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
I have extreme pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety or depression				
I am not anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]
I am moderately anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]
I am extremely anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]

n=number of patients in each category; m=number of subjects evaluable.
EQ-5D = EuroQol 5D questionnaire ; mg = milligram

EQ-5D was used to assess health status of patients but no assessment of EQ-5D outcomes is provided in the CS or supplementary materials supplied to the ERG by the company. The ERG has reviewed the reported values and considers them [redacted].

Radiographic outcomes

MEASURE 1 unlike MEASURE 2 provided results for radiographic outcomes. The MEASURE 1 trial assessed a number of radiological secondary endpoints in a subset of patients, reporting changes from baseline for up to two years. Assessments included x-rays of the cervical, thoracic and lumbar spine at week 104 analysed according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) and MRI scans at weeks 16, 52 and 104 to assess sacroiliac and spinal inflammation. The mean ± SD change in mSASSS from baseline to week 104 was 0.30 ± 1.93 in the secukinumab 150 mg arm and [redacted] in the placebo-secukinumab 150 mg arm. No radiographic progression of the disease was observed in approximately 80% of patients randomised to secukinumab at baseline after 104 weeks of treatment (mSASSS change ≤0).

Pain (as captured by ASAS and BASDAI criteria)

Pain is assessed in a number of different ways but no composite assessment of pain is provided in the company submission. Pain is captured by ASAS and BASDAI criteria as well as featuring in health related quality of life measures (e.g. EQ-5D and SF-36) and as part of treatment emergent adverse events reported in tables 60/62 (week 16) and table 61/63 (week 104) of the CS for MEASURE 2/ MEASURE 1 (oropharyngeal pain, injection site pain, pain in extremity, upper abdominal pain), respectively.[1]

ERG comment: The ERG note that MEASURE 1 loading doses are based on intravenous administration of secukinumab whereas MEASURE 2 is based on subcutaneous administration. This is recognised by the company as being a potential limitation of the evidence, with MEASURE 1 loading dosage not being reflective of the subcutaneous loading schedule. A recent review of optimal medication methods undertaken by Jin et al. suggested that it would be "inappropriate to simply say that one injection route is overwhelmingly better than another one" and it would be unwise, in the absence of further research, to conclude that inclusion of evidence based on intravenous administration was in some way beneficial to the company submission.[24] The ERG agrees with the company, that, although not ideal, inclusion of MEASURE 1 seems reasonable in the light of limited evidence for subcutaneous administration.

The ERG requested the following as part of its letter of clarification "*Please provide data separately (...) for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials and, if available, all other trials included in the network meta-analysis."*

The company did not provide 12 week data in a format comparable to the 16 week data in the CS (see Tables 4.8 to 4.11) for all outcomes specified in the scope. This means that comparisons with other trials which report outcomes after 12 weeks should be viewed with a degree of scepticism. The company provided input MTC input values for key outcomes at 12 weeks for both, MEASURE 1 and MEASURE 2 (see Section 4.3), but the ERG was unable to reconcile these values with the week 12 data provided for MEASURE 2 in the CSR.[22] This being said, the performance of secukinumab in relation to placebo seems relatively stable between 12 and 16 weeks for the main outcomes the ERG has been able to assess from appendices to the MEASURE 2 clinical study report (see Tables 4.8 to 4.11).

The ERG notes that outcomes relating to pain, adverse effects of treatment and health related quality of life (all part of the original scope) have been provided for MEASURE 1 and MEASURE 2. Whilst pain was not examined as a discrete entity or single composite measure, [redacted]

[redacted]. The ERG notes that the low numbers of events for adverse effects of treatment is a key factor limiting meaningful comparative analysis. The ERG also notes that evidence from MEASURE 1 and MEASURE 2 [redacted].

The ERG was not able to assess significant adverse event profile for MEASURE 2 at week 16 because results were not available. It was noted that secukinumab was [redacted] in MEASURE 1 at week 16 and week 52 and in MEASURE 2 at week 52.

4.3 Critique of trials identified and included in the indirect comparison and/or mixed treatment comparison

The CS[1] reported the inclusion/exclusion of studies in the MTC on page 49 (Table 4.22).

Table 4.22: Inclusion and exclusion of RCTs in the MTC
(Based on Table 8 of CS[1])

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
A2209 trial	Two doses of i.v. secukinumab (10 mg/kg) given 3 weeks apart	Two doses of i.v. placebo given 3 weeks apart	30 patients aged 18-65 with moderate-to-severe AS were randomly assigned to treatment	To assess the efficacy and safety of secukinumab in treating patients with active AS	Baeten et al. 2013 [CS 22]	NA	No – treatment regimen is unlicensed use of secuki-numab at dose of 10 mg/kg 3 weeks apart
ANSWERS	Etanercept (25 mg) s.c. once weekly	Etanercept (50 mg) s.c. once weekly	47 patients responded to etanercept (50 mg weekly) in the first phase of the trial, and were randomised to either continue on 50 mg weekly or reduce to 25 mg weekly	To evaluate maintenance of response to etanercept following dose reduction	Gaffney et al. 2014 [CS 88]	NA	No – dose reduction strategy not relevant
ASCEND	Etanercept (50 mg) s.c. once weekly	Sulfasalazine titrated to a maximum of 3 g/day	566 patients, at least 18 years of age, with active AS, who had	To compare the efficacy and safety of etanercept with that of sulfasalazine	Braun et al. 2011 [CS 89]	Braun et al. 2012 [CS 90] Moots et al. 2012 [CS 91]	No – sulfasalazine does not act as a

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
			previously failed treatment with at least 1 NSAID were randomly assigned to treatment	after 16 weeks of treatment in patients with axial and peripheral manifestations of AS			comparator arm in the network and is not a treatment of interest
ASSERT	Infliximab (5 mg/kg) i.v. at Weeks 0, 2, 6, 12, and 18	Placebo at weeks 0, 2, 6, 12, and 18	279 adult patients with AS for at least three months were randomly assigned to treatment	To evaluate the efficacy and safety of infliximab in patients with AS	van der Heijde et al. 2005 [CS 92]	Machado et al. 2010 [CS 4] Braun et al. 2009 [CS 93] Braun et al. 2006 [CS 94] Braun et al. 2008 [CS 95]	Yes
ATLAS	Adalimumab (40 mg) s.c. every other week	Placebo every other week	315 patients, at least 18 years of age, with active AS, were randomly assigned to treatment	To evaluate the safety and efficacy of adalimumab in patients with active AS	van der Heijde et al. 2006 [CS 96]	van der Heijde et al. 2015 [CS 97] Sieper et al. 2012 [CS 98] Maksymowych et al. 2010 [CS 99] van der Heijde et al. 2009 [CS 100] van der Heijde	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
						et al. 2009 [CS 101] Revicki et al. 2008 [CS 102] van der Heijde et al. 2008 [CS 103] Davis et al. 2007 [CS 104] Sieper et al. 2014 [CS 105] van der Heijde et al. 2008 [CS 106]	
CANDLE	Infliximab (3 mg/kg) i.v. at weeks 0, 2, 6, 14 and every 8 weeks thereafter	Placebo at weeks 0, 2 and 6, then infliximab at Weeks 14, 16, 22 and every 8 weeks thereafter	76 patients with active AS were randomised	To evaluate the efficacy and safety of low-dose (3 mg/kg) infliximab in the treatment of AS	Inman et al. 2010 [CS 107]	Maksymowych et al. 2010 [CS 108] Inman et al. 2008 [CS 109] Maksymowych et al. 2008 [CS 110]	No – treatment regimen is unlicensed use of infliximab at dose of 3 mg/kg

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
Giardina et al. 2010	Etanercept (50 mg) s.c. weekly	Infliximab (5 mg/kg at week 0, 2, 6 and every 6 weeks	50 patients who were non-responders to oral NSAIDs	To compare the efficacy and safety of etanercept and infliximab	Giardina et al. 2010 [REF 29]	NA	Yes
GO-RAISE	Golimumab (50 mg or 100 mg) s.c. every 4 weeks	Placebo every 4 weeks	356 adult patients, with active AS, were randomly assigned to treatment	To evaluate the efficacy and safety of golimumab in patients with AS	Inman et al. 2008 [CS 111]	Deodhar et al. 2015 [CS 112] van der Heijde et al. 2014 [CS 113] Braun et al. 2014 [CS 114] van der Heijde et al. 2013a [CS 115] Braun et al. 2012b [CS 116] Braun et al. 2012c [CS 117] Deodhar et al. 2010 [CS 118] van der Heijde	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
						et al. 2013b [CS 119] Deodhar et al. 2013 [CS 120] Braun et al. 2013 [CS 121] Deodhar et al. 2014a [CS 122] Inman et al. 2013 [CS 123] Van Der Heijde et al. 2013c [CS 124] Kay et al. 2015 [CS 125]	
Gorman et al. 2002	Etanercept (25 mg) s.c. twice a week	Placebo twice a week	40 patients with evidence of active AS despite accepted treatments	To investigate the efficacy of etanercept in patients with AS	Gorman et al. 2002 [CS 126]	NA	No – the study did not report any endpoints of interest
Hu et al. 2012	Adalimumab (40 mg) s.c. every other week during the	Placebo every other week	46 patients who had been treated	To investigate whether	Hu et al. 2012	NA	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
	initial 12 week double-blind period. This regimen continued throughout the ongoing open-label period	during the initial 12 week double-blind period. At week 12, all patients began receiving adalimumab (40 mg) s.c. every other week, and this regimen continued throughout the ongoing open-label period	unsuccessfully (nonresponsive or lack of tolerance) with ≥ 1 NSAID	adalimumab is effective for active AS patients and whether it has an impact on the formation of fatty deposition lesions and serum Dickkopf homolog 1 (Dkk-1) levels in AS patients	[CS 127]		
Huang et al. 2010	Etanercept (50 mg) s.c. once weekly	Placebo once weekly for 6 weeks, then etanercept (50 mg) once weekly	152 Chinese patients with active AS were randomised	To evaluate the short-term efficacy and safety of etanercept treatment in Chinese patients with active AS	Huang et al. 2010 [CS 128]	NA	No – there was no comparator arm after 6 weeks
Huang et al. 2011	Etanercept (5 mg) s.c. once weekly	Placebo once weekly for 6 weeks, then etanercept	381 Chinese patients completed the trial	To evaluate the efficacy and safety of etanercept 50 mg once-weekly	Huang et al. 2011 [CS 129]	NA	No – there was no comparator arm after

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
		(50 mg) once weekly		treatment of Chinese patients with active AS			6 weeks
Huang et al. 2014	Adalimumab (40 mg) s.c. every other week	Placebo every other week	334 patients with inadequate response or intolerance to prior treatments	To evaluate the efficacy and safety of adalimumab in Chinese patients with AS	Huang et al. 2014 [CS 130]	NA	Yes
LOADET	Etanercept (50 mg) s.c. twice a week	Etanercept (50 mg) once a week	108 patients aged 18-70 with a diagnosis of AS and who had failed treatment with at least two NSAIDs were randomly assigned to treatment	To evaluate the efficacy and safety of etanercept 100 mg vs. 50 mg/ week in patients with AS	Navarro-Sarabia et al. 2011 [CS 131]	NA	No – comparison was to an unlicensed dose of etanercept
Marzo-Ortega et al. 2005	Infusions of infliximab (5 mg/kg) i.v. at weeks 0, 2, 6, 14, and 22. In addition, all subjects were provided at week 0 with a prescription for oral methotrexate at a dose of 7.5 mg with folic acid cover (5 mg twice a	Infusions of placebo at weeks 0, 2, 6, 14, and 22. In addition, all subjects were provided at week 0 with a	42 patients with persistent inflammatory back pain and CRP>10 mg/l despite treatment with NSAIDs or DMARDs	To examine the efficacy and safety of infliximab combined with methotrexate compared with methotrexate alone in the treatment of	Marzo-Ortega et al. 2005 [CS 132]	NA	No – the study did not connect to the network

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
	week), which would be eventually increased to 10 mg a week	prescription for oral metho-trexate at a dose of 7.5 mg with folic acid cover (5 mg twice a week), which would be eventually increased to 10 mg a week		AS			
MEASURE 1	Secukinumab given as i.v. loading doses (10 mg/kg) at weeks 0, 2 and 4, followed by secukinumab (75 or 150 mg) s.c. at week 8 and injected every 4 weeks	Placebo given i.v. at weeks 0, 2 and 4, followed by placebo s.c. at week 8 and 12	371 patients, at least 18 years old, with moderate to severe active AS were randomly assigned to treatment	To demonstrate the efficacy on signs and symptoms at week 16 and to assess the long term safety, tolerability and efficacy on signs, symptoms and spine structure of secukinumab in subjects with active AS despite current or previous NSAID, DMARD and/or TNFα inhibitor	Baeten et al. 2015a[25]	Baeten et al. 2014 [CS 133] Deodhar et al. 2014 [CS 134] Baeten et al. 2015 [CS 23] Baraliakos et al. 2015 [CS 26] Deodhar et al. 2015 [CS 135] Baeten et al. 2015 [CS 28]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
				therapy		Baraliakos et al. 2015 [CS 136] Wei et al. 2015 [CS 137]	
MEASURE 2	Secukinumab (75 mg or 150 mg) plus placebo (150 mg or 75 mg) s.c. once weekly at weeks 0, 1, 2, 3 and 4, followed by dosing every four weeks starting at week 4	Placebo 75 mg and placebo 150 mg s.c. once weekly at weeks 0, 1, 2, 3 and 4, followed by dosing every four weeks starting at week 4	219 patients, at least 18 years of age, with moderate to severe active AS were randomly assigned to treatment	To provide 16-52 weeks efficacy, safety and tolerability data to support use of the secukinumab PFS for s.c. self-administration in patients with active AS despite current or previous NSAID, DMARD and/or TNFα inhibitor therapy	Baeten et al. 2015a[25]	Sieper et al. 2014 [CS 138] Baeten et al. 2015 [CS 28] Braun et al. 2015 [CS 139] Braun et al. 2015 [CS 140] Deodhar et al. 2015 [CS 135] Deodhar et al. 2015 [CS 141] Sieper et al. 2015 [CS 27] Sieper et	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
						al. 2015 [CS 142]	
M03-606 Canadian AS Study	Adalimumab (40 mg) s.c. every other week for 24 weeks, then open label adalimumab	Placebo every other week for 24 weeks, then open label adalimumab	82 patients with active AS who had inadequate response, or were intolerant to >1 NSAID; and had no prior exposure to anti-TNF therapy	To compare the progression of structural damage in the spine in patients with AS treated with adalimumab for up to 2 years versus patients who had not received TNF antagonist therapy	Lambert et al. 2007 [CS 143]	Sieper et al. 2014 [CS 105] Van der Heijde et al. 2009 [CS 144]	No – the study did not report any endpoints of interest
RAPID-axSpA	Certolizumab pegol (200 mg) s.c. every 2 weeks or certolizumab pegol (400 mg) s.c. every 4 weeks	Placebo	325 patients, at least 18 years of age, with active axial spondylo-arthritis including patients with AS and non-radiographic axial spondyloarthritis	To evaluate the efficacy and safety of certolizumab pegol after 24 weeks in patients with axial spondylitis and non-radiographic axial spondylitis	Landewe et al. 2014 [CS 145]	Sieper at al. 2015 [CS 146] Landewe et al. 2012 [CS 147] Sieper et al. 2014 [CS 148]	Yes

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
			were randomly assigned to treatment			Maksymowych et al. 2014 [CS 149] Sieper et al. 2014 [CS 150] Mease et al. 2014 [CS 151] Van der Heijde et al. 2013 [CS 152] Landewe et al. 2013 [CS 153] Sieper et al. 2013 [CS 154] Sieper et al. 2013 [CS 155] Landewe et al. 2013 [CS 156] Sieper et al. 2014	

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
						[CS 157] Rosenbaum et al. 2014 [CS 158] Rudwaleit et al. 2014 [CS 159] Sieper et al. 2014 [CS 160] Sieper et al. 2015 [CS 161]	
SPINE	Etanercept (50 mg) s.c. once weekly	Placebo once weekly	82 patients who were refractory to NSAIDs but biologic-naive	To evaluate the effect of etanercept in patients with advanced AS	Dougados et al. 2011 [CS 162]	Dougados et al. 2012 [CS 163]	Yes
Tam et al. 2014	Golimumab (50 mg) s.c. monthly	Placebo monthly	41 patients with AS who had an inadequate response to at least two NSAIDs during a 3-month period, failure of i.a. steroids or failure of SSZ (in	To ascertain the efficacy of golimumab compared with placebo in the prevention of atherosclerosis and arterial stiffness in AS	Tam et al. 2014 [CS 164]	NA	No – the study did not report any endpoints of interest

Trial acronym	Intervention	Comparator	Population	Aim/objectives of the study	Primary study reference	Secondary references	Study included in MTC?
			patients with predominantly peripheral arthritis)				
Zhang et al. 2009	Etanercept s.c. for 12 weeks	Placebo for 6 weeks, then etanercept for 6 weeks	86 patients with active AS were randomised	To evaluate the short-term efficacy of etanercept in patients with active AS	Zhang et al. 2009 [CS 165]	NA	No – there was no comparator arm after 6 weeks
Zhang et al. 2012	Etanercept 50 mg s.c. for 12 weeks	Placebo for 6 weeks, then etanercept for 6 weeks	127 patients with active AS were randomised	To evaluate the efficacy of etanercept in the treatment of active AS with enthesitis	Zhang et al. 2012 [CS 166]	NA	No – there was no comparator arm after 6 weeks

AS = Ankylosing spondylitis; CRP = c-reactive protein; CS = company submission; DMARD = Disease modifying anti-rheumatic drug; g = gram; i.a. = intra-articular; i.v. = intravenous; kg = kilogram; mg = milligram; MTC = Mixed treatment comparison; NA = not applicable; NSAID = Non-steroidal anti-inflammatory drugs; PFS = Progression-free survival; RCT = randomised controlled trial; s.c. = subcutaneous; SSZ = Sulfasalazine; TNF = Tumour Necrosis Factor

ERG comment: The selection of studies for incorporation in the MTC is consistent with the inclusion criteria. The reason for the exclusion of one study (Marzo-Ortega et al. 2005 [CS reference 132]) was questioned by the ERG in the clarification letter (Question A16). The explanation provided by the company in response was that patients in both arms of this study received concomitant methotrexate therefore the placebo arm in this study cannot be considered equivalent to the placebo arms of other studies in the network.[6] The ERG considers this a satisfactory reason for the exclusion of this study.

On page 30 of the response to the clarification letter[6] the company acknowledged that two studies had been omitted in error from the original set of analyses

- *The ATLAS study had been excluded from the BASFI change from baseline networks in error*
- *The Huang (2014) study had not been included in the biologic-naïve networks. Initially this study was categorised as being "unclear" regarding whether the population was biologic naïve or biologic experienced. On further review, the article includes the statement "Prior exposure to TNF-α inhibitors, natalizumab or efalizumab at any time, or use of traditional Chinese medicines within 28 days of baseline was not allowed". This indicates that the study was conducted amongst biologic naïve patients. Therefore revised analyses, including Huang (2014) in the biologic naïve networks are, presented in Section D.*

ERG comment: The inclusion of additional studies fundamentally changes the respective networks. This renders the results for the corresponding networks in the original CS redundant. As indicated above, the evidence on the efficacy of secukinumab in these scenarios should be evaluated according to the revised results presented in Section D of the response to the clarification letter.[6]

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The methods of analysis were detailed on page 117 of the CS.[1]

"The BASDAI 50, ASAS20 and, [sic!] *ASAS40 scores were modelled as binomial endpoints. For binomial data, a generalised linear model with logit link function and binomial likelihood was used.*

BASFI change from baseline and BASDAI change as continuous outcomes were modelled with a normal likelihood MTC setup with an identity link function. This was consistent with the method described by Dias et al. in NICE DSU Technical Support Document 2. [CS reference 187]

For all endpoints, Bayesian models for fixed effects (FE) and random effects (RE) were considered. FE models were selected as preferable, for the reasons outlined in Section 4.10.9 and all results presented in the main body of the submission are therefore based on FE models.

Meta-regression adjustments for specific baseline characteristics were not feasible for the baseline characteristics that were extracted. Meta-regression adjustments can also be extended to include the mean placebo effect as a covariate. [CS reference 187] *This captures many characteristics within a single measure, akin to the random-effects adjustments for heterogeneity. This model views the study effects themselves as effect modifiers to the treatment. The model that was applied to this end was the baseline natural history model, which is described in detail in the NICE DSU Technical Support Document 5. (NICE TSD5: Dias et al). Analyses using placebo-response adjustments were explored, but were often not feasible, particularly within random-effects modelling.*

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method implemented in the OpenBUGS and JAGS software packages. For each model, the first 50,000 iterations from the OpenBUGS/JAGS sampler were discarded as 'burn-in' and the inferences were based on an additional 50,000 iterations using two chains. Convergence of the chains was confirmed by the Gelman-Rubin statistic. All analyses were performed using R version 3.1.2 (http://www.r-project.org/) and OpenBugs/JAGS version 3.2.3 (OpenBUGS/JAGS Project Management Group)".

ERG comment: The application of the MTC methodology appears to be appropriate in line with the NICE Technical Support documents as cited in the CS. Dichotomous endpoints were modelled using a binomial likelihood and a logit link function whereas continuous outcomes were modelled using a normal likelihood and an identity link function. The CS reports an appropriate assessment of the mixing and convergence of chains. The ERG queried the calculation of absolute response, the assessment of inconsistency and the assessment of heterogeneity in the clarification letter. In all three cases the company response indicated that this had been carried out appropriately.[6] There were some concerns over the selection of data for inclusion in the MTC model and the assumption of a fixed effect rather than a random effects model (see below).

Page 114 of the CS[1] reported that the base case MTC pooled data from week 12-16 time points. The justification given was that data were taken from the primary endpoint of each of the included studies. Sensitivity analysis was also reported in the CS using only data from the 12 week time point (page 134).[1]

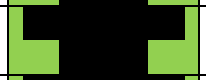
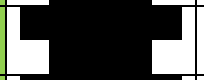
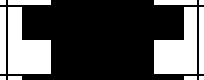
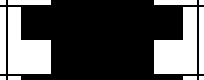
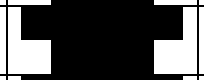
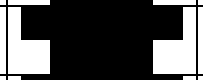
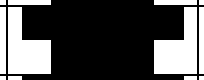
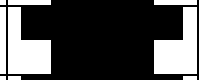
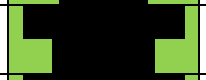
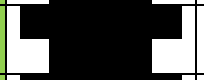
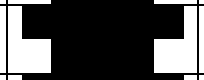
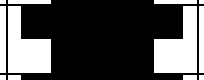
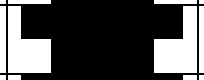
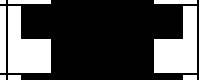
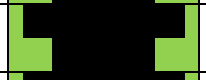
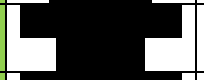
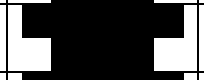
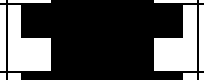
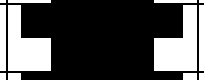
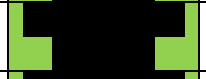
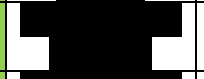
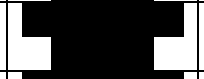
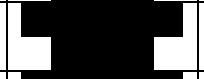
ERG comment: Pooling data across different time points is not considered appropriate as treating patients for longer increases the likelihood that the patient will respond to treatment.[26] This creates a bias in favour of those treatments assessed in studies with longer primary endpoints. The argument that data were taken from the primary endpoint of each study is not a sound justification for pooling data across time points since the designation of a given endpoint as 'primary' is essentially arbitrary. There were only three studies included in the MTC that reported data at time points >12 weeks: GO-RAISE, MEASURE 1 and MEASURE 2. This implies that the bias introduced by treating patients for a longer period primarily acts in favour of secukinumab. All three of GO-RAISE, MEASURE 1 and MEASURE 2 also reported data at 12 weeks. In the opinion of the ERG the base case MTC should have been based on 12 week data for all networks. It should be noted that this would result in the exclusion of GO-RAISE from the networks for ASAS40 and BASDAI 50 as these outcomes were only reported after 14 weeks. This would eliminate the comparison of secukinumab versus golimumab 50 mg or golimumab 100 mg however the robustness of the other treatment comparisons would be increased as a result. A comparison of the base case results with the results of the sensitivity analysis using only 12 week data illustrates the bias introduced by pooling data across time points. In the base case secukinumab showed a statistically significant increase in the probability of achieving a response relative placebo as measured by ASAS20, ASAS40 and BASDAI 50. In the 12 week sensitivity analysis the same comparisons are still statistically significant but the magnitude of the treatment effect is reduced for all three outcomes. A similar reduction in the effectiveness of secukinumab compared to all other treatments when the analysis in based on 12 week data from all studies. The same effect is observed in both the whole population (Table 4.23) and the biologic naïve population (Table 4.24) for each of ASAS20, ASAS40 and BASDAI 50.

A similar bias is observed for the continuous outcomes in both the whole population (Table 4.25) and the biologic naïve population (Table 4.26). There was less improvement from baseline in both

BASDAI and BASFI for secukinumab relative to placebo when the analysis was based on only 12 week data compared to the base case analysis. The change from baseline in BASDAI and BASFI for secukinumab relative to adalimumab 40 mg, certolizumab pegol 200 mg, certolizumab pegol 400 mg and etancercept 50 mg qw is reduced or in some cases reversed in the sensitivity analysis compared to the base case. The effect of secukinumab relative to golimumab 50 mg, golimumab 100 mg and infliximab is increased in the sensitivity analysis compared to the base case.

Table 4.23: Whole population – binomial endpoints

(Based on Tables 13 and 17 of response to clarification letter[20] and Table 8 of CS[6])

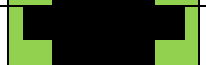
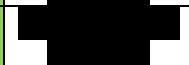
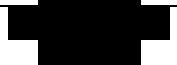
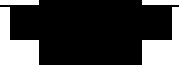
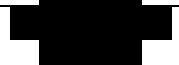
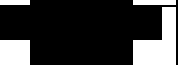
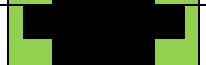
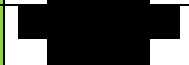
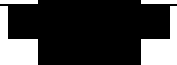
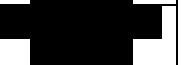
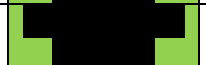
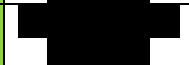
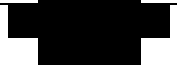
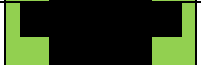
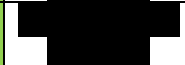
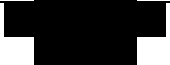
Endpoint	Analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
ASAS20	Base Case								
	12 week data								
ASAS40	Base Case								
	12 week data								
BASDAI 50	Base Case								
	12 week data								

Green cells represent statistically meaningful result;– =not analysed (i.e. could not be included in network)

ADA 40 = adalimumab 40 mg; ASAS = Assessment of Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CZP 200 = certolizumab pegol 200 mg; CZP 400 = certolizumab pegol 400 mg; ETN 50 = etanercept 50 mg; GOL = golimumab; INF = infliximab; PBO = placebo; QW = once weekly

Table 4.24: Biologic naïve – binomial endpoints

(Based on Tables 13 and 17 of response to clarification letter[20] and Table 8 of CS[6])

Endpoint	Analysis	PBO	ADA40	CZP200	CZP400	ETN50QW	GOL100	GOL 50	INF5
ASAS20	Base Case								
	12 week data								
ASAS40	Base Case								
	12 week data								
BASDAI 50	Base Case								
	12 week data								

Green cells represent statistically meaningful result;– =not analysed (i.e. could not be included in network)

ADA 40 = adalimumab 40 mg; ASAS = Assessment of Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CZP 200 = certolizumab pegol 200 mg; CZP 400 = certolizumab pegol 400 mg; ETN 50 = etanercept 50 mg; GOL = golimumab; INF = infliximab; PBO = placebo; QW = once weekly

Table 4.25: Whole population – continuous endpoints

(Based on Tables 14 and 18 of response to clarification letter[20] and Table 8 of CS[6])

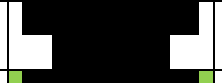
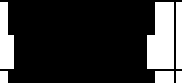
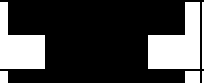
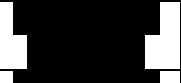
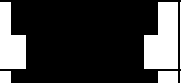
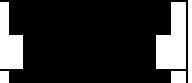
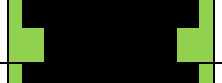
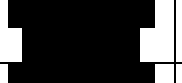
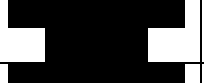
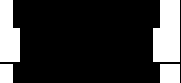
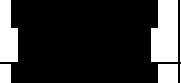
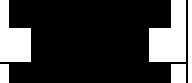
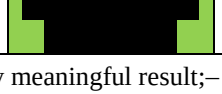
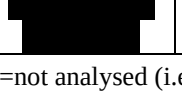
Endpoint	Analysis	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
BASDAI change from baseline	Base Case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	12 week data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline	Base Case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	12 week data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Green cells represent statistically meaningful result;– =not analysed (i.e. could not be included in network)

ADA 40 = adalimumab 40 mg; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CZP 200 = certolizumab pegol 200 mg; CZP 400 = certolizumab pegol 400 mg; ETN 50 = etanercept 50 mg; GOL = golimumab; INF = infliximab; PBO = placebo; QW = once weekly

Table 4.26: Biologic naïve – continuous endpoints

(Based on Tables 14 and 18 of response to clarification letter[20] and Table 8 of CS[6])

Endpoint	Analysis	PBO	ADA40	CZP200	CZP400	ETN 50QW	GOL100	GOL50	INF 5
BASDAI change from baseline	Base Case								
	12 week data								
BASFI change from baseline	Base Case								
	12 week data								

Green cells represent statistically meaningful result;– =not analysed (i.e. could not be included in network)

ADA 40 = adalimumab 40 mg; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CZP 200 = certolizumab pegol 200 mg; CZP 400 = certolizumab pegol 400 mg; ETN 50 = etanercept 50 mg; GOL = golimumab; INF = infliximab; PBO = placebo; QW = once weekly

Page 140 of the CS[1] states that a fixed effect model was preferred over random effects models for all networks. The justification given was that random effects models were not mathematically feasible for some networks in the biologic naïve population and there was no substantial difference in the deviance information criterion (DIC) between fixed effect and random effect models. The results from random effects models were provided in the response to the clarification letter for those networks where a random effects was mathematically feasible (page 31)[6]. These results were based on the revised networks including the ATLAS study in the BASFI networks and Huang 2014 in the biologic naïve networks. These studies were omitted in error from the original analyses, see Section 4.3 above.

ERG comment: The results from the random effects models showed only small numerical changes in the estimated treatment effects of secukinumab versus other treatments on ASAS20, ASAS40 and BASDAI 50. The degree of uncertainty surrounding the estimated treatment effects was increased as shown by the wider 95% credible intervals observed in the random effects model compared to the fixed effect model. The same comments apply to the continuous outcomes BASDAI change from baseline and BASFI change from baseline. The increased uncertainty in the random effects models is most likely due to the small number of studies informing each treatment comparison which makes the variation between studies difficult to estimate in the random effects model. This may also be part of the reason why random effects models were not mathematically feasible for some networks in the biologic naïve population. The evidence networks presented in the CS were all based on relatively small numbers of studies with only one to three studies informing each treatment comparison. Treatment effects estimated based on such limited evidence should be expected to have a high degree of uncertainty. The variation between studies and thus the magnitude of the uncertainty is difficult to estimate in networks based on few studies. In other words, the degree of uncertainty is itself uncertain. The fact that the uncertainty is difficult to estimate should not be taken as evidence that uncertainty is not present. The fixed effect model may be a reasonable approach in cases where the variation between studies cannot be reliably estimated however it should be noted that this approach is likely to underestimate the true variation in the treatment effect, i.e. the resulting estimates will be over precise. The comments above regarding 12 week data versus 12-16 week data in the original analyses also apply to the revised analyses and to the random effects model.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The evidence presented is relevant to the scope of the decision problem. The selection of studies for inclusion in the MTC appears to be appropriate and the application of the MTC methodology seems to be correct. There are some potential limitations which may lead to bias in the results. The quality assessment of the studies included in the MTC highlighted a potential imbalance between treatment arms at study onset in three studies (Huang et al. 2014, RAPID-ax SpA, SPINE). In two of these three studies (RAPID-ax SpA, SPINE) patients in the placebo arm had less severe disease than those patients randomised to active treatment. The effect of this imbalance is difficult to predict. The base case MTC analysis pooled data from time points between 12 and 16 weeks based on the primary endpoint of the individual studies. This creates a potential bias in favour of those treatments in studies with longer endpoints. The sensitivity analysis reported in the CS which limited analysis to only data reported at 12 weeks showed reduced effectiveness for secukinumab for most outcomes.

The base case MTC analysis reported results from a fixed effect model based on the justification that there was no difference in the DIC statistic between fixed or random effects models and that a random effects model was not mathematically feasible in some cases. The difficulty in obtaining results from random effects is likely to be a result of the small number of studies for each treatment comparison in the evidence networks. This means that the variation between studies is estimated based on a small number of data points. Although the estimation of the variability in the treatment effects is difficult due to the lack of data it is unlikely that the variability is zero as defined in a fixed effect model. The use of a fixed effect model is likely to underestimate the true variation in the treatment effects.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Objective of cost effectiveness review

The objective of the cost effectiveness review in the company submission (CS) was to identify and review evidence from economic analyses relating to the use of secukinumab and/or other relevant comparator regimens for the treatment of adult patients with active ankylosing spondylitis.

The CS includes an original systematic literature review (SLR) until January 2015 and an update of the SLR (until 14 September 2015, including one-year overlap with the original SLR). The start of the date range for database searches was January 1999, whereas for conference abstract searches, the date range was from January 2013.

The search strategies for the cost-effectiveness review are discussed in detail in Section 4.1.1.

ERG comments: The ERG thinks that the objective of the cost effectiveness review is in line with the aim of the submission. The search strategies in "clinicaltrials.gov" and International Clinical Trials Registry Platform (ICTRP) were not provided in the submission. The date range for conference abstracts was different from that for databases, because high-quality studies reported in abstract form before 2013 were expected to have been subsequently published in a peer-reviewed journal and therefore captured by database searches. The ERG thinks that there can be high quality abstracts that were published before 2013 but not yet published in a peer-reviewed journal.

5.1.2 Inclusion/exclusion criteria used in the study selection

Table 5.1 presents an overview of inclusion and exclusion criteria used for the review.

Table 5.1: Inclusion and exclusion criteria used for the review
(Based on Table 65 of the CS[1])

Criteria	Include	Exclude
Population	Patients with AS	None
Interventions[1]	• Secukinumab • Certolizumab pegol • Etanercept • Adalimumab • Infliximab • Golimumab	Non-biologic treatments for AS (e.g. DMARDs)
Study Type	• Economic evaluation studies (e.g. cost-effectiveness, cost-utility, cost-minimisation analyses) • Utility studies (including studies where utility weights were mapped from other instruments, e.g. disease-specific patient-reported outcome measures) • Prospective/retrospective studies	• Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews • Articles reporting cost estimates that are not based on data (e.g. commentaries making general reference to cost burden)

Criteria	Include	Exclude
	reporting costs or resource utilisation • Systematic reviews of economic analyses, utility, resource-use, or cost studies (for the identification of primary studies)	
Outcomes	Economic Evaluation outcomes • Incremental cost effectiveness ratios (ICERs) • Costs • Quality adjusted life years (QALYs) Cost outcomes • Direct healthcare related costs (e.g. medication, resource use etc.) • Indirect costs (e.g. productivity loss, out-of-pocket expenses) Utility outcomes • EuroQoL 5 Dimensions (EQ-5D) • Short Form 6 Dimensions (SF-6D) • Health utilities index (HUI) • Other dermatological utility measures	• Studies reporting Quality of life (QoL) data but not utility outcomes
Language of publication	No Limit	None
Date of publication	Database searches: January 1999 onwards Conference abstracts: January 2013 onwards	None

[1] Applied to economic evaluations only: Utility, resource-use, and cost studies that are relevant to AS were included regardless of interventions and comparators.

AS = Ankylosing spondylitis; CS = company submission; DMARD = disease modifying anti-rheumatic drug; EQ-5D = European Quality of Life-5 Dimensions; HUI = Health Utilities Index; ICER = Incremental cost-effectiveness Ratio; QALY = Quality-adjusted Life Year; QoL = Quality of life; SF-6D = Short form-6 dimension

ERG comments: The ERG has no comments on this section.

5.1.3 Included/excluded studies in the cost effectiveness review

In the CS, 138 potentially relevant studies were identified. Of those 138 publications, 28 were economic evaluations, 89 were cost and resource use studies and 45 of them were utility studies. A number of publications fell within more than one category.

Among the 28 economic evaluation studies identified in the SLR, 12 analyses were conducted in UK. Hence these studies were considered to be relevant for the decision problem and are briefly discussed

below. No studies have been conducted on the economic analysis of secukinumab. A summary of all identified UK and non UK based studies are presented in Appendices 2 and 3, respectively.

Ara 2007

In Ara et al. 2007, etanercept vs. non-steroidal anti-inflammatory drugs (NSAIDs) were compared. In the scenario with the longest time horizon (25 years), the analysis resulted in incremental costs of £35,978 and QALYs of 1.585 years per patient, leading to an ICER around £22,700 per QALY gained.[27]

Armstrong 2013

In Armstrong et al. 2013, the single technology appraisal for the NICE submission of golimumab was conducted. The comparators of golimumab were conventional care, etanercept and adalimumab.[28]

In the base case of the submission, 20 years of time horizon was assumed. Conventional care was shown to be the treatment with the lowest QALY and cost estimates. The comparison of golimumab vs. conventional care resulted in an incremental cost of £5,119, incremental QALYs of 0.193 years, leading to an ICER around £26,500 per QALY gained. Etanercept and adalimumab were extendedly dominated by golimumab.

In the base case of the external review group, lifetime was selected as the time horizon. Conventional care was again the treatment with the lowest QALY and cost estimates. The comparison of etanercept vs. conventional care resulted in an incremental cost of £13,120, incremental QALYs of 0.485 years, leading to an ICER around £27,000 per QALY gained. Golimumab and adalimumab were extendedly dominated by etanercept.

Botteman 2007

In Botteman et al. 2007, adalimumab was compared to conventional care. In the scenario with the longest time horizon (30 years), the analysis resulted in an incremental cost of £23,857 and incremental QALYs of 1.033 years per patient, leading to an ICER around £23,000 per QALY gained.[29]

Kobelt 2004

In Kobelt et al. 2004, infliximab was compared to conventional care. In the scenario with the longest time horizon, when only healthcare related costs were included, the analysis resulted in an incremental cost of £87,700, incremental QALYs of 2.62 years, leading to an ICER around £33,500 per QALY gained.[30]

Kobelt 2007

In Kobelt et al. 2007, infliximab was compared to conventional care. Six scenarios with life time horizon and NHS perspective were conducted, three scenarios per reference clinical trial on which treatment effectiveness was based (ASSERT and BRAUN).[31] Each scenario had differing assumptions concerning disease progression under infliximab (100%, 50% and 0% of disease progression under conventional care). These scenarios resulted in differing ICERs within the £25,000- £50,000 per QALY band.

McLeod 2007

In McLeod et al. 2007, conventional care, infliximab, etanercept and adalimumab were compared. Identical costs and effects were assumed for etanercept and adalimumab.[32] In the scenario with the

longest time horizon (20 years), when compared to conventional care, etanercept/adalimumab resulted in an ICER of £98,910 per QALY and infliximab resulted in an ICER around £175,000 per QALY.

Submissions to Scottish Medicine Consortium

Six different HTA submissions to the Scottish Medicine Consortium (SMC) in 2005, 2006, 2011, 2014 and 2015 with different interventions/comparators and time horizons were considered.[33-38] According to the CS, not all submissions reported incremental QALYs and ICER. In the reported ones, analyses resulted in varying ICER values.

Quality assessments of these 12 UK studies presented above were presented in the Appendix Q of the CS and were based on NICE methodology checklist for economic evaluations.[1]

ERG comments: It was not clear to the ERG why the MTA model (from the previous NICE assessment TA 383[7]), was not listed as identified study nor critically assessed by the company, especially given that that model was used as the basis for the de novo model. The ERG finds the critical assessment of a model before adopting its structure is essential, since a bad model can lead to unreliable estimates. The ERG has no other comments on the included/excluded studies.

5.1.4 Conclusions of the cost effectiveness review

No specific conclusions from the economic review were provided in the CS. The ERG thinks that the identified studies contain valuable information regarding costs, utilities and model structure, but that they do not negate the necessity of developing a de novo model for the current comparison.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2 presents a summary of the de novo economic model developed by the company.

Table 5.2: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in CS)
Model	A cost effectiveness model that consist of a decision tree which represents the 3-month induction period combined with a Markov cohort model describing the long term disease progression after the induction period. After the induction period, the efficacy of the biologic is assessed and the biologic is continued if the patient shows a BASDAI 50 response. Non-responders move to conventional care. BASDAI and BASFI scores change in each cycle (3 month long) and define costs and QALYs per cycle. Sequential treatment (2nd line only) was considered for biologic naïve patients in an exploratory analysis.	The economic model aimed to reflect the clinical pathway of care with biologic treatment for patients with active AS for whom conventional therapy, or prior biologic therapy, has been inadequately effective or not tolerated. The modelling approach is in line with the previous modelling approach in TA 383.[7, 9]	Section 5.2.2 (p. 179)
States and events	In the decision tree we distinguish the following events: • Death • BASDAI 50 response • No BASDAI 50 response In the Markov model three health states are distinguished: • Biologic treatment (maintenance) • Conventional care • Dead BASDAI and BASFI of a patient are traced throughout his/her life. The progression of BASDAI and BASFI differs according to the state, and the treatment received and the duration of the treatment received. At the end of the induction (3 month) patients with BASDAI 50 response continue to receive the biologic treatment for the maintenance, non-responders to receive conventional care. In later cycles, a patient who receives biologics may move to conventional care only due to withdrawal. Death can happen in all alive states.	Health states were based upon the treatment that the patient receives throughout the disease. The treatment determines the response and the BASDAI and BASFI scores.	Section 5.2.2 (p. 179)
Comparators	For the biologic experienced subgroup, conventional care only was considered as the only comparator to secukinumab. For the biologic naïve subgroup, conventional care and the other anti	For the biologic naïve patients, all five TNFα inhibitors were considered because they are licensed for the treatment of	Section 5.2.3 (p. 185)

	Approach	Source/Justification	Signpost (location in CS)
	TNFα inhibitors (certolizumab pegol, etanercept, adalimumab, infliximab and golimumab) were considered as comparators to secukinumab.	active AS and were included in the previous NICE MTA (TA 383).[7] For biologic experienced patients, only conventional care was considered due to lack of effectiveness data for other biologics in this population.	
Natural history	Natural history is based on how disease progresses under the conventional care arm.	BASDAI 50 response and BASDAI and BASFI change rates of conventional care were based on MTC for the biologics naïve population. For biologic experienced patients, they were derived from corresponding data from MEASURE 1 and MEASURE 2 trials.	Section 5.3 (p. 188)
Treatment effectiveness	Treatment influences the BASDAI 50 response rate, which determines the percentage of patients switching to conventional care. Treatment also influences BASDAI and BASFI scores.	BASDAI 50 response and BASDAI and BASFI change rates of the biologic treatments were based on MTC for the biologics naïve population. For biologic experienced patients, they were derived from corresponding data from MEASURE 1 and MEASURE 2 trials.	Section 5.3 (p. 188)
Adverse events	The only adverse events considered in the economic model were serious infections. The serious infections were categorised as TB reactivation and other serious infections.	The inclusion of serious infections was based on the results of a Cochrane systematic literature review.[39] The review found that serious infections were the only specific adverse events that were statistically significantly raised amongst patients treated with biologics compared to control.	Section 5.3.6 (p. 195)

	Approach	Source/Justification	Signpost (location in CS)
Health related QoL	The model uses a mapping algorithm to link BASDAI and BASFI scores to a generic utility measure. The linear model for utility used in the base case model has BASDAI, BASFI scores, age and gender as the covariates. In scenario analyses, other mapping algorithms in the literature were used.[32, 40]	The utility mapping algorithm uses the patient level data (BASDAI, BASFI scores, age and gender and EQ5D results) from MEASURE 1 and MEASURE 2 trials.	Section 5.4 (p. 196)
Resource utilisation and costs	Treatment cost (e.g. technology acquisition and administration costs of secukinumab and other biologics, monitoring costs and tests) and health state costs (disease management costs based on BASFI score) and other costs for adverse events.	Based on literature and UK reference costs.	Section 5.5 (p. 199)
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case	Section 5.2.2.3 (p. 184)
Sub groups	Two subgroups were considered: biologic naïve and biologic experienced. No further subgroups were considered.	The subgroups for biologic naïve and biologic experienced were considered because of the differences of effectiveness for secukinumab between these two subgroups.	Section 5.9 (p. 236)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges based on observed confidence intervals and assumptions.	Section 5.8 (p. 222)

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CS = Company submission; MTA = Multiple Technology Appraisal; NICE = National Institute for Health and Care Excellence; QALY = National Institute for Health and Care Excellence; TA = Technology Appraisal; TNF = Tumour Necrosis Factor; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: Comparison of company submission model to the NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes/No	Yes, for biologic naïve subgroup. For biologic experienced subgroup, relevant therapies excluded due to the lack of data
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is 58 years, average starting age is 42.37.
Synthesis of evidence in outcomes	Systematic review	Yes/No	Most parameters were based on the MTC. However, some parameters were identified by a non-systematic search
Measure of health effects	QALYs	Yes	
Source of data for measurement HRQoL	Reported directly by patients and/or carers.	No	Even though HRQoL was measured in the trial, in the model a mapping algorithm is used.
Source of preference data for valuation of changes in HRQoL	Sample of public	Yes	
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	

HRQoL = Health-related Quality of Life; NHS = National Health Services; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = Quality-adjusted Life Year

5.2.2 Population

According to the CS, secukinumab was indicated for adult population of patients with active AS, as defined by the modified New York criteria, and for whom conventional therapy (i.e. NSAIDs alongside physiotherapy), or prior biologic therapy, has been inadequately effective or not tolerated.[1] Within this licensed indication, the submission model considered two distinct patient populations:

- the population of patients who are naïve to biologic therapy,
- the population of patients who have previously received one or more biologic therapies.

These two subgroups are examined in separate analyses.

The first subgroup represents the population of patients for whom conventional care has been inadequately effective or not tolerated but in whom a biologic treatment has not yet been administered. The second subgroup refers to the population of patients who have previously received one or more unsuccessful (inadequately effective or not tolerated) biologic therapies.

ERG comments: The population of the cost effectiveness analysis seems to be broadly in line with the scope. However, it should be noted that according to TA 383[7] the market authorisations for adalimumab, etanercept, golimumab and infliximab were for severe AS patients who responded inadequately to conventional therapy and for certolizumab pegol, market authorisations were for severe AS patients who responded inadequately or were intolerant to non-steroidal inflammatory drugs (NSAIDs).

In the CS, clear definitions for mild, moderate and severe form of AS were lacking and there was no consideration for the severity in the CS.[1] After the request for further clarification from the ERG, the company stated that there was no consensus on the definitions of mild, moderate and severe AS and mentioned that the inclusion criteria for secukinumab trials was for moderate to severe active AS.[6] This could potentially create a bias against other comparators, if the evidence of these comparators were generated from a different population in terms of disease severity. For instance on page 164 of the CS[1], the purpose of Ara et al. 2007[27] was summarised as "*…to provide costs and benefits associated with long-term (25-year) etanercept treatment for patients with severe AS in the UK…*". However, in the absence of any definition for moderate or severe AS, the ERG cannot say anything about the presence, size and direction of such bias.

Another issue relates to the biologic experienced population. This patient population consists of patients who were intolerant to a biologic or who responded inadequately to a biologic. Even though there can be potential clinical differences between these two subgroups, in the cost effectiveness analysis these two subgroups were assumed to be clinically same and no justification was provided for this assumption.

5.2.3 Model structure

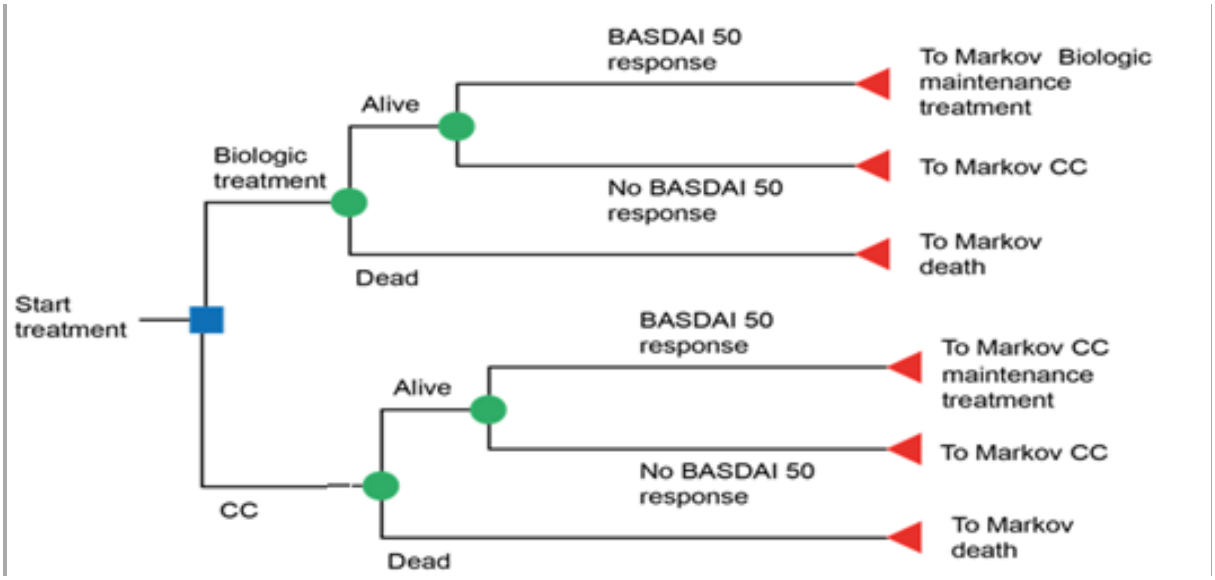
In the CS, the cost effectiveness of secukinumab was compared to other biologic treatments for the biologic naïve subpopulation and only to conventional care for the biologic experienced subpopulation. Both comparisons used the submission model that was developed in Microsoft Excel®. The submission model consisted of a short term, three month (12 weeks) decision tree model, representing the period covering the induction therapy for the biologic and placebo treatment arms. End nodes of the decision tree were connected to a long-term Markov model consisting of three states. This Markov model represents the post-induction period of a patient (maintenance therapy or post-induction conventional care therapy).

Patients who enter the decision tree model start with either biologic treatment or conventional care. The patients are assumed to receive their treatment during the whole induction period (12 weeks) unless they die before. At week 12, response of a patient is assessed according to that patient's BASDAI 50 status (more than 50% decrease compared to baseline BASDAI score) for the base case

analysis, whereas in the CS[1], scenarios were explored using different response definition criteria (i.e. more than 50% decrease or two absolute units of drop from the baseline BASDAI score). The treatment the patient received during induction therapy, the response and the alive/death status of that patient at week 12, all jointly determine in which state the patient will enter the Markov model that represents the post-induction therapy phase.

The decision tree structure of the induction period part of the model is presented in Figure 5.1 below. Note that it has been corrected to show that both death and response with conventional care are possibilities that were implemented in the Excel model submitted by the company.

Figure 5.1: Decision tree model structure for the first three months, during induction period
(Based on figure 32 of the CS[1])



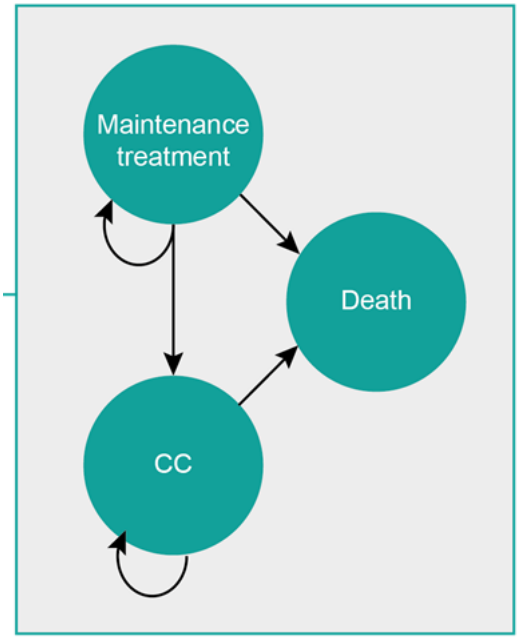
The Markov model that represents the post-induction therapy phase consists of three states: maintenance therapy (represents the continuation of the treatment received during the induction therapy period), post-induction conventional care therapy and death.

At each cycle, from the maintenance therapy state, a patient can stay in the maintenance therapy state, can withdraw from the treatment received in the maintenance therapy and can have a transition to post-induction conventional care (CC) therapy or can have a transition to death (due to mortality). From the post-induction conventional care therapy state, no transitions are possible to the maintenance therapy state; hence once a patient is in post-induction conventional care therapy state, s/he can either stay in the same state or can have a transition to death.

A patient starts the Markov model in the maintenance therapy state if that patient responded to the treatment s/he had received at week 12 according to response definition criteria used. On the other hand, a non-responder patient at week 12 starts the Markov model from the post-induction conventional care therapy state. If a patient died before week 12, irrespective of the treatment administered during induction period, s/he would start the Markov model from death state (so that no patients are 'lost' when moving from the decision tree to the Markov model). The structure of the Markov model that represents the post-induction period is presented in Figure 5.2. Note that the CC state referred to in the figure represents only conventional care given no response as opposed to given

a response to treatment. Also note that the maintenance treatment state applies to those who have responded on either biologic treatment or conventional care.

Figure 5.2: Markov structure of the post-induction period part of the model
(Based on Figure 33 of the CS[1])



CC: conventional care

The post-induction Markov model incorporated treatment-related adverse events as well. Patients continuing on biologic therapy were at risk of experiencing major adverse events (e.g. serious infection). The probability of these events was applied directly in the "maintenance therapy" health states. Major adverse events do not lead to discontinuation of the maintenance therapy; they have an implication only on costs in the base case.

The model structure is the same for secukinumab and all of its comparators in the base case analysis of both biologic naïve and biologic experienced subgroups.

In an exploratory analysis for the biologic naïve subgroup, upon the discontinuation of the first biologic treatment (either due to no response at week 12 or withdrawal in the post-induction period), another biologic treatment is allowed for 75% of the patients, whilst assuming that 25% of patients would not try a second biologic (based on expert clinical feedback). Note that this exploratory analysis did not incorporate third/further line biologics.

In this exploratory analysis, for secukinumab or other biologics, when a patient did not respond to the first line treatment at week 12 or when s/he withdrew from the first line treatment given in the maintenance therapy state of the Markov model, that patient would enter another decision tree model with the same structure as depicted in Figure 5.1 with a probability of 75% (whilst moving to the conventional care state with 25% probability). The decision tree the patient would enter this time represents the second line biologic induction period. At the end of the second line induction period, the patient would enter another Markov model with the same structure as depicted in Figure 5.2. The Markov model that the patient would enter this time, represents the post-induction period after the second line biologic treatment.

In the CS, a "treatment basket" approach was followed for the second line biologics.[1] In this approach, for the exploratory analyses where second line biologics were allowed, upon discontinuation of the first line biologic treatment, patients received a basket therapy, which was assumed to consist of all other relevant biologic treatments with the exception of the one that had been used in the first-line. The cost and the efficacy of this basket therapy were assumed to be the weighted average of the biologics in the basket. The weight of each biologic was assumed to be the same. In the base case of this exploratory analysis, clinical effectiveness estimates for biologic treatments applied in the second line were assumed to be smaller than those applied in the first line. The reduction in effect of 45.1% that was applied was derived from the comparison of clinical effectiveness data for biologic experienced vs. naïve patients from the secukinumab arms of MEASURE 1 and MEASURE 2.

The model tracks the disease progression via short and longer term changes in BASDAI and BASFI scores. Patients who receive biologics are assumed to experience an improvement in terms of BASDAI and BASFI. The BASDAI and BASFI score of a patient in each state are translated to that patient's health state utility and cost estimates with the help of regression equations which also use patients' age and gender. The BASDAI and BASFI scores at each cycle are driven by the baseline BASDAI and BASFI scores, the state that the patient is in, and the time patient spent during the biologic treatment. How BASDAI and BASFI scores change over time will be explained in detail in Section 5.2.6.

ERG comments: The model structure is conceptually similar to the York model developed for TA383.[9] The ERG holds the opinion that even though the model structure reflects the key elements of the AS disease progression with and without biologic treatment, there could be more suitable modelling types such as patient level simulation, which would reflect the patient heterogeneity and the dependence between baseline BASDAI/BASFI values, change from baseline values and response rates at the end of the induction period.

The BASDAI and BASFI scores of the patient in a cycle are the key determinants of that patient's cost and QALY estimate for that cycle. This is in line with previous modelling efforts of the AS (e.g. Armstrong 2011 and Corbett 2014).[9, 28]

In clinical practice, the consequences of treatment can be described as follows. First, the AS patient receives a treatment and as a result of this treatment, there can be improvement on his/her BASDAI or BASFI score at the end of the induction period, compared to the baseline. The relation between the baseline BASDAI value and BASDAI improvement from the baseline determines the response status of that patient at the end of induction period (week 12).

In the cost effectiveness analysis, the way the response and BASDAI/ BASFI change from baseline were modelled did not follow the consequences of treatment as described above. First, the response rates for the biologics and absolute change from baseline values were derived independently from evidence synthesis. Afterwards, conditional (based on response) baseline BASFI and BASDAI values and change from baseline estimates were derived from the response rates. This approach has created a situation that the baseline BASDAI and BASFI scores of responders and non-responders were different. In the final appraisal document for TA383, the committee expressed concerns over this assumption, mentioning that this difference may imply that patients with more severe disease (higher

baseline values) may not benefit as much from the biologics as patients with less severe disease.[7] In Section 5.3, the ERG presents some exploratory analyses regarding this assumption.

Also, in the modelling of the conventional care treatment for the biologic experienced patients, the ERG had questions on the relevance of the model states to the clinical practice. The ERG agrees that it is possible that a patient may reach response under conventional care, however explicitly modelling a separate induction period for conventional care differentiates the conventional care given in the first three months from the conventional care given in other cycles. Also the ERG had difficulties in interpreting the meaning of a withdrawal from conventional care maintenance therapy in the post-induction period. Even though patients received the same treatment (conventional care treatment) in all of these states (induction period, maintenance therapy and post-induction, post-maintenance conventional care therapy), the implications of receiving the same treatment in these different states are translated differently in terms of the average BASDAI and BASFI scores, leading to differences in costs and QALYs. In Section 5.3, the ERG will conduct some exploratory analyses regarding this assumption.

5.2.4 Interventions and comparators

The intervention considered in the model was secukinumab 150 mg, in line with the licensed dose of secukinumab that is the subject of this appraisal.

Biologic naïve patients

For the first subgroup, the biologic naïve patients' subgroup, TNF-alpha inhibitors were considered as comparators, following previous NICE recommendation and BSR guideline.[7, 41] There are currently five TNFα inhibitors that are licensed in UK for the treatment of AS: adalimumab, etanercept, golimumab, infliximab and certolizumab pegol.

For etanercept, certolizumab pegol and golimumab, multiple licensed doses are available. In the CS, it was not considered necessary to model all different doses of certolizumab pegol and golimumab, and it was stated that different administration dosages/ schedules did not lead to differences in effectiveness and there were no cost differences between the two certolizumab pegol administration schedules and between two golimumab doses (due to patient access scheme; PAS).[1] Hence, the efficacy inputs for different administrations for these therapies were assumed to be the same as those for certolizumab pegol 200 mg every two weeks and golimumab 50 mg. In terms of etanercept, only the 50 mg weekly licensed dose was considered in the CS as it was mentioned that there was no efficacy data for the 25 mg twice weekly dose.[1]

Biologic experienced patients

For the second subgroup, the biologic experienced patients, conventional care was considered as the only comparator in the base case. In the CS, this decision was based on the argument that no valid data were available for the effectiveness of the use of one of the other biologics for the biologic experienced population.[1] In an exploratory analysis, biologics were also considered as comparators to secukinumab, with reduced clinical effectiveness estimates by the same reduction method applied for the second line biologic treatments in the exploratory analysis conducted in biologic naïve subgroup, as explained in Section 5.2.3.

Key details from the summary of product characteristics (SmPC) of each included biologic are summarised in Table 5.4. All biologics were considered within the model according to their dosing schedules as described in Table 5.4.

ERG comment: The ERG thinks the comparators included in the cost effectiveness analysis were broadly consistent with the final scope. In the original submission[1], the biosimilar version of etanercept was not included. However, after a request by the ERG, biosimilar etanercept was included as a comparator to the updated cost effectiveness analyses in the response to the clarification letter.[6] For biologic experienced patients, in the base case analysis "conventional care" was considered as the only comparator, but in the exploratory analyses, other anti TNF-alpha biologics were considered as comparators, as well. The assumptions surrounding the treatment effectiveness of other biologics than secukinumab for the biologic experienced population will be discussed in Section 5.2.6 in detail.

Table 5.4: Summary of marketing authorisations of included biologics
(Based on Table 68 of the CS[1])

	Secukinumab[42]	**Adalimumab[43]**	**Etanercept[44]**	**Golimumab[45]**	**Infliximab[46]**	**Certolizumab pegol[47]**
Indication of marketing authorisation	Patients with active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.	Patients with severe, active ankylosing spondylitis who have had an inadequate response to conventional therapy.	Patients with severe, active ankylosing spondylitis who have had an inadequate response to conventional therapy.	Patients with severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.	Patients with severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.	Patients with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to NSAIDs.
Posology	150 mg by s.c. injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4.	40 mg adalimumab administered every other week as a single dose via s.c. injection.	25 mg twice weekly or 50 mg once weekly via s.c. injection.	50 mg given once a month via s.c. injection, on the same date each month. For patients with a body weight >100 kg whose disease does not respond adequately after 4 doses (50 mg each), increasing the dosage to 100 mg once a month may be considered.	5 mg/kg given as an i.v. infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks.	*Loading dose:* 400 mg (as 2 s.c. injections of 200 mg each) at weeks 0, 2 and 4. *Maintenance dose***:** 200 mg every 2 weeks or 400 mg every 4 weeks.
Continuation rule	Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks	Continued therapy past 12 weeks should be carefully reconsidered in a patient not responding within this time period	Continued therapy past 12 weeks should be carefully reconsidered in a patient not responding within	Continued therapy past 12 to 14 weeks should be reconsidered in patients who show no evidence of	No additional treatment with infliximab should be given if the patient does not respond by 6 weeks.	Continued therapy should be carefully reconsidered in patients who show no

	Secukinumab[42]	Adalimumab[43]	Etanercept[44]	Golimumab[45]	Infliximab[46]	Certolizumab pegol[47]
	of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks		this time period	therapeutic benefit within this time period.		evidence of therapeutic benefit within the first 12 weeks of treatment.
CS = company submission; kg = kilogram; mg = milligram; NSAID = Non-steroidal anti-inflammatory drug; s.c. = subcutaneous						

5.2.5 Perspective, time horizon and discounting

In the base case analysis, a lifetime (58 years) horizon was chosen and discount rate of 3.5% was used for costs and effects. The model adopted the perspective of NHS/PSS and had a cycle length of three months.

ERG comments: The ERG has no specific comments on these choices of perspective, time horizon and the discount rates.

5.2.6 Treatment effectiveness and extrapolation

In the base case, the treatment effectiveness of the biologics was translated to the model in terms of BASDAI 50 response, change from baseline BASDAI and BASFI scores and long term BASFI changes.

All clinical treatment effectiveness parameters for the biologic naïve population were based on the pooled TNFα inhibitor naïve subpopulation data from MEASURE 2 and MEASURE 1 trials as well as the base case MTC (for relative effectiveness estimates of the biologics in the biologic naïve population). The results of this MTC were presented in Section 4.10 of the CS.[1]

In the CS, it was mentioned that there was no evidence for the effectiveness of some of the TNFα inhibitor comparators on the end points relevant to the model.[1] For those, the average of the available endpoints from the MTC for the other TNFα inhibitors was used.

Note that during the clarification procedure, a couple of critical errors were identified by the ERG. The company stated that they had corrected these errors and an updated model was attached to the response to the clarification letter.[6] These critical errors included omitting some RCTs in the evidence networks used in the MTCs, as well as implementing MTC outputs incorrectly into the economic model. In addition, some coding errors were present in the calculation of conversion factors used in scenario analyses and random effects model results from the MTC were not presented in the original submission but presented in the response to the clarification letter. For the sake of simplicity, in the rest of the report, only the inputs and results from the updated model that was provided in the response to the clarification letter will be reported.[6]

In the biologic experienced population, for the base case analysis, all clinical treatment effectiveness parameters for secukinumab and conventional care were based on the pooled subpopulation data from MEASURE 2 and MEASURE 1 trials. The subpopulation consisted of patients who were intolerant or showed insufficient response to TNFα inhibitors. In the base case analysis for biologic experienced subpopulation, secukinumab was compared only to conventional care. In an exploratory analysis for this biologic experienced population, secukinumab was compared to other biologics, and reduced effectiveness were assumed for each biologic treatment in comparison to the effectiveness parameters derived for the biologic naïve population. These reductions in effectiveness were derived from the observed ratio of the average secukinumab efficacy data in biologic experienced patients compared to the average secukinumab efficacy data in biologic naïve patients.

For both biologic naïve and experienced subgroup populations, different scenario analyses were conducted on the choice of the secukinumab trial that the secukinumab treatment effectiveness parameters were derived from. As in MEASURE 1 loading doses of secukinumab were administered as an intravenous therapy different from its SmPC, several scenario analyses explored the impact of choosing the MEASURE 2 trial only as the source trial for the treatment effectiveness of

secukinumab. This and other scenario analyses on evidence synthesis will be explained further in subsequent sections.

5.2.6.1 Baseline characteristics other than BASDAI and BASFI scores

The base case inputs for the model in terms of patient age, gender distribution and weight are detailed in Table 5.5. These inputs were derived from MEASURE 1 and MEASURE 2 trials. These parameters play a role in deriving state based utility and cost estimates in the model.

Table 5.5: Patient characteristics in the model

Model parameter	Value
Mean age, years	42.37
Percentage male/female	69.5%
Mean (SD) weight, kg	78.20 (16.88)
kg = kilogram; SD = Standard deviation	

ERG comments: The ERG considers the baseline characteristics (other than BASDAI/BASFI scores) used in the model to be broadly consistent with the baseline characteristics used in previous cost-effectiveness analyses conducted for UK (e.g. in Corbett et al. 2014, the York report for the NICE TA 383).[9]

The ERG also noted that for these baseline characteristics, the estimates given in Table 5.5 were not updated for different populations (biologic naïve and biologic experienced) or for different scenarios (e.g. when only MEASURE 2 trial was used as the source trial for the treatment effectiveness of secukinumab). However, the ERG does not expect that implementing updates would lead to significant differences in the cost-effectiveness results.

5.2.6.2 Response assessment at the end of the induction period

In the original model, for the base case analysis, the response of a patient to the induction therapy was assessed according to that patient's BASDAI 50 status after week 12. A responder patient would continue to receive the corresponding treatment s/he had received during the induction period as a maintenance therapy after week 12. The treatment specific BASDAI 50 response rates used in the model were derived for biologic naïve and biologic experienced subgroups separately.

For the biologic naïve population, in the base case, BASDAI 50 response rates for conventional care, etanercept, adalimumab, golimumab and secukinumab treatments were calculated from the log-odds (of achieving response) scores obtained from the fixed effects binomial model conducted as a part of the MTC analysis for the TNFα inhibitor naive population. The details of this fixed effect binomial model were explained in Section 4.10 and Appendix K of the CS[1] and in Section D of the response to the clarification letter.[6] Note that the MTC in the CS[1] was updated in the response to the clarification letter [6] after the identification of the errors by the ERG.

For the biologic naïve population, in the base case, BASDAI 50 response rate data was missing for certoluzimab pegol and infliximab, therefore in the model it is assumed that their log-odds scores would be equal to the average of the log odd scores of other three TNFα inhibitors: etanercept, adalimumab and golimumab.

For the biologic experienced population, in the base case, only comparator to secukinumab was conventional care (placebo) and BASDAI 50 response rates used in the model were directly derived from the pooled data of the biologic experienced patients from MEASURE 1 and MEASURE 2 studies.

Even though the length of the induction period was assumed to be 12 weeks in the economic model, in the base case, as part of the MTC, the fixed effect binomial model used some data collected later than week 12. In the CS, it was mentioned that the submission attempted to use the BASDAI 50 response rates from the primary endpoints of the included RCTs as much as possible.[1] Hence, the BASDAI 50 data from primary endpoints were used if the primary endpoint of a trial was between week 12 and week 16. If the primary endpoint was later than week 16, the latest time point after week 12 with BASDAI 50 assessment was considered (e.g. for the ASSERT trial, week 12 BASDAI 50 data are used because the primary endpoint of ASSERT trial was 24 weeks).

Several scenario analyses were conducted concerning the assumptions surrounding the response assessment at the end of the induction period. These scenarios have explored the uncertainties around:

a. source(s) of secukinumab trial data for estimating treatment effectiveness (MEASURE 1&2 or MEASURE 2 only)
b. time point(s) that the response data from the trials was measured (week 12 to week 16 or strictly week 12)
c. criteria used for response assessment (BASDAI 50 only or BASDAI 50 or 2 units of drop in BASDAI score)

In order to explore the uncertainties mentioned in bullet points a and b, five different MTCs were conducted. These MTCs used fixed or random effects binomial models. The details of these MTCs (MTC input, WinBUGS code and MTC results) were discussed in Appendix K of the CS[1] and Section D of the response to the clarification letter [6], where the errors identified by ERG were corrected. The main characteristics of the MTCs are given in Table 5.6.

Table 5.6: The main characteristics of the five MTCs conducted for the BASDAI 50 response rates in the biologic naïve population

MTC Type	MTC #1 (Base Case)	MTC #2	MTC #3	MTC #4	MTC #5
Type of model	Fixed effects	Fixed effects	Fixed effects	Fixed effects	Random effects
a. Source(s) of secukinumab trial data	MEASURE 1 MEASURE 2	MEASURE 2	MEASURE 1 MEASURE 2	MEASURE 2	MEASURE 1 MEASURE 2
b. Time point(s) the response data was collected in the trials	Week 12-16	Week 12-16	Week 12	Week 12	Week 12-16
Which trial data was used in this MTC?	GO-RAISE MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE	GO-RAISE MEASURE 2 ATLAS Huang 2014 SPINE	MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE	MEASURE 2 ATLAS Huang 2014 SPINE	GO-RAISE MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE
Which treatments were included in this MTC?	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab	Placebo, Secukinumab, Etanercept, Adalimumab	Placebo, Secukinumab, Etanercept, Adalimumab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; MTC = Mixed treatment comparison

On top of the MTCs above, upon the ERG's request, additional MTCs were conducted adopting MTC approaches A3-A5 and B and C in Appendix 9 from Corbett et al. 2014, which is the York report for TA383.[9] These additional analyses as well as the critique of original and additional MTCs will be discussed under the "ERG comments" at the end of this section.

Concerning the uncertainties surrounding the definition of response, as mentioned in bullet point c. (above), predetermined conversion factors were used to transform the response rate estimates based on "BASDAI 50 only" criterion to response rates based on "BASDAI 50 or at least two units decrease in BASDAI score" criteria, a definition more consistent with BSR guideline [41], except for the condition on VAS scores. This approach was followed, as the response rates based on these alternative definitions were not available for the comparators included in the MTCs. For this conversion, the estimates based on "BASDAI 50 only" criterion were multiplied by a predefined conversion constant, differentiated by the treatment received ([redacted] for conventional care and [redacted] for all other biologic treatments). These conversion constants were derived from the pooled MEASURE 1 and MEASURE 2 response data from biologic naïve patients measured at week 12 (see Table 5.7).

Table 5.7: Derivation of conversion constants for response based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score" for biologic naïve patients

	Secukinumab 150 mg			Placebo		
	n	N	%	n	N	%
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop in BASDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]			[redacted]		
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; mg = milligram						

A list of all the scenarios and their underlying assumptions for the response rate estimates of biologic naïve patients at the end of induction period are summarised in Table 5.8 below.

Table 5.8: List of all possible scenarios on the assumptions surrounding the response rates at the end of the induction period for the biologic-naïve patients

Scenario no. for response rate estimates in biologic naïve patients	Choice of secukinumab trial data	Time point(s) that the response data was based on	MTC that the treatment effectiveness results were based on	Response assessment definition criteria	Type of the model used in the MTC (Fixed effect/ random effect)
1 (Base case)	MEASURE 1 and MEASURE 2	Week 12-16	MTC#1 (base case)	BASDAI 50 only	Fixed
2	MEASURE 1 and MEASURE 2	Week 12-16	MTC#1 (base case)	BASDAI 50 or at least 2 units of drop in BASDAI score	Fixed
3	MEASURE 2	Week 12-16	MTC#2	BASDAI 50 only	Fixed
4	MEASURE 2	Week 12-16	MTC#2	BASDAI 50 or at least 2 units of drop in BASDAI score	Fixed
5	MEASURE 1 and MEASURE 2	Strictly week 12	MTC#3	BASDAI 50 only	Fixed
6	MEASURE 1 and MEASURE 2	Strictly week 12	MTC#3	BASDAI 50 or at least 2 units of drop in BASDAI score	Fixed
7	MEASURE 2	Strictly week 12	MTC#4	BASDAI 50 only	Fixed
8	MEASURE 2	Strictly week 12	MTC#4	BASDAI 50 or at least 2 units of drop in BASDAI score	Fixed
9	MEASURE 1 and MEASURE 2	Week 12-16	MTC#5	BASDAI 50 only	Random

Scenario no. for response rate estimates in biologic naïve patients	Choice of secukinumab trial data	Time point(s) that the response data was based on	MTC that the treatment effectiveness results were based on	Response assessment definition criteria	Type of the model used in the MTC (Fixed effect/ random effect)
10	MEASURE 1 and MEASURE 2	Week 12-16	MTC#5	BASDAI 50 or at least 2 units of drop in BASDAI score	Random
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; MTC = Mixed treatment comparison					

For the scenarios listed above for biologic naïve patients, response rates used in the model for the corresponding treatments are given in Table 5.9.

Table 5.9: Response rates applied in the model at the end of the induction period for different scenarios in the biologic naïve population

Therapy	Scenario 1 (Base case) MTC#1	Scenario 2 MTC#1*	Scenario 3 MTC#2	Scenario 4 MTC#2*	Scenario 5 MTC#3	Scenario 6 MTC#3*	Scenario 7 MTC#4	Scenario 8 MTC#4*	Scenario 9 MTC#5	Scenario 10 MTC#5*
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Estimates for scenarios 2 to 10 are derived by applying the conversion factors to the column on the left hand side (base case).
mg = milligram; MTC = Mixed treatment comparison

For the biologic experienced subpopulation, in the base case, pooled BASDAI 50 response data at week 16 from MEASURE 2 and MEASURE 1 trials were used (12/61 for secukinumab and 2/62 for placebo). Different scenarios analysed the impact of using different criteria in response assessment by using predefined conversion constants, differentiated by the treatment received (2.395 for conventional care and 1.709 for secukinumab). In Table 5.10, the derivation of these constants for placebo (used for conventional care) and secukinumab are explained.

Table 5.10: Derivation of conversion constants for response based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score" for biologic experienced patients based on 12-week response data from MEASURE 1 and 2

	Secukinumab 150 mg			Placebo		
	n	N	%	n	N	%
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop in BASDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]			[redacted]		

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; mg = milligram

A list of all the scenarios that can be conducted in the model for the response rates of biologic experienced patients is summarised in Table 5.11 below. Even though other scenarios that were possible for biologic naïve patients could be selected from pull-down menus in the Excel model, they had no impact on the response rates of the biologic experienced population in the base case.

Table 5.11: List of all possible scenarios on the assumptions surrounding the response rates at the end of the induction period for biologic experienced patients

Scenario no	Response assessment definition criteria	Choice of Secukinumab trial data	Time point of response assessment
1 (Base case)	BASDAI 50 only	MEASURE 1 and MEASURE 2	Week 16
2	BASDAI 50 or 2 units of drop in BASDAI score	MEASURE 1 and MEASURE 2	Week 16

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

For the scenarios listed above for biologic experienced patients, response rates used in the model for the corresponding treatments were given in Table 5.12.

Table 5.12: Response rates applied in the model at the end of the induction period for different scenarios in the biologic experienced population

Therapy	Scenario 1 (Base case)	Scenario 2
Secukinumab 150 mg	[redacted]	[redacted]
Conventional care	[redacted]	[redacted]

Besides the scenario analyses for the biologic naïve and experienced patients above, additional exploratory analyses were conducted for both biologic naïve and experienced populations. For the biologic naïve patient population, effects of having another sequential biologic treatment were

explored. In these analyses, 75% of the patients whose first line biologic treatment was unsuccessful, received a second line biologic treatment. As discussed in Section 5.2.3, a "basket therapy" approach was followed. The percentage of BASDAI 50 responders in the second line was based on the average response rates of the other five biologic treatments in the basket, which excluded the biologic that was used in the first-line. A relative efficacy reduction of 45.1% was applied for all the treatments used in the second line. This efficacy reduction value was derived from the response data from MEASURE trials at week 16, based on the reduction in response observed with secukinumab in experienced patients compared to naïve patients. Details of the calculation of this relative reduction can be found in Table 5.13.

Table 5.13: BASDAI 50 relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150 mg			Placebo			Treatment effect (SEC150 response minus PBO response)	Relative reduction in BASDAI 50 response
	n	N	% response	n	N	% response		
Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. response rates in the experienced group are (1-0.45) = 0.55 x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; mg = milligram; PBO = placebo; SEC150 = Secukinumab 150 mg

All scenarios listed in Table 5.8 can be also applied for the response rates in the second line in this exploratory analysis for biologic naïve population.

In the exploratory analysis conducted for biologic experienced population, secukinumab was not only compared with conventional care but also with all other biologics. In this analysis, all the response rates for biologics were multiplied by the 55% (1-45%), proportional efficacy reduction factor, which was calculated in Table 5.13. All scenarios listed in Table 5.8 can be also applied for the response rates applied in this exploratory analysis. Note that when applying these scenarios in this exploratory analysis, to adjust the response rates for different response assessment criteria than BASDAI 50, pre-defined conversion rates for biologic experienced patients ([redacted] for conventional care and [redacted] for secukinumab and other biologics) derived in Table 5.10 were used.

ERG comment: As mentioned earlier, in the original CS[1], Huang et al. 2014[19] study was omitted from the MTC. In the response to the clarification letter, an updated MTC was conducted, in which Huang et al. 2014 was included. The results were presented in Section E.[6] However, the inputs used in the MTCs from Huang et al. 2014[19] were not provided, therefore the MTC results provided in the response to the clarification letter [6] could not be verified.

Also, in the original CS, results from the random effects model were not provided.[1] After a request from the ERG, the random effects binomial model results were provided in the response to the clarification letter, however only for the base case analysis.[6] This MTC is represented by MTC#5 in Table 5.6.

The choice of the MTC has a large impact on the response rates. In Table 5.9, it can be seen that the BASDAI 50 response rates for secukinumab ranges from 38% to 59%. Response rates from other comparators also change according to the choice of MTC: certolizumab-pegol from 37% to 44%; etanercept from 32% to 37%; adalimumab from 43% to 49%; infliximab from 37% to 44% and golimumab from 37% to 47%. However, using the random effects model (MTC#5) instead of the fixed effect model (MTC#1) had very little impact.

MTC#1 represents the base case of the CS[1], however, the ERG finds the assumptions from MTC#3 the most plausible. It is essential that all studies have the same time point (12 weeks) for the response assessment, otherwise, the MTC would give biased results for treatments whose trial endpoints were longer than 12 weeks. Furthermore, it is in line with the clinical practice recommendations (e.g. in NICE TA 383[7] after week 12, if response was not achieved, stopping treatment was recommended) as well as the model structure, where the induction period was assumed to have a duration of 12 weeks.

In MTC#3, secukinumab effectiveness data was based on both MEASURE 2 and MEASURE 1 as in MTC#1. In the MEASURE 1 study loading doses of secukinumab were administered intravenously, even though the posology of secukinumab was specified to be subcutaneously in its SmPC.[42] Nevertheless, to the best of the ERG's knowledge, in the literature there is no clear evidence for or against the efficacy difference between intravenous and subcutaneous administrations of secukinumab.[24] Thus, the ERG opted not to limit the response data to only the MEASURE 2 study, as this would lead to a loss of power.

In MTC#3, GO-RAISE trial was dropped from the analysis, as there was no BASDAI 50 response data available in GO-RAISE at week 12. Since GO-RAISE was the only study with golimumab effectiveness data in the evidence network for biologic naïve population, its omission from the analysis lead to a situation that MTC#3 does not provide BASDAI 50 estimates for golimumab. Therefore, for the analyses in which MTC#3 is used, same approach used for infliximab and certolizumab-pegol was followed, and its efficacy was assumed to be the same as the average of all other anti TNF-alphas.

If the response assessment definition is selected to be "BASDAI 50 or two units of decrease in BASDAI score", the choice of MTC has a larger absolute impact on the response rates. Based on the MTC type choice, the response rate for secukinumab ranges from 59%-91%; for certolizumab-pegol: 58%-68%; for etanercept: 49%-57%; for adalimumab: 67%-76%; for infliximab: 58%-68 and for golimumab: 58%-73%.

The ERG noted a small implementation error for the conversion factors applied when response definition is changed to "BASDAI 50 or two units' drop of BASDAI score". The error concerns the exploratory analysis of the biologic naive population, when patients were allowed for a second line biologic. In this analysis, for the second line biologic treatments, when the response definition was changed to "BASDAI 50 or two units drop of BASDAI score", instead of the conversion factor for the biologic experienced patients receiving biologics (1.709 for secukinumab from Table 5.10), the conversion factor for the biologic naïve patients receiving conventional care (2.045 for placebo from Table 5.7) was applied.

In addition, the ERG identified another potential error in the exploratory analysis for biologic experienced population. In this exploratory analysis, an efficacy reduction of 45.1% was applied to the response rates for all biologics in the biologic naïve population to derive an estimate for response

rates for biologic experienced population. In this analysis, no efficacy reduction factor was applied to conventional care response rates. However, a reduction in the response rates can be also seen in conventional care between biologic naïve patients and biologic experienced patients as well. This potential error would have an impact only on the incremental results of the secukinumab versus conventional care in that exploratory analysis.

The errors mentioned above were corrected by the ERG.

In TA383, the appraisal committee adopted another definition of response, as used by the BSR, which is "*a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more*".[7] At the request of the ERG, the company provided results based on this BSR definition.[6]

In their response to the clarification letter, the company stated that between 13% and 19% of patients could not be included in the response analysis based on the BSR definition, because the data for VAS were missing. However, after non-responder imputation, the following response estimates and conversion factors were derived in Table 5.14.

Table 5.14: Derivation of conversion constants for response based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score and 2 cm of more drop in spinal pain VAS score" for biologic naïve and biologic experienced patients

	Secukinumab 150 mg			Placebo		
	n	N	%	n	N	%
Biologic naïve						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit BASDAI drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]			[redacted]		
Biologic experienced						
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit BASDAI drop + 2 cm VAS drop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]			[redacted]		

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; mg = milligram; VAS = visual analogue scale

As it can be seen from Table 5.14, all the constants are greater than one and smaller than the corresponding conversion factors for "BASDAI 50 or two units of drop in BASDAI score" response definition. This is in line with the expectations, since the BSR definition is a bit stricter than the "BASDAI 50 or two units of drop in BASDAI score" definition, but still less strict than the "BASDAI 50" definition. Therefore, resulting response rates based on the BSR definition will lie between the response rates based on the "BASDAI 50" definition and those based on the "BASDAI 50 or two units of drop in BASDAI" definition.

In the response to the clarification letter [6], at the request of the ERG, the company had made an effort to conduct the evidence synthesis approaches from Corbett et al. 2014[9]. In the Excel model provided, the results for modelling approach A3 (independent modelling for BASDAI 50, BASDAI and BASFI;

assuming identical effectiveness for all anti TNF-alpha biologics; fixed effects), A4 (independent modelling for BASDAI 50, BASDAI and BASFI; assuming identical effectiveness for all anti TNF-alpha biologics; random effects) and A5 (independent modelling for BASDAI 50, BASDAI and BASFI; assuming exchangeable effectiveness for all anti TNF-alpha biologics; fixed effects) were incorporated.

The response rate of all anti TNF-alphas as a class was 43.07% for approach A3, 43.03% for approach A4. For approach A5, the rates for the biologics varied between 41.06% and 44.10%. In all these A3-A5 approaches the effectiveness of secukinumab was higher than those of the anti TNF-alphas.

In addition, the company had made an effort to conduct approaches B4 and C4 from Corbett et al.[9], as well. In approach B4, BASDAI 50 and BASDAI outcomes were modelled jointly, assuming identical treatment effectiveness for anti TNF-alphas and random effects. In approach C4, BASDAI 50, BASDAI and BASFI scores were modelled jointly, assuming identical treatment effectiveness for anti TNF-alphas and random effects. In the response to the clarification document[6], the company had mentioned that the WinBUGS code in Corbett et al. 2014[9] generated some errors, therefore they made some amendments and could not replicate the results in Corbett et al. 2014#43}.

The results of these approaches were provided in the report, however the way it is incorporated into the Excel model was not explained in the response to the clarification letter.[6] The response rate of all agents as a class was 43.3% for approach B4, and 40.5% for approach C4.

Even though the ERG appreciates all the efforts to conduct these analyses, from the data tables (e.g. Table 57 and 58) provided in the response to the clarification letter [6], it came to the ERG's attention that the input data came from a mixed population, where the biologic naïve and experienced patients were pooled together, e.g. Rapid ax-SPA trial results were in the data tables. Therefore, the MTC results for these approaches are unfortunately not directly useful for the cost-effectiveness analysis of secukinumab in biologic naïve and biologic experienced patients.

5.2.6.3 Baseline BASDAI and BASFI scores

The model used absolute BASDAI and BASFI scores at each cycle to determine cycle based utilities and costs. The estimates for absolute BASDAI and BASFI score of a patient at each cycle were conditional on the baseline BASDAI/BASFI values, the treatment that was administered, the time since the start of that treatment and patient's response to that treatment.

The baseline BASDAI and BASFI scores were the starting points for the model cohorts at the beginning of each treatment. In the base case, they were derived from the corresponding average baseline values from the pooled MEASURE 2 and MEASURE 1 trials, separately for biologic naïve and biologic experienced patients. The overall baseline BASDAI and BASFI scores for biologic naïve and experienced patients are given in Table 5.15.

Table 5.15: Overall baseline BASDAI and BASFI for the biologic naïve and biologic experienced populations

Input	Biologic-naïve	Biologic experienced
Overall baseline BASDAI	6.51	6.52
Overall baseline BASFI	5.90	5.89

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index

Note that in the model, in the base case, the overall baseline BASDAI and BASFI scores given in Table 5.15 were only used in the first cycle, and they represented the BASDAI/BASFI scores of the patients during the induction period. For the following cycles, while calculating the absolute BASDAI and BASFI scores of the patients in the states representing the post-induction period (post-induction maintenance therapy and conventional care), conditional baseline BASDAI and BASFI scores (conditional on the treatment and the response status) were used.

In the base case, the conditional baseline BASDAI and BASFI scores were also derived from pooled MEASURE 1 and MEASURE 2 trials. Data from secukinumab 150 mg arm of those trials was used to derive the response conditional baseline scores for all biologics (secukinumab as well as other anti-TNFα treatments); and data from the placebo arm of those trials was used to derive the response conditional baseline scores for conventional care. These response conditional specific baseline BASDAI and BASFI values used in the model are given in Table 5.16 below.

Table 5.16: Conditional baseline BASDAI and BASFI (conditional on the treatment and on the BASDAI 50 response) values derived from MEASURE 1 and MEASURE 2 trials

Input	Biologic naive		Biologic experienced	
	Biologics (Secukinumab and other anti TNFα)	**Conventional Care**	**Biologics (Secukinumab and other anti TNFα)**	**Conventional Care**
Baseline BASDAI				
Responders	6.42	6.12	6.59	6.24
Non-responders	6.39	6.73	6.48	6.61
Baseline BASFI				
Responders	5.44	4.75	5.39	5.49
Non-responders	6.07	6.22	6.04	5.85

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; TNF = Tumour Necrosis Factor

If the choice for the source of secukinumab trial data was selected as "MEASURE 2 only" instead of "MEASURE 1 & 2", the economic model uses the overall baseline (used for induction period) and the conditional baseline BASDAI and BASFI values derived from MEASURE 2 trial only, as presented in Table 5.17 below.

Table 5.17: Overall and conditional baseline BASDAI and BASFI (conditional on BASDAI 50 response) values derived from MEASURE 2 trial

Input	Biologic naïve		Biologic experienced	
	Biologics (Secukinumab and other anti TNFα)	Conventional Care	Biologics (Secukinumab and other anti TNFα)	Conditional Care
Baseline BASDAI				
Overall	6.75		6.59	
Responders	6.23	6.34	7.07	6.68
Non-responders	6.90	6.88	6.28	6.70
Baseline BASFI				
Overall	6.38		5.82	
Responders	5.69	5.77	6.20	6.41
Non-responders	6.83	6.38	5.81	5.69

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; TNF = Tumour Necrosis Factor

In the exploratory analyses for treatment naïve patients, if sequential second line biologic treatments were incorporated, the overall baseline BASDAI score applied during the second line biologic induction period would be equal to the conditional BASDAI score for the non-responders to the first line biologic treatment (6.9 if MEASURE 2 only is chosen for secukinumab data source; and 6.39 otherwise). The conditional baseline BASDAI scores applied in the post-induction states representing second line biologic post-induction period were assumed to be the same conditional baseline scores of the first line.

For the BASFI baseline scores applied for the second line biologics, the BASFI at the median cycle of discontinuation of first line treatment was calculated. In case the difference between the estimated BASFI score at discontinuation and the initial (1st line) overall baseline BASFI score of the population was non-positive, the 2nd line BASFI scores would be the same as the 1st line BASFI scores. Otherwise, the positive BASFI difference should be added to the 1st line baseline BASFI scores (both overall and conditional scores). These additional steps were taken to reflect the long-term BASFI progression during the first treatment until first treatment discontinuation.

ERG comment: As mentioned before, in NICE TA383[7], the committee expressed concerns regarding using response conditional baseline BASDAI and BASFI scores in modelling the BASDAI and BASFI scores of post-induction states in the subsequent cycles. Their main concern was the potential implication of this approach, i.e. that patients with more severe disease (higher baseline values) do not benefit as much from the biologics as patients with less severe disease. In Tables 5.16 and 5.17, the imbalances between responder and non-responder baseline BASFI and BASDAI scores can be seen especially for biologic naïve population.

Note that in Tables 5.16 and 5.17, according to the response to the clarification letter[6], the conditional averages of baseline BASDAI and BASFI scores were calculated based on the assumption that the response definition was "BASDAI 50 only" and the response assessment was at week 12. In the Excel model, the response conditional baseline BASDAI and BASFI values remain unchanged even if

different response definitions than BASDAI 50 (e.g. "BASDAI 50 or two units of drop in BASDAI score") or different time point of response assessment (like week 16) were selected in the economic model.

The failure to reflect the effects of different response definitions and assessment time points on the response conditional baseline BASDAI and BASFI scores jeopardises the validity of the results of the scenarios in which those different response definitions and assessment time points were assumed.

Due to the concerns listed above, the ERG conducted the analyses presented in Section 5.3, where the BASDAI and BASFI progression in the post-induction states uses overall BASDAI and BASFI baseline scores instead of response conditional ones.

Also, the ERG identified a small programming error in the electronic model. In the exploratory analysis for the biologic naïve patient population, during the calculation of the BASFI score at the median discontinuation cycle, a wrong cell reference was given. Because of this error, the model gives the BASFI score of a patient at the median discontinuation cycle, who had discontinued in the first cycle. However, the model was supposed to give the BASFI score of a patient at the median discontinuation cycle who discontinued at that median discontinuation cycle. Correction of this error did not lead to any changes in costs and effects, in any of the scenarios submitted in the CS[1], however it is an error that may lead to a potentially wrong results in Probabilistic Sensitivity Analysis (PSA) as well as future ERG scenarios, therefore it was corrected by the ERG.

5.2.6.4 Short-term BASDAI and BASFI changes

In the model, during the 12-week induction period, patients were assumed to experience improvements in BASDAI and BASFI scores dependent upon the treatment they receive. These short-term changes in BASDAI and BASFI were considered to be conditional on BASDAI 50 response.

For the biologic naïve population, in order to calculate response-conditional change from baseline at three months, data from the MEASURE 2 and MEASURE 1 trials of secukinumab and published conditional data for adalimumab (ATLAS) and golimumab (GO-RAISE) from the York model assessment report[9] were used to compute the ratio of change from baseline for BASDAI 50 responders compared to non-responders for secukinumab, adalimumab and golimumab, respectively.

For the other comparators (etanercept, infliximab, certolizumab pegol and conventional care), the average ratio of change from baseline was derived from the other biologics and used. In the CS[1], it was mentioned that this approach was deemed reasonable by clinical experts.

The ratios (responder/non-responder) of change from baseline for each treatment for BASDAI and BASFI scores are given in Tables 5.18 and 5.19 below. Both in the CS[1] and response to the clarification letter[6], it was not clear at which time point the response specific BASDAI and BASFI scores were measured in the trials that the ratio calculations were derived from.

Table 5.18: Available ratios of conditional BASDAI changes from baseline

BASDAI Change from baseline	MEASURE 1	MEASURE 2*	ATLAS	GO-RAISE	Overall average**	MEASURE 1 & 2 average
Responders	-4.77	-4.51	-4.64	-4.74	4.37	4.27
Non-responders	-1.42	-0.99	-0.82	-1.22		
Ratio of responders to non-responders	3.96	4.57	5.66	3.89		

* Values in this column are used in the scenario analyses in which MEASURE 2 was selected as the only Secukinumab data source. For all the other scenarios, MEASURE 1&2 average is used

** This value is used for all the other comparators (etanercept, infliximab, certolizumab pegol and conventional care)

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index

Table 5.19: Available ratios of conditional BASFI changes from baseline

BASFI Change from baseline	MEASURE 1	MEASURE 2*	ATLAS	GO-RAISE	Overall average**	MEASURE 1 & 2 average
Responders	-3.76	-4.28	-2.92	-3.03	4.06	3.21
Non-responders	-1.15	-1.34	-0.72	-0.53		
Ratio of responders to non-responders	3.23	3.19	4.06	5.72		

*Values in this column are used in the scenario analyses in which MEASURE 2 was selected as the only Secukinumab data source. For all the other scenarios, MEASURE 1&2 average is used

** This value is used for all the other comparators (etanercept, infliximab, certolizumab pegol and conventional care)

BASFI = Bath Ankylosing Spondylitis Functional Index

If the absolute change from baseline BASDAI or BASFI score of one of the treatments for BASDAI 50 responders was denoted as "*Responder Δ"* and that of non-responders was denoted as "*Non-responder Δ*", the ratios given in Tables 5.18 and 5.19 could be represented as: *Responder Δ/ Non-responder Δ.*

Note that the overall unconditional absolute change from baseline "*Overall Δ*" can be represented as a function of "*Responder Δ*" and "*Non-responder Δ*" as follows:

*Overall Δ = Responder Δ * (% BASDAI 50 responders) + Non-responder Δ* (1-% BASDAI 50 responders)*

The equation above was necessary to obtain the response conditional BASDAI and BASFI change from baseline estimates, because from evidence synthesis, only overall change from baseline estimates can be obtained.

Similar to the response assessment at the end of the induction period, the scenario analyses listed in Table 5.8 were conducted for change from baseline values for BASDAI and BASFI scores, as well. Some of these scenarios required additional MTCs, whereas some of them were handled by

conversion factors, which will be explained in detail below. In all the analyses, BASDAI and BASFI change from baseline were modelled independently.

Five different MTCs were conducted in order to explore the uncertainties surrounding source(s) for secukinumab data (MEASURE 1 & 2 or MEASURE 2 only) and time point(s) when the change from baseline were measured (week 12 only or between week 12 and 16). These MTCs used fixed or random effects models for continuous outcomes to estimate the change from baseline for BASDAI and BASFI for infliximab, secukinumab, golimumab, adalimumab, etanercept and conventional care. Due to a lack of data, for certoluzimab pegol, it was assumed that the overall BASDAI/BASFI absolute change from baseline at the end of the induction period would be equal to the average of the other four anti-TNFα agents (infliximab, golimumab, adalimumab and etanercept).

Different BASFI and BASDAI change from baseline inputs were used for MTC#1, MTC#2, MTC#3 and MTC#4. For MTC#5 same MTC inputs as MTC#1 were used but a random effects modelling approach was followed. The details of these five MTCs were discussed in Appendix K of CS[1] and Section D from the response to the clarification letter[6], where the errors identified by the ERG were corrected. The main characteristics of the MTCs are given in Table 5.20 below.

Table 5.20: The main characteristics of the five MTCs conducted for the BASDAI and BASFI change from baseline scores in the biologic naïve population

MTC Type	MTC#1 (Base Case) Fixed effects	MTC#2 Fixed effects	MTC#3 Fixed effects	MTC#4 Fixed effects	MTC#5 Random effects
Source(s) of secukinumab trial data	MEASURE 1 MEASURE 2	MEASURE 2	MEASURE 1 MEASURE 2	MEASURE 2	MEASURE 1 MEASURE 2
Time point(s) the change from baseline data was collected in the trials	Week 12-16	Week 12-16	Week 12	Week 12	Week 12-16
Which trial data was used in this MTC?	GO-RAISE MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE Giardina 2010	GO-RAISE MEASURE 2 ATLAS Huang 2014 SPINE Giardina 2010	GO-RAISE MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE Giardina 2010	GO-RAISE MEASURE 2 ATLAS Huang 2014 SPINE Giardina 2010	GO-RAISE MEASURE 1 MEASURE 2 ATLAS Huang 2014 SPINE Giardina 2010
Which treatments were included in this MTC?	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab, Infliximab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab, Infliximab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab, Infliximab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab, Infliximab	Placebo, Secukinumab, Etanercept, Adalimumab, Golimumab, Infliximab

MTC = Mixed treatment comparison

In addition to the MTCs above, at the ERG's request, additional MTCs were conducted adopting MTC approaches A3-A5 and B & C from the York report for TA383[9]. These analyses as well as their critique will be discussed under "ERG Comments" at the end of this section.

From the different MTCs conducted in Table 5.20 and from the "*Responder Δ/ Non-responder Δ"* ratios given in Tables 5.18 and 5.19, conditional absolute change estimates from the baseline for responders (*Responder Δ*) and non-responders (*Non-responder Δ*) were calculated. These estimates were calculated based on the response definition of "BASDAI 50 only" criterion.

For the uncertainties surrounding the definition of response ("BASDAI 50 only" or "BASDAI 50 only or two units of drop in BASDAI"), predetermined conversion factors were used. To transform the response conditional change from baseline estimates based on "BASDAI 50 only" criterion to those based on "BASDAI 50 or at least two units decrease in BASDAI score" criterion, the estimates based on "BASDAI 50 only" criterion were multiplied by predefined conversion constants, differentiated by the treatment received. These conversion constants were derived from the pooled MEASURE 1 and MEASURE 2 response data from biologic naïve patients measured at week 12. In Table 5.21, the derivation of these constants for placebo (used for conventional care) and secukinumab (used for all other treatments) are explained.

Table 5.21: Derivation of conversion constants for `BASDAI and BASFI change from baseline scores based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score" for biologic naïve patients

	Secukinumab 150 mg		Placebo	
	n	**Change from baseline**	**n**	**Change from baseline**
Biologic naïve – responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – non-responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – non-responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram

With the conversion constants given in Table 5.21, response conditional BASDAI and BASFI change from baseline estimates can be derived for all of the scenarios listed in Table 5.8 for biologic treatment naïve population from the overall change from baseline estimates. BASDAI and BASFI change from baseline estimates given BASDAI 50 response and no BASDAI 50 response are provided in Tables 5.22 and 5.23 below, respectively.

Table 5.22: BASDAI and BASFI change from baseline estimates given BASDAI 50 response

Therapy	Scenario 1 (Base case) MTC#1	Scenario 2 MTC#1*	Scenario 3 MTC#2	Scenario 4 MTC#2*	Scenario 5 MTC#3	Scenario 6 MTC#3*	Scenario 7 MTC#4	Scenario 8 MTC#4*	Scenario 9 MTC#5	Scenario 10 MTC#5*
BASDAI change from baseline given BASDAI 50 response										
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI change from baseline given BASDAI 50 response										
Secukinumab 150 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*These estimates are derived by applying the conversion factors to the column on the left hand side.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram; MTC = Mixed treatment comparison

Table 5.23: BASDAI and BASFI change from baseline estimates given no BASDAI 50 response

Therapy	Scenario 1 (Base case) MTC#1	Scenario 2 MTC#1*	Scenario 3 MTC#2	Scenario 4 MTC#2*	Scenario 5 MTC#3	Scenario 6 MTC#3*	Scenario 7 MTC#4	Scenario 8 MTC#4*	Scenario 9 MTC#5	Scenario 10 MTC#5*
BASDAI change from baseline given no BASDAI 50 response										
Secukinumab 150 mg	[redacted]									
Adalimumab	[redacted]									
Etanercept	[redacted]									
Golimumab	[redacted]									
Infliximab	[redacted]									
Certolizumab pegol	[redacted]									
CC	[redacted]									
BASFI change from baseline given no BASDAI 50 response										
Secukinumab 150 mg	[redacted]									
Adalimumab	[redacted]									
Etanercept	[redacted]									
Golimumab	[redacted]									
Infliximab	[redacted]									
Certolizumab pegol	[redacted]									
CC	[redacted]									

*These estimates are derived by applying the conversion factors to the column on the left hand side.
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram; MTC = Mixed treatment comparison

For the biologic experienced subpopulation, in the base case, response-conditional change from baseline estimates were derived directly from MEASURE 2 and MEASURE 1 trials data at week 12. In the Excel model, it is not possible to conduct an analysis that is based on only MEASURE 2 data for the biologic experienced population. Different scenarios analysed the impact of using different criteria in response assessment at the end of the induction period by using predefined conversion constants given in Table 5.24.

Table 5.24: Predefined conversion constants used in converting conditional change from baseline estimates based on BASDAI 50 definition to estimates based on BSR definition for biologic experienced patients

	Secukinumab 150 mg		Placebo	
	n	**Change from baseline**	**n**	**Change from baseline**
Biologic experienced – responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – non-responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – non-responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram

With the predefined conversion constants above, response conditional BASDAI and BASFI change from baseline estimates can be derived for all of the scenarios listed in Table 5.11 for biologic experienced population.

Based on the explanations above, conditional changes in BASDAI (Table 5.25) and BASFI (Table 5.26) at three months from baseline are given below for the biologic experienced patients for the base case, in which the response definition was based on BASDAI 50 criterion only, and for the scenario, in which the response definition was based on BASDAI 50 or drop by two units in BASDAI score.

Table 5.25: Conditional changes from baseline at three months for BASDAI in biologic experienced population

Defined as BASDAI 50	SEC	CC	Defined as BASDAI 50 or 2 units of drop in BASDAI	SEC150	CC
Responders	-4.980	-3.814	Responders	-4.063	-3.350
Non-responders	-0.941	-0.357	Non-responders	-0.400	0.097
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CC = conventional care; mg = milligram; SEC150 = secukinumab 150 mg					

Table 5.26: Conditional changes from baseline at three months for BASFI in biologic experienced population

Defined as BASDAI 50	SEC	CC	Defined as BASDAI 50 or 2 units of drop in BASDAI	SEC150	CC
Responders	-3.788	-2.726	Responders	-3.234	-1.131
Non-responders	-0.726	0.058	Non-responders	-0.216	0.066
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CC = conventional care; mg = milligram; SEC150 = secukinumab 150 mg					

In the exploratory analysis for biologic naïve patients, when the second line biologics were allowed, for the second line biologic treatments, the change from baseline estimates would be the average change from baseline estimates of all biologics in the basket therapy. Recall that the basket therapy applied in the second line excluded only the biologic used at first line. After the average change from baseline values were calculated for the basket therapy, a relative efficacy reduction of 41.9% was applied for BASDAI and 50.4% was applied for BASFI change from baseline scores to account for the clinical expectation that the patients would respond worse to a second-line biologic. These efficacy reduction values were derived from the change from baseline data from MEASURE trials, based on the reduction observed with secukinumab in experienced patients compared to naïve patients. Details of the calculation of these relative reduction values can be found in Table 5.27.

Table 5.27: BASDAI and BASFI change from baseline relative reduction between biologic naïve and biologic experienced populations – pooled MEASURE 1 and MEASURE 2 data

Sub-group	Secukinumab 150 mg		Placebo		Treatment effect (SEC response minus PBO response)	Relative reduction in BASDAI change from baseline
	n	Change from baseline	n	Change from baseline		
Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. BASDAI cfb in the experienced group are (1-0.42) = 0.58 x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Sub-group	**Secukinumab 150 mg**		**Placebo**		**Treatment effect (SEC150 response minus PBO response)**	**Relative reduction in BASFI change from baseline**
	n	**Change from baseline**	**n**	**Change from baseline**		
Biologic naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] i.e. BASFI cfb in the experienced group are (1-0.50) = 0.50 x those of the naïve group
Biologic experienced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; cfb = change from baseline; mg = milligram; PBO = placebo; SEC150 = secukinumab 150 mg

The same approach was followed for the exploratory analysis conducted in the biologic experienced subgroup, in which comparator biologics other than secukinumab were also included. In this exploratory analysis, the changes from baseline parameters for the biologic naïve population were multiplied with corresponding relative reductions in Table 5.27.

The initial change from baseline in BASDAI was assumed to remain constant for the entire post-induction period when the treatment that patient had responded to was maintained. For BASFI score, in the model, it was assumed that the BASFI scores increase in time during the post-induction period, albeit at different rates, at a slower rate if the patient was on biologics during the maintenance therapy. These long-term BASFI changes during the post-induction period will be explained in the next section.

ERG comment: As mentioned earlier, in the original CS[1], Huang et al. 2014[19] study was omitted from the MTCs for all outcomes and ATLAS study [48] was omitted from the MTCs for BASFI related outcomes. In the response to the clarification letter[6], an updated MTC was conducted It included Huang et al. 2014[19] and ATLAS study[48]. The results were presented in Section E. However, the inputs used in the MTCs from Huang et al. 2014[19] were not provided, therefore the MTC results provided in the response to the clarification letter [6] could not be verified.

Also, in the original CS[1], results from the random effects model were not provided. After a request from the ERG, the random effects binomial model results were provided in the response to the clarification letter [6], however only for the base case analysis. This MTC is represented by MTC#5 in Table 5.20.

The choice of the MTC has a large impact on the change from baseline estimates, especially for conditional change from baseline estimates given BASDAI 50 response. In Table 5.22, for secukinumab it can be seen that the change from baseline given BASDAI 50 response estimates range [redacted] for BASDAI and from [redacted] for BASFI. Estimates for other comparators also change according to the choice of MTC: certolizumab-pegol from [redacted] for BASDAI and [redacted] for BASFI; etanercept from [redacted] for BASDAI and [redacted] for BASFI; adalimumab from [redacted] for BASDAI and [redacted] for BASFI; infliximab from [redacted] for BASDAI and [redacted] for BASFI; and golimumab from [redacted]. However, using the random effects model (MTC#5) instead of the fixed effect model (MTC#1) seems to have limited impact.

MTC#1 represents the base case of the CS[1], however, the ERG finds the assumptions from MTC#3 the most plausible, following the same line of reasoning discussed in the "ERG comments" in Section 5.2.6.2. Note that all of the MTCs were able to provide BASFI and BASDAI change from baseline estimates for all biologics, except for certolizumab pegol. For certolizumab pegol, the average changes from baseline estimates from all other anti TNF-alpha agents were used.

If the response assessment definition is selected to be "BASDAI 50 or two units of decrease in BASDAI score", the change from baseline estimates become smaller compared to the "BASDAI 50". This can be explained by the fact that the responders needed to satisfy the less strict criteria: "BASDAI 50 or two units of decrease in BASDAI score" with smaller change from baseline values. This makes the impact of the MTC choice for absolute change from baseline estimates smaller than that of "BASDAI 50". Based on the MTC type choice, the change from baseline estimates given response at the end of the induction period are as follows: from [redacted] (BASDAI) and [redacted] (BASFI) for secukinumab; [redacted] (BASDAI) and [redacted] (BASFI) for certolizumab-pegol; [redacted] (BASDAI) and [redacted] (BASFI) for etanercept; [redacted] (BASDAI) and [redacted] (BASFI) for adalimumab; [redacted] (BASDAI) and [redacted] (BASFI) for infliximab; and [redacted] (BASDAI) and [redacted] (BASFI) for golimumab.

The ERG has identified a very minor error in the economic model. In the economic model, the conversion factor for BASFI change from baseline for non-responders is slightly different from what had been reported (i.e. [redacted] is used in the model instead of [redacted] reported in Table 5.24). This error would affect only the scenarios where the conversion factors for "BASDAI 50 or two units drop in BASDAI score" response definition were used.

In TA383[7], the appraisal committee adopted another definition of response, as used by the British Society for Rheumatology (BSR), which is "*a reduction of the BASDAI to 50% of the baseline value, or a reduction of 2 units or more, together with a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more*". At the request of the ERG, the company provided results based on this BSR definition[6].

Despite the missing VAS data on spinal pain, the following response estimates and conversion factors were derived after non-responder imputation, for biologic naïve population (Table 5.28) and biologic experienced population (Table 5.29), respectively.

Table 5.28: Derivation of conversion constants for conditional change from baseline estimates based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score and 2 cm of more drop in spinal pain VAS score" for biologic naïve patients

	Secukinumab 150 mg		Placebo	
	n	**Change from baseline**	**n**	**Change from baseline**
Biologic naïve – responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop in BASDAI + 2 cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – non-responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic naïve – non-responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2 cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram; VAS = Visual analogue scale

Table 5.29: Derivation of conversion constants for conditional change from baseline estimates based on "BASDAI 50 only" to "BASDAI 50 or two units drop in BASDAI score and 2 cm of more drop in spinal pain VAS score" for biologic experienced patients

	Secukinumab 150 mg		Placebo	
	n	Change from baseline	n	Change from baseline
Biologic experienced – responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – non-responders, BASDAI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	
Biologic experienced – non-responders, BASFI change from baseline at week 12				
BASDAI 50	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI 50 or 2 unit drop + 2cm drop in VAS	[redacted]	[redacted]	[redacted]	[redacted]
Conversion constant	[redacted]		[redacted]	

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram; VAS = Visual analogue scale

As it can be seen from tables above, almost all of the conversion constants are smaller than one and greater than the corresponding conversion factors for "BASDAI 50 or two units of drop in BASDAI score" response definition. This is in line with the expectations, since the BSR definition is a bit stricter than the "BASDAI 50 or two units of drop in BASDAI score" definition, but still less strict than "BASDAI 50" definition. For a response based on BSR definition, a patient requires less change from baseline compared to that required for "BASDAI 50" but more required for "BASDAI 50 or two units of drop in BASDAI score". Therefore, resulting change from baseline estimates based on the BSR definition will generally lie between the estimates based on "BASDAI 50" definition and those based on "BASDAI 50 or two units of drop in BASDAI" definition.

Based on the discussions from Corbett et al. 2014[9], the ERG was interested in an approach where all the biologics were considered as a class, and therefore the treatment effects of all biologics were identical. In the response to the clarification letter[6], at the request of the ERG, the company had incorporated the evidence synthesis approach A3 (independent modelling for BASDAI 50, BASDAI and BASFI; assuming identical effectiveness for all anti TNF-alpha biologics; fixed effects), A4 (independent modelling for BASDAI 50, BASDAI and BASFI; assuming identical effectiveness for all anti TNF-alpha biologics; random effects) and A5 (independent modelling for BASDAI 50,

BASDAI and BASFI; assuming exchangeable effectiveness for all anti TNF-alpha biologics; fixed effects) from Corbett et al. 2014 [9].

The changes from baseline estimates (overall, not response conditional) of all anti TNF-alphas as a class were [redacted]

Baseline BASDAI, BASDAI 50 and absolute BASDAI change from baseline are all correlated parameters. In the CS[1], BASDAI 50 and absolute BASDAI change from baseline were modelled separately, although the latter with the baseline BASDAI value determine the BASDAI 50 status of a patient jointly. However, all the evidence synthesis approaches in Table 5.6 and Table 5.20, estimated these input parameters independently. In order to incorporate all these evidence synthesis results to the economic model, which necessitates response conditional BASDAI and BASFI change from baseline estimates, the company had used responder/non-responder ratios given in Table 5.18 for BASDAI and in Table 5.19 for BASFI. These responder/non-responder ratios were derived independently for the available agents (secukinumab, adalimumab and golimumab) from MEASURE 1 and 2, ATLAS and GO-RAISE trials, and for the rest the average of the three ratios were assumed. It was not obvious which time point (week 12 or week 16) was used in the derivation of these responder/non-responder ratios.

The ERG thinks that this approach, independent synthesis of the evidence for BASDAI 50, BASDAI and BASFI and no synthesis at all for BASDAI and BASFI baseline values and responder/non-responder ratios, is problematic. This problem not only violates the natural correlation between these parameters, but also creates implausible results. For instance in Table 5.22 [redacted]. In a similar vein, the change from baseline estimates for conventional care for responders is less than 50% of the assumed baseline BASDAI score in the scenarios where the response is defined as "BASDAI 50". Therefore, the ERG had requested the company to conduct the joint evidence synthesis approaches (approaches B and C) from Corbett et al.[9].

In response to the clarification letter [6], the company had made an effort to conduct these approaches (B4 and C4 from Corbett et al.[9]). In approach B4, BASDAI 50 and BASDAI outcomes were modelled jointly, assuming identical treatment effectiveness for anti TNF-alphas and random effects. In approach C4, BASDAI 50, BASDAI and BASFI scores were modelled jointly, assuming identical treatment effectiveness for anti TNF-alphas and random effects.

The results of these approaches were provided only in the report, however the Excel implementation was not clear and the explanation of the implementation was lacking in the technical report. For approach B4, the change from baseline estimates for BASDAI were between [redacted]. For approach C4, the change from baseline estimates for BASDAI were between

[redacted], and for BASFI between [redacted]. In both of these approaches, [redacted].

Even though the ERG appreciates all the efforts to conduct these analyses, from the data tables (e.g. Tables 57 and 58) provided in the response to the clarification letter [6], it came to the ERG's attention that the input data came from a mixed population, where the biologic naïve and experienced patients were pooled together (e.g. rapid ax-SPA trial results were in the data tables). Therefore, the MTC results for these approaches are unfortunately, not directly useful for the cost effectiveness analysis of secukinumab in biologic naïve and biologic experienced patients.

For the biologic experienced population analyses, it came to the ERG's attention that in the base case, the change from baseline estimates in Tables 5.25 and 5.26 were derived from week 12, whereas the response rates in Table 5.12 were derived from week 16. In order to correct for the mismatch between response rates and response conditional change from baseline estimates, the ERG decided to use the week 12 estimates for the response rates.

In addition, it was not clear to the ERG in which time point (week 12 or week 16), the efficacy reduction factors in Table 5.27 were derived from. These reduction factors are utilised in the exploratory analyses for both biologic naïve and biologic experienced population.

5.2.6.5 Long-term BASFI changes

In the model, after the initial changes in BASDAI and BASFI scores in the three month induction period, patients receiving maintenance therapy and who continue to respond to biologic treatment were assumed to benefit from a slower rate of BASFI progression over the longer term. Long-term changes in BASFI were estimated based on the approach taken in the York report for TA 383.[9]

In the CS[1], it was assumed that the natural history of BASFI progression is not related to disease severity/activity (BASDAI) and only related to the progression of radiographic disease (measured by the modified Stoke Ankylosing Spondylitis Spinal Score; mSASSS).

The differences in BASDAI from baseline were assumed to remain constant over the longer-term horizon, for as long as patients continued on their initial treatment. Therefore, the changes which might affect BASFI were assumed to be originated from change in mSASSS.

Using this approach, in the CS[1], the annual rate of BASFI change was calculated as:

$$Annual\ rate\ of\ BASFI\ change = annual\ rate\ of\ mSASSS\ change\ x\ BASFI\ change\ with\ 1\ unit\ change\ in\ mSASSS$$

The independent effect of one-unit change in mSASSS on BASFI scores was taken as the coefficient in the multivariate model reported in Landewe et al. 2009 (mean: 0.057; SE: 0.0049).[49]

The annual rate of mSASSS change was taken as 1.440, based on the annual rate of change in a subgroup of patients with baseline mSASSS ≥10 in the Ramiro et al. 2013 study, which was considered to more accurately reflect the population likely to be eligible to receive biologic therapy than the full study population.[50]

Hence, with the equation above, the annual rate of BASFI change, 0.082, was calculated. This figure represents the annual rate of change without any biologic treatment, therefore it was applied if the patient is on conventional care.

In the CS[1], it was assumed that when patients were on biologic treatment, they were associated with a slower rate of mSASSS change compared to the rate under conventional care. Therefore, a relative rate taken from Haroon et al. 2013[51], 0.42, is applied to the rate of mSASSS change when patient is on conventional care. In the CS[1], it was mentioned that this approach was consistent with the York report for TA 383[9]. This relative rate is applied to all therapies other than conventional care.

In a scenario analysis, based on findings from MEASURE 1, which was reporting a mean mSASSS change from baseline at week 104 (mean ± SD = 0.30 ± 1.93) for patients receiving secukinumab, a relative rate of 0.15 (0.30/2=0.15) was considered for secukinumab. This was lower than the rates of other biologics.

In the CS[1], the effect of biologic treatment on BASFI change was modelled to occur from the outset of treatment in the base case analysis. A scenario analysis was conducted to explore the impact of considering treatment effect on BASFI beginning four years after treatment initiation, in line with the York report for TA 383[9].

ERG comment: The ERG concurs with the assumptions (BASFI changes at an annual rate of 0.082 per year and a relative ratio of 0.42 is applied for the progression with biologics) concerning the long term BASDAI and BASFI changes. These assumptions are in line with the previous models (e.g. the York report for NICE TA 383[9]).

5.2.6.6 Rebound in BASFI and BASDAI

The short term improvements (during the first three months in induction period) in BASDAI and BASFI were assumed to be maintained as long as the patients remain on biologic treatment. In addition, patients who remained on biologic treatment experienced a slower rate of BASFI progression as well.

Upon discontinuation, improvements in BASFI and BASDAI resulting from biologic treatment were assumed to be vanished. For BASDAI, after discontinuation, it was assumed that the BASDAI score reverts to baseline.

In the CS[1], for BASFI, two alternative ways of modelling the rebound in BASFI upon discontinuation of biologics were considered. These two alternatives were consistent with the scenarios applied in the York report prepared for TA 383[9].

1. "Rebound to baseline" scenario: Upon discontinuation of biologic therapy, BASFI deteriorates by an amount that is equal to the improvement achieved during response to biologic therapy (equal to the responders' average BASFI change from baseline).
2. "Rebound to natural history" scenario: Upon discontinuation, BASFI deteriorates to the level that would have been if there had not been any response initially and BASFI had progressed like there had been no biologic treatment.

In the base case, the "Rebound to baseline" scenario was selected, and the "Rebound to natural history" scenario was modelled as a scenario analysis.

ERG comment: The ERG considers that the assumptions surrounding the rebound in BASFI and BASDAI are reasonable and in line with the approach followed by the York report for NICE TA383[9].

Note that after discontinuation of the biologics, the BASDAI score of a responder patient becomes equal to the baseline BASDAI score of a non-responder patient, therefore the amount of the BASDAI rebound may be a bit different from the initial BASDAI gain due to response.

5.2.6.7 Withdrawal of biologic therapy

In the CS[1], withdrawal from the biologic therapy was incorporated into the model for the post-induction maintenance states in each cycle. In the economic model, it was assumed that the probabilities were treatment-specific and they were derived from annual withdrawal risks associated with each biologic for year 1 and years 2+ separately. If there was no available information on a treatments withdrawal rate for subsequent years, that treatments withdrawal rate for subsequent years was assumed to be the same as the withdrawal rate of the first year. The annual withdrawal probabilities applied in the model are given in Table 5.30.

In addition, a scenario analysis was conducted in which a constant annual withdrawal rate of 11.0% was assumed across all biologics. This rate (11%) was based on the York report for TA383[9].

Table 5.30: Annual withdrawal probabilities applied in the model in the base case

	Secukinumab	Certolizumab Pegol	Etanercept	Adalimumab	Infliximab	Golimumab
Year 1	15.2%	12.6%	25.1%	13.0%	2.1%	13.7%
Years 2+	6.0%	11.0%	25.1%	9.3%	15.7%	6.6%
Source	MEASURE 2 Clinical Study Reports[22, 52] MEASURE 1 Clinical Study Reports[4, 23]	Sieper et al. 2015[53]	Dougados et al. 2012[21], Navarro-Sarabia et al. 2011[54]	Sieper et al. 2012[55]	van der Heijde et al. 2005[56], Braun et al. 2008[57]	Deodhar et al. 2015[58]

ERG comment: Besides the sources, no details were given in CS[1] about how these withdrawal probabilities were derived in Table 5.30. Therefore, considering the list of justifications provided in Corbett et al. 2014[9], the ERG considers using 11% as the withdrawal probability (both for year 1 and year 2+), for all biologics, more reasonable.

It is also worth to note that the withdrawal probabilities remain unchanged when different definitions of response were selected in the economic model. The ERG thinks that for a less restrictive definition of response, it may be possible that the discontinuation from a biologic due to lack of efficacy would be higher. Nevertheless, since there is no evidence for or against this, it was assumed that the withdrawal rates do not change with different definitions of response.

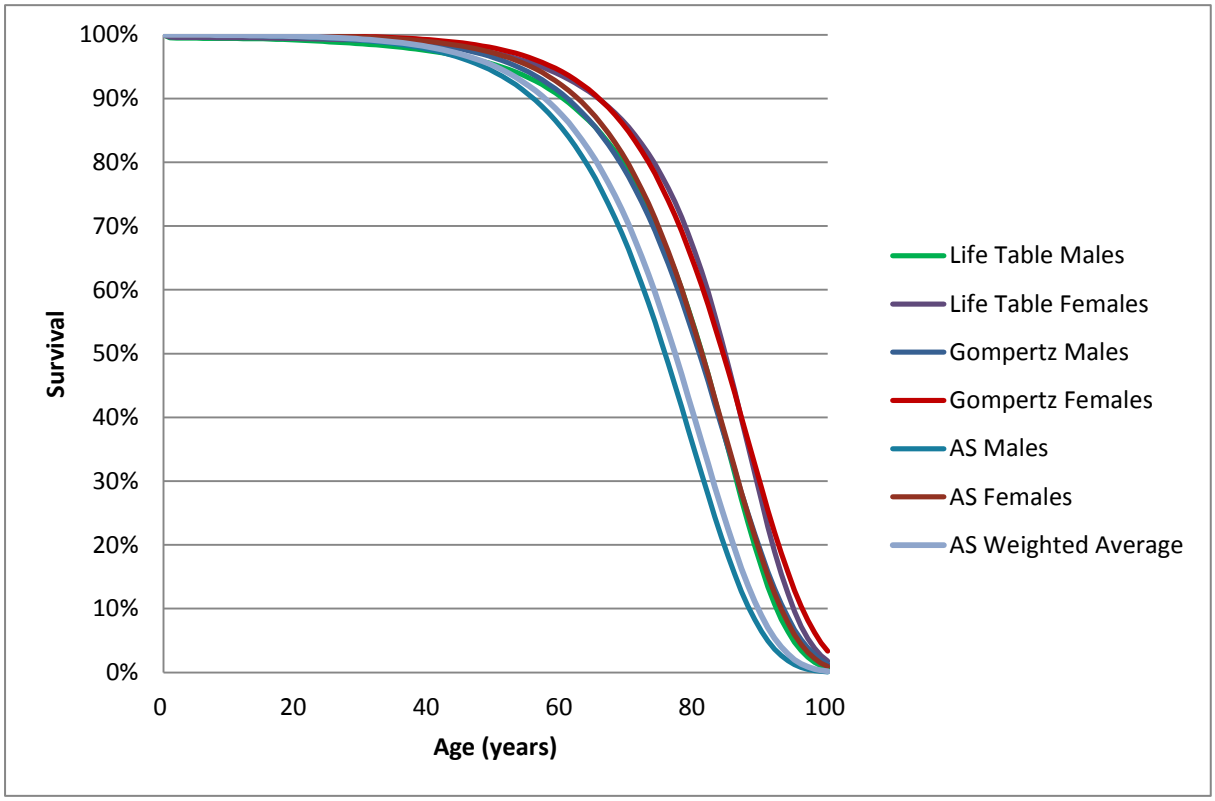
5.2.6.8 Mortality

In the CS[1], it was assumed that AS is associated to an additional mortality. This AS-related mortality is applied by a relative risk of death to general population mortality rates. The relative risks applied were gender-specific (1.63 for males 1.38 for females) and are derived from Bakland et al. 2011.[59]

The general population mortality rates (for males and females) were derived from general population life tables from the Office for National Statistics 2014 dataset. Gompertz distributions were fitted to the survival curves of the general population and the relative risks for AS-related mortality were applied to the Gompertz curves.

ERG comment: The ERG accepts the approach of the CS[1] as reasonable. In Figure 5.3, it can be observed that the Gompertz functions demonstrate a good fit with the actual life tables, only after the age of 95 years, Gompertz survival for females is a bit over-estimated. Note that to prevent unlikely alive patients due to the tail of the Gompertz function, all patients were assumed dead at the age of 100 years.

Figure 5.3: Survival functions for the economic model



AS = ankylosing spondylitis

5.2.6.9 Adverse events

In the model, only serious infections were incorporated as adverse events for all of the biologic treatments. Serious infections were categorised as tuberculosis reactivation and other serious infections.

It was assumed that 5% of the serious infections would be tuberculosis and the remaining 95% would be other serious infections, based on the reported rates in Singh et al. 2011.[39] The overall probability of serious infections was assumed to be treatment-specific. Per-cycle probabilities of adverse events are presented in Table 5.31, derived from the sources noted.

Table 5.31: Adverse event risks

Drug	Serious Infection	Source
Secukinumab	0.16%	MEASURE 2 Clinical Study Report[22], MEASURE 1 Clinical Study Report[52]
Certolizumab pegol	0.67%	Sieper et al. 2015[53]
Etanercept	0.00%	Dougados et al. 2012[21], Navarro-Sarabia et al. 2011[54]
Adalimumab	0.35%	Sieper et al. 2012[55]
Infliximab	0.52%	Braun et al. 2008[57]
Golimumab	0.32%	Deodhar et al. 2015[58]
Conventional care	0.00%	-

The adverse events given in Table 5.31 have a very limited impact on costs but no impact on utilities.

ERG comment: No evidence synthesis methods were used in deriving the adverse event rate estimates. However, since the impact of the adverse events is very limited, the ERG applied the rates used in the CS[1].

Note that the adverse events (serious infections) do not trigger a treatment switch in the model. However, in the response to clarification letter[6], it was discussed that the adverse events were one of the underlying reasons for the biologic withdrawals mentioned in section 5.2.6.7. Hence, the ERG interprets that the adverse event risks given in Table 5.31 are the adverse events that do not lead to a biologics withdrawal.

5.2.7 Health related quality of life (HrQoL)

5.2.7.1 HrQoL from clinical trials

The MEASURE 2 and MEASURE 1 trials of secukinumab in AS collected ASQoL and FACIT-FATIGUE quality of life outcomes, as well as the EQ-5D-3L health utilities instrument. The results for the EQ-5D questionnaire at baseline and week 16 can be found in the CS, Appendices F and G.

5.2.7.2 Published HrQoL studies

In addition to the EQ-5D data from MEASURE 1 and MEASURE 2 trials, as part of the systematic literature review, utility data associated with AS were identified and reviewed.

A total of 45 publications reporting utility data were identified and out of these 45 studies, 43 used EQ-5D. Details of these identified studies, which were deemed relevant to the submission (n=42) were presented in Appendix N of the CS[1].

No studies reporting utilities/ disutilities for any specific adverse events were found. The details of the targeted literature search for the adverse event disutilites were not provided in the CS[1].

5.2.7.3 HrQoL used in the cost effectiveness analysis

The health economic model used a mapping algorithm to link BASDAI and BASFI scores to a generic utility measure. The mapping algorithm consists of a regression model for utility of a patient with BASDAI score, BASFI score, gender and age as covariates.

In the CS[1], it was mentioned that a linear mixed model was used to fit EQ-5D utility score as a response variable and BASDAI and BASFI scores, age and gender as predictors, using patient level data from MEASURE 1 and MEASURE 2. It was mentioned that the effect of correlation within the data was explored using subject as a random effect to account for the within-subject correlation between assessments.

The final linear regression model based on the analysis of MEASURE 2 and MEASURE 1 data was as follows:

*Utility = 0.9610 – 0.0442 * BASDAI – 0.0330 * BASFI – 0.0111 * Sex [1=male, 0=female] + 0.0005 * Age*

This linear model derived from MEASURE 2 and MEASURE 1 trial data was used in the base case analysis. The selection method of the covariates, was not described in the CS and also not clarified in the response to the clarification letter [6].

Scenario analyses explored the use of two alternative linear models: 1) the linear model reported in Wailoo et al. 2015[40], 2) the linear model reported in McLeod et al. 2007[32].

The model by Wailoo et al.[40] was one of the models that were presented in the MTA report of the NICE TA 383[9]. Both of the alternative models were developed based on UK AS populations.

The parameter values for the linear models used in the base case and scenario analyses are summarised in Table 5.32.

Table 5.32: Summary of utility values for cost-effectiveness analysis
(Mean, standard error)

	Intercept	BASDAI coefficient	BASFI coefficient	Male coefficient	Age coefficient
MEASURE 2 and MEASURE 1 model (base case)	0.9610 (0.02503)	-0.0442 (0.00312)	-0.0330 (0.00316)	-0.0111 (0.01335)	-0.0005 (0.00049)
Wailoo et al. 2015[40]* (scenario analysis)	0.7220	$(BASDAI/100)^2$: -0.4700	BASFI/100: -0.2140 $(BASFI/100)^2$: -0.2330	-	0.0030
McLeod et al. 2007[32] (scenario analysis)	0.8772	-0.0384	-0.0323	-0.0279	0.0017

*Note: the Wailoo et al. 2015[40] model included age, $(BASDAI/100)^2$, BASFI/100 and $(BASFI/100)^2$ as explanatory variables
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index

.

ERG comment: The approach of developing a regression model to link BASDAI and BASFI is in line with the approach used in the York report for TA383[9] and is reasonable given that both BASDAI and BASFI contain elements of health-related quality of life, e.g. pain and self-care.

In general, trial data may be less appropriate to find a valid regression model over the whole range of BASDAI and BASFI scores. In the MEASURE 1 and 2 studies, patients had to have a BASDAI>4 to be eligible for inclusion. However, already after four weeks, patients were observed with a BASDAI<1 so the range of possible BASDAI values is most likely represented in the dataset used for the regression analysis.[4]

In the CS only the final, selected, regression model was presented, without any details regarding the selection process for covariates or the possible exploration of interaction terms and non-linear specifications.[1] These details were also not provided after they were requested in the clarification letter, so the ERG cannot judge the rigor with which the current model specification was selected. Comparison of the coefficients derived from MEASURE 1 and 2 to those from Wailoo et al. 2015[40] and McLeod et al. 2007[32] shows that the most striking difference is that the latter both have a positive coefficient for age, whereas the coefficient for age from the MEASURE 1 and 2 studies is negative. The scenario analyses performed on the base case using the two alternative regression models show that the total number of QALYs per treatment is indeed affected by the choice of regression model. However, these differences are relatively minor and have no impact on the conclusions (see also Section 5.2.10).

5.2.8 Resources and costs

5.2.8.1 Literature review

As part of the systematic literature review, studies that report cost or resource utilisation estimates associated with AS were identified and reviewed. A total of 89 studies containing relevant cost or resource utilisation data were identified from the SLR. Ten studies reported cost or resource use estimates from the UK. Details of these studies, and a list of non-UK studies meeting the eligibility criteria of the systematic review, are provided in the CS[1], Appendix O.

5.2.8.2 Intervention and comparators' costs and resource use

The unit costs and resource use associated with the acquisition and administration of the intervention and comparator biologic therapies are provided in Table 5.33. The monitoring costs associated with these therapies, (e.g. laboratory tests and requirements for medical visits) are provided in Table 5.34.

Note that in conventional care, no drug acquisition or administration costs were incorporated in the model, based on the assumption that biologic treatments would be administered as add-on to conventional care. The PAS is reflected in the price for secukinumab in all cost-effectiveness results.

Drug acquisition costs for infliximab

The price of infliximab (purchased in 100 mg vials) is £419.62 per 100 mg vial for Remicade® (originator) and £377.66 for Remsima® and Inflectra® (biosimilars). All infliximab products are administered at a dose of 5 mg/kg, in line with their SmPCs.[46, 60, 61] Hence, it was necessary to incorporate the patient weights to accurately calculate the drug acquisition costs for infliximab.

The average infliximab cost per infusion was calculated based on a mean weight of 78.20 kg (standard deviation: 16.88), which is the pooled average weight of patients across the MEASURE 2 and MEASURE 1 studies. It was assumed that the weight was normally distributed, which resulted in a per dose drug acquisition cost estimation of £1,850.59 for Remicade® and £1,665.54 for biosimilar infliximab. In Table 5.35, calculations for drug acquisition costs were presented.

Table 5.33: Unit costs and resource use associated with drug acquisition and administration

Items	Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
Unit cost							
Acquisition cost	**List price:** £1,218.78 per pack of two 150 mg pre-filled syringes/ SensoReady® pens **PAS price:** [redacted] per pack of two 150 mg pre-filled syringes/ SensoReady® pens	**List price:** £357.50 per 200 mg pre-filled syringe **PAS price:** The first 12 weeks of treatment are provided free.	**Originator Etanercept:** £178.75 per 50 mg pre-filled syringe **Biosimilar Etanercept:** Benepali: £164.00 per 50 mg/ml solution for injection in pre-filled syringe or pre-filled pen	£352.14 per 40 mg pre-filled syringe	**Originator infliximab:** Remicade®: £419.62 per 100 mg vial Average cost per dose calculated as £1,850.59 – see "Infliximab cost calculations" **Biosimilar infliximab:** Remsima: £377.66 per 100 mg vial Inflectra: £377.66 per 100 mg vial Average cost per dose calculated as £1,665.54 – see "Infliximab cost	**List price:** £762.97 per pre-filled syringe for Golimumab 50 mg, £1,525.94 for Golimumab 100 mg **PAS price:** Both Golimumab 50 mg and Golimumab 100 mg are £762.97 per pre-filled syringe	BNF 2016 and MIMS

Items	Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
					calculations"		
Administration cost (for subcutaneous therapies – first administration only)	£43.00	£43.00	£43.00	£43.00	NA	£43.00	Assumed self-administered following 1 hour of nurse training on first administration, PSSRU 2015[62]
Administration (intravenous therapy [infliximab] – per administration)	NA	NA	NA	NA	£326.46*	NA	NHS Reference Costs 2014-15 (health resource group code: SB15Z: Deliver subsequent elements of a chemotherapy cycle [63])
Frequency of resource use							
No. of doses (month 1- 3) – induction period	7.00	0‡	13.00	6.52	3.00	3.00	BNF 2015
No. of doses (month 4 - 6) – maintenance period	3.00	6.52	13.00	6.52	2.00	3.00	BNF 2015
No. of doses (three-monthly period from month 7+) – maintenance period	3.00	6.00	13.00	6.52	1.63	3.00	BNF 2015

Items	Secukinumab 150 mg	Certolizumab pegol 200 mg	Etanercept 50 mg QW	Adalimumab 40 mg	Infliximab 40 mg	Golimumab 50 mg	Reference
[*]An alternative cost of intravenous infliximab administration is available in the costing template for the adalimumab NICE submission in psoriasis and use of this alternative cost was explored as a scenario analysis.[64]; [‡] Note that patients actually receive 9.76 doses during the induction period. However, these are free per the PAS. AS = ankylosing spondylitis; BNF = British National Formulary; HRG = Healthcare Resource Group; mg = milligram; MIMS = Mixed-effect model repeated measures; ml = millilitre; NA = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PAS = Patient Access Scheme; PSSRU = Personal Social Services Research Unit; QW = once weekly							

Table 5.34: Unit costs and resource use associated with monitoring

Cost parameter	Unit costs		Frequency of resource use (all interventions)		
	Unit cost	Reference	First 3 months	Subsequent 3 month periods	Reference
Medical visits					
GP visits	£44.00	Cost of an 11-minute GP appointment, with qualifications, PSSRU 2015[62]	0	0	York report for TA 383[9]
Specialist visits	£137.23	NHS Reference Costs 2014-15 HRG code WF01A[63]	2	0.5	York report for TA 383[9]
Laboratory tests					
Full blood counts	£2.99	Costs sourced from the ERG report for psoriatic arthritis (TA199)[65] and updated to 2015 prices using the HCHS inflation index from PSSRU 2015[62]	2	1	York report for TA 383[9]
Erythrocyte sedimentation rate	£2.96		2	1	York report for TA 383[9]
Liver function test	£0.75		2	1	York report for TA 383[9]
Urea and electrolytes test	£1.39		2	1	York report for TA 383[9]
Chest radiograph	£26.23		1	0	York report for TA 383[9]
Tuberculosis Heaf test	£8.74		1	0	York report for TA 383[9]
Antinuclear antibodies	£4.66		1	0	York report for TA 383[9]
DNA double-strand test	£4.66		1	0	York report for TA 383[9]

BSR = British Society for Rheumatology; DNA = deoxyribonucleic acid; ERG = Evidence review group; GP = general practitioner; HCHS = Hospital and community health services; HRG = Healthcare Resource Group; PSSRU = Personal Social Services Research Unit; TA = Technology appraisal

Table 5.35: Calculation of infliximab acquisition cost based on patient weight

Patient weight (kg)	Total dose at 5 mg/kg	Number of vials required	Distribution	Cost per dose (Remicade®)	Cost per dose (biosimilar)
≤ 20	100 mg	1	--	--	--
>20 and ≤ 40	200 mg	2	1.18%	£9.93	£8.93
>40 and ≤ 60	300 mg	3	12.87%	£162.01	£145.81
>60 and ≤ 80	400 mg	4	40.20%	£674.73	£607.26
>80 and ≤ 100	500 mg	5	35.92%	£753.68	£678.32
>100 and ≤ 120	600 mg	6	9.16%	£230.69	£207.62
>120 and ≤ 140	700 mg	7	0.65%	£19.13	£17.22
>140 and ≤ 160	800 mg	8	0.01%	£0.42	£0.38
Total weighted average cost				**£1,850.59**	**£1,665.54**

5.2.8.2 Health state unit costs and resource use

Health state costs were modelled as disease management costs. Disease management costs were estimated based on an exponential regression model, in which the BASFI score is the only covariate. The approach taken was the same as that used in the MTA report of TA383[9], and the equation was based on the resource use data from the Outcomes in Ankylosing Spondylitis International Study (OASIS).[66]

The disease management costs estimation was based on the following equation:

*Disease management cost in a state = £1,284.19 * exp (0.213 * BASFI score in that state)*

5.2.8.3 Adverse reaction unit costs and resource use

Two types of adverse event costs were events considered in the model: tuberculosis (TB) reactivation costs and costs for other serious infections. These costs were single event costs, and were incurred each time the adverse event occurred within the model (see Table 5.36).

In the derivation of the unit cost for tuberculosis infection, a similar approach was followed as in the MTA report for TA383.[9] The unit cost was calculated as the weighted average cost of relevant HRG codes for pulmonary, pleural or other tuberculosis events of varying severity from the NHS Reference Costs 2014-15.[63]

For the unit cost for "other serious infection" (i.e. serious infection other than tuberculosis), a similar approach was followed. The unit cost estimate was derived from the weighted average cost of relevant infection-related HRG codes, weighted by activity, from NHS reference costs 2014-15.[63]

Table 5.36: Unit costs of adverse events included in the analysis

Adverse event	Cost	Cross-reference
Tuberculosis infection	£2,570.71	See table 85 of CS
Other serious infection	£1,299.38	See table 86 of CS
CS = company submission		

In the CS[1], during the selection of infection-relevant 2014-2015 HRG codes, the 2012-2013 HRG codes[67] used in the MTA report for TA 383[9] were taken into account. If a HRG code used in the MTA report was not anymore in the NHS reference costs 2014-2015[63], a relevant replacement for this HRG code was found, if possible.

ERG comment: The approach to include all relevant costs in the analysis is the same as the approach used in the York report for TA 383[9]. The estimation of drug acquisition and administration costs is clear and accurate (i.e., after the correction of the number of doses of certolizumab included in the cost calculation), as is the estimation of the adverse event costs.

Less clear is how accurate the estimation of health state costs is. In line with TA 383[9], the regression equation based on the OASIS study was used.[66] This study was a two-year prospective study of 208 AS patients from four centres in France, Belgium and the Netherlands. Patients were included between September 1996 and March 1997 and were followed up for two years. Hence, the outcomes of this study are quite old, the question may be raised how relevant they are for current UK clinical practice.

A recent UK study included 570 people with a diagnosis of AS confirmed by a rheumatologist, from across Wales. Participants were invited to complete questionnaires between mid-2009 and mid-2010, and gave consent for their data to be linked to routine primary and secondary care clinical datasets.[68] This study showed that the average NHS costs per year for an AS patient was £3,230.

However, from the current health economic model, the results indicate that the average costs per year amount to about £5,000. This higher estimate could be explained by the use of an exponential cost equation; with that equation we find costs that vary between £1,300 per year for patients with a BASFI score of 0 to £11,000 for a score of 10. It is unclear if this upper value has any face validity.

In their response to the clarification letter (Table 69 in response to clarification request[6]), the company provided a one-way sensitivity analysis on the two parameters of the cost equation. The results showed that the total costs for each treatment are strongly influenced by any changes in the parameters of the equation, but that the incremental costs of secukinumab, and hence the cost-effectiveness, are barely affected. Thus, the ERG did not explore any additional scenarios for these costs.

5.2.9 Base case analysis

5.2.9.1 Summary of base-case de novo analysis inputs

Summary of the inputs of the model are given in Table 5.37 below. Note that in the original submission[1], the provided model contained errors and after ERG had identified these errors, a new model and its results were provided by the company in the response letter to clarification.[6] For the sake of avoiding unnecessary complexity, only the inputs from the corrected model are presented here.

Table 5.37: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
Model settings			
Time horizon	Lifetime (58 years)	NA – not varied in PSA	Section 5.2.5
Discount rate (costs and outcomes)	3.5%	NA – not varied in PSA	
Mean age at baseline (years)	42.37	NA – not varied in PSA	Section 5.2.6.1
Percentage male	69.5%	NA – not varied in PSA	
Mean weight at baseline (kg)	78.20	NA – not varied in PSA	
Clinical inputs			
BASDAI 50 response at 3 months (normally distributed)			Section 5.2.6.2
Secukinumab 150 mg	Biologic naïve population: [redacted] Biologic experienced population: 19.7%	Log odds SE: [redacted] Log odds SE: 0.322	
Certolizumab pegol	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Etanercept	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Adalimumab	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Infliximab	Biologic naïve population: [redacted] Biologic experienced population: NA	Log odds SE: [redacted]	
Golimumab	Biologic naïve population: [redacted] Biologic experienced population: NA;	Log odds SE: [redacted]	
Conventional care	Biologic experienced population: 3.2%;	Log odds SE: 0.719	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
Short-term changes in BASDAI and BASFI			
Baseline BASDAI			
Baseline at induction period	Biologic naïve: 6.51 Biologic experienced: 6.52	SE: 0.060	Section 5.2.6.3
Responders	Biologic naïve: 6.42 (biologics) Biologic experienced: 6.59 (SEC150); 6.24 (CC)	SE: 0.060 0.060; 0.060	
Non-responders	Biologic naïve: 6.39 (biologics) Biologic experienced: 6.48 (SEC150); 6.61 (CC)	SE: 0.060 0.060; 0.060	
Baseline BASFI			
Baseline at induction period	Biologic naïve: 5.90 Biologic experienced: 5.89	SE: 0.087	Section 5.2.6.3
Responders	Biologic naïve: 5.44 (biologics) Biologic experienced: 5.39 (SEC150); 5.49 (CC)	SE: 0.087 0.087; 0.087	
Non-responders	Biologic naïve: 6.07 (biologics) Biologic experienced: 6.04 (SEC150); 5.85 (CC)	SE: 0.087 0.087; 0.087	
Change in BASDAI at 3 months (normally distributed)			
BASDAI 50 responders	Data presented for biologic naive population/biologic experienced population • SEC150: -4.65/ -4.98 • CZP: -5.63/NA • ETN: -4.49/NA • ADA: -4.61/NA • INF: -8.09/NA • GOL: -5.35/NA • CC: NA/-3.81	• SEC150: 0.239/ 0.498 • CZP: 0.412/NA • ETN: 0.454/NA • ADA: 0.176/NA • INF: 0.609/NA • GOL: 0.409/NA • CC: NA/0.669	Section 5.2.6.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
BASDAI 50 non-responders	Data presented for biologic naive population/biologic experienced population • SEC150: -1.09/-0.94 • CZP: -1.29/NA • ETN: -1.03/NA • ADA: -0.81/NA • INF: -1.85/NA • GOL: -1.38/NA • CC: NA/-0.36	• SEC150: 0.239/0.227 • CZP: 0.412/NA • ETN: 0.454/NA • ADA: 0.176/NA • INF: 0.609/NA • GOL: 0.409/NA • CC: NA/ 0.2628	Section 5.2.6.4
Change in BASFI at 3 months (normally distributed)			
BASDAI 50 responders	Data presented for biologic naive population/biologic experienced population • SEC150: -3.59/ -3.79 • CZP: -3.96/NA • ETN: -3.53/NA • ADA: -3.22/NA • INF: -5.16/NA • GOL: -4.18/NA • CC: NA/-2.73	• SEC150: 0.219/ 0.756 • CZP: 0.369/NA • ETN: 0.408/NA • ADA: 0.165/NA • INF: 0.544/NA • GOL: 0.361/NA • CC: NA/0.765	Section 5.2.6.4
BASDAI 50 non-responders	Data presented for biologic naive population/biologic experienced population • SEC150: -1.12/ -0.73 • CZP: -0.98/NA • ETN: -0.87/NA • ADA: -0.79/NA • INF: -1.27/NA	• SEC150: 0.219/0.231 • CZP: 0.369/NA • ETN: 0.408/NA • ADA: 0.165/NA	Section 5.2.6.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
	• GOL: -0.73/NA • CC: NA/0.06	• INF: 0.544/NA • GOL: 0.361/NA • CC: NA/0.237	
Long-term changes in BASFI			
Annual rate of mSASSS change	1.440	SE: 0.133 (Normal)	Section 5.2.6.5
BASFI change with 1 unit change in mSASSS	0.057	SE: 0.005 (Normal)	
Biologic treatment effect on progression	0.420	SE: 0.122 (Normal)	
Time to treatment effect (years)	0 (at treatment initiation)	NA	
Annual withdrawal rates			
Year 1/ Year 2+	• SEC150: 15.2%/ 6.0% • CZP: 12.6%/ 11.0% • ETN: 25.1%/ 25.1% • ADA: 13.0%/ 9.3% • INF: 2.1%/ 15.7% • GOL: 13.7%/ 6.6%	0.030/0.012 0.025/0.022 0.050/0.050 0.026/0.019 0.004/0.031 0.027/0.013	Section 5.2.6.7
Adverse event rates			
Infection	• SEC150: 0.16% • CZP: 0.67% • ETN: 0.00% • ADA: 0.35% • INF: 0.52% • GOL: 0.32%	• SE: 0.000 • SE: 0.001 • SE: 0.000 • SE: 0.001 • SE: 0.001 • SE: 0.001	Section 5.2.6.9

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
	• CC: 0.0%	• SE: 0.000 (Beta for all therapies)	
Distribution of infection (tuberculosis vs. other serious infection)	5% tuberculosis 95% other serious infection	0.008 (Beta distribution)	
Mortality inputs			
Relative risk of mortality for AS patient			
Male	1.63	SE: 0.326 (Log-normal)	Section 5.2.6.8
Female	1.38	SE: 0.276 (Log-normal)	
Utility inputs			
Parameters for utility weight regression model in the base case			
Intercept	0.9610	SE: 0.02503 (Beta)	Section 5.2.7
BASFI coefficient	-0.0330	SE: 0.00316 (Beta)	
BASDAI coefficient	-0.0442	SE: 0.00312 (Beta)	
Male coefficient	-0.0111	SE: 0.01335 (Beta)	
Age coefficient	-0.0005	SE: 0.00049 (Beta)	
Cost and resource use inputs			
Drug acquisition and administration			
Biologic acquisition costs (per dose)	• SEC: [redacted] (PAS price) • CZP: £357.50 (free first 3 months) • ETN: £178.75 (originator), £164 (biosimilar) • ADA: £352.14 • INF: £1,850.59 (Remicade®); £1,665.54 (biosimilar) • GOL: £762.97	N/A	Section 5.2.8

Variable	Value (reference to appropriate table or figure in submission)				Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
s.c. drug administration (first dose only)	£43.00				SE: 8.60 (Normal)	
i.v. drug administration (per administration)	£326.46				SE: 65.292 (Normal)	
Number of doses	**Treatment**	**Months 1 - 3**	**Months 4 - 6**	**Subsequent 3 month periods**		
	SEC150	7.00	3.00	3.00	NA – not varied in PSA	
	CZP	0	6.52	6.00	NA – not varied in PSA	
	ETN	13.00	13.00	13.04	NA – not varied in PSA	
	ADA	6.52	6.52	6.52	NA – not varied in PSA	
	INF	3.00	2.00	1.63	NA – not varied in PSA	
	GOL	3.00	3.00	3.00	NA – not varied in PSA	
Monitoring costs						
	Cost (per test)	**Frequency (first 3 months)**	**Frequency (subsequent 3 month periods)**			Section 5.2.8
GP visit	£44.00	0.00	0.00		SE: 8.800 (Gamma)	
Specialist visit	£137.23	2.00	0.50		SE: 27.446 (Gamma)	
Full blood count	£2.99	2.00	1.00		SE: 0.598 (Gamma)	
Erythrocyte sedimentation rate	£2.96	2.00	1.00		SE: 0.591 (Gamma)	
Liver function test	£0.75	2.00	1.00		SE: 0.151 (Gamma)	
Urea and electrolytes test	£1.39	2.00	1.00		SE: 0.277 (Gamma)	
Chest radiograph	£26.23	1.00	0.00		SE: 5.247 (Gamma)	
Tuberculosis Heaf test	£8.74	1.00	0.00		SE: 1.748 (Gamma)	

Variable	Value (reference to appropriate table or figure in submission)			Measurement of uncertainty and distribution: CI (distribution)	Reference to section in the ERG report
Antinuclear antibodies	£4.66	1.00	0.00	SE: 0.932 (Gamma)	
DNA double-strand test	£4.66	1.00	0.00	SE: 0.932 (Gamma)	
Health state cost					
Intercept	£1,284.19			SE: 0.165 (Log-normal)	Section 5.2.8
BASFI coefficient	0.213			SE: 0.038 (Normal)	
Adverse event costs					
Tuberculosis	£2,570.71			SE: 514.142 (Gamma)	Section 5.2.8
Other serious infection	£1,299.38			SE: 259.876 (Gamma)	

ADA = adalimumab; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CC = conventional care; CI = confidence interval; CZP = certolizumab pegol; DNA = deoxyribonucleic acid; ERG = Evidence Review Group; ETN = etanercept; GOL = golimumab; GP = general practitioner; i.v., intravenous; INF, infliximab; kg = kilogram; mg = milligram; mSASS = modified Stoke Ankylosing Spondylitis Spine Score; NA, not applicable; PAS = Patient Access Scheme; PSA = Probabilistic Sensitivity Analysis; s.c. = subcutaneous; SE = standard error; SEC150 = secukinumab 150 mg

5.2.9.2 Base case incremental cost effectiveness results

The summary cost effectiveness results of the base case analysis are presented in Table 5.38 for the biologic naïve population and Table 5.39 for the biologic experienced population. Note that in the original submission[1], the provided model contained errors and after ERG had identified them, a new model and results were provided in the response letter to clarification [6]. For the sake of avoiding unnecessary complexity, only the results from the corrected model are presented here.

Table 5.38: Summary base case results – biologic naïve population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus baseline	Fully incremental ICER (£/QALY)
Secukinumab	£113,216	9.805				
Etanercept biosimilar	£114,234	8.759	£1,018	-1.046	Secukinumab dominated	Secukinumab dominated
Etanercept	£115,249	8.759	£2,033	-1.046	Secukinumab dominated	Secukinumab dominated
Certolizumab pegol – with PAS	£122,418	9.447	£9,202	-0.359	Secukinumab dominated	Secukinumab dominated
Adalimumab	£128,516	9.446	£15,300	-0.359	Secukinumab dominated	Secukinumab dominated
Golimumab	£129,919	9.830	£16,703	0.025	£674,914	£674,914
Infliximab biosimilar	£135,865	9.590	£22,649	-0.216	Secukinumab dominated	Secukinumab dominated
Infliximab	£139,439	9.590	£26,223	-0.216	Secukinumab dominated	Secukinumab dominated
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year						

Table 5.39: Summary base case results – biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£107,417	8.161			
Secukinumab	£109,164	8.939	£1,747	0.778	£2,245
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

5.2.9.3 Clinical outcomes from the model

The proportion of BASDAI 50 responders at 12 weeks and time spent in a BASDAI 50 responder state can be deducted from the model outcomes and are given in Tables 5.40 and 5.41 for biologic naïve and biologic experienced patients.

Table 5.40: Clinical outcomes from the model – biologic naïve population

	SEC150	CZP	GOL	ETN	ADA	INF
BASDAI 50 responders at 12 weeks	0.494	0.414	0.446	0.340	0.459	0.414
Time spent in BASDAI 50 responder state (years)	5.774	3.329	5.057	1.206	4.136	3.017

ADA = adalimumab, BASDAI = Bath Ankylosing Spondylitis Disease Activity Score; CZP = certolizumab pegol; ETN = etanercept; GOL = golimumab; INF = infliximab; mg = milligram; SEC150 = secukinumab 150 mg

Table 5.41: Clinical outcomes from the model – biologic experienced population

	SEC	CC
BASDAI 50 responders at 12 weeks	0.197	0.032
Time spent in BASDAI 50 responder state (years)	2.300	0.008

BASDAI = Bath Ankylosing Spondylitis Disease Activity Score; CC = conventional care; mg = milligram; SEC150 =secukinumab 150 mg

Disaggregated discounted QALYs and life years (LYs) by health state are reported in Tables 5.42 and 5.43 for the biologic naïve and biologic experienced population, respectively. Note that in terms of LYs, model results in longer times of the induction treatment duration of three months (0.25 years). This mismatch can be explained by the fact that the model uses half cycle correction.

Table 5.42: Summary of QALYs and LYs by health state – biologic naïve population

QALYs				
	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	0.168	3.154	6.484	9.805
Certolizumab pegol	0.168	2.179	7.100	9.447
Golimumab	0.168	2.987	6.675	9.830
Etanercept (originator or biosimilar product*)	0.168	0.833	7.758	8.759
Adalimumab	0.168	2.408	6.870	9.446
Infliximab (originator or biosimilar product*)	0.168	2.277	7.145	9.590
LYs				
	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	0.374	4,054	15,378	19,805
Certolizumab pegol	0.374	2,601	16,830	19,805
Golimumab	0.374	1,070	18,361	19,805
Etanercept (originator or biosimilar product*)	0.374	3,139	16,293	19,805
Adalimumab	0.374	2,490	16,941	19,805
Infliximab (originator or biosimilar product*)	0.374	3,604	15,827	19,805

*The use of the originator or biosimilar does not affect the QALY gain as equal efficacy is assumed.
LY = life year, QALY = Quality-adjusted life year

Table 5.43: Summary of QALYs and LYs gain by health state – biologic experienced population

QALYs				
	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	0.168	1.281	7.489	8.939
Conventional care	0.168	0.000	8.179	8.161
LYs				
	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	0.374	1.615	17.816	19.805
Conventional care	0.374	0.008	19.423	19.805
LY = life year, QALY = Quality-adjusted life year				

5.2.9.4 Cost outcomes from the model

Disaggregated costs by health state for biologic naïve and biologic experienced patients are given in Tables 5.44 and 5.45, respectively.

Table 5.44: Summary of costs by health state – biologic naïve population

	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	[redacted]	[redacted]	[redacted]	£113.216
Certolizumab pegol	[redacted]	[redacted]	[redacted]	£122.418
Golimumab	[redacted]	[redacted]	[redacted]	£129.919
Etanercept	[redacted]	[redacted]	[redacted]	£115.249
Etanercept biosimilar	[redacted]	[redacted]	[redacted]	£114.234
Adalimumab	[redacted]	[redacted]	[redacted]	£128.516
Infliximab	[redacted]	[redacted]	[redacted]	£139.439
Infliximab biosimilar	[redacted]	[redacted]	[redacted]	£135.865

Table 5.45: Summary of costs by health state – biologic experienced population

	Induction treatment	**Maintenance treatment**	**Conventional care**	**Total**
Secukinumab	[redacted]	[redacted]	[redacted]	£109,164
Conventional care	[redacted]	[redacted]	[redacted]	£107,417

Also, the disaggregated costs based on cost types are presented in Tables 5.46 and 5.47 below.

Table 5.46: Summary of disaggregation of costs according to cost types-biologic naïve population

	Biologic drug costs	Background disease costs	Administration costs	Monitoring costs	Costs due to infection	Total
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£113,216
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£122,418
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,919
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,249
Etanercept biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£114,234
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£128,516
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£139,439
Infliximab biosimilar	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£135,865

Table 5.47: Summary of disaggregation of costs according to cost types-biologic experienced population

	Biologic drug costs	Background disease costs	Administration costs	Monitoring costs	Costs due to infection	Total
Secukinumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£109,164
Conventional care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,417

5.2.9.5 Exploratory analyses

In the exploratory analysis for the biologic naïve population, a second line biologic treatment was allowed. As mentioned in Section 5.2.3, it is assumed that a mixed treatment is administered in the second line, which is a basket of the biologics, consisting of all but one of the biologics, the one that was used in the first line. The summary results for the exploratory analysis of the biologic naïve population, including sequencing, are provided in Table 5.48 below.

Table 5.48: Summary results – exploratory sequencing analyses on biologic naïve population

Treatment pathway	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Secukinumab -> Mixed Tx	£121,209	9.987			
Etanercept -> Mixed Tx	£124,499	9.047	£3,684	-0.940	Secukinumab dominates
Etanercept biosimilar-> Mixed Tx	£125,886	9.047	£4,677	-0.940	Secukinumab dominates
Certolizumab pegol -> Mixed Tx	£131,066	9.655	£9,857	-0.332	Secukinumab dominates
Adalimumab -> Mixed Tx	£136,401	9.648	£15,192	-0.339	Secukinumab dominates
Golimumab -> Mixed Tx	£137,515	10.017	£16,305	0.030	£545,767
Infliximab biosimilar -> Mixed Tx	£142,884	9.791	£22,069	-0.196	Secukinumab dominates
Infliximab -> Mixed Tx	£146,628	9.791	£25,419	-0.196	Secukinumab dominates
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; Tx = Treatment					

In addition to the exploratory analysis on biologic naïve patients above, another exploratory analysis on the biologic experienced population had been conducted. In that analysis, other comparators than conventional care (biologics) were also included. The summary results for the exploratory analysis of the biologic experienced population, comparing secukinumab to the other biologic therapies, are provided in Table 5.49.

Table 5.49: Summary results – exploratory comparison with TNFα inhibitors in biologic experienced population

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	Fully incremental ICER (£/QALY)
Conventional care	£107,379	8.166			
Etanercept	£110,928	8.463	£3,549	0.297	Extendedly dominated by Secukinumab
Etanercept biosimilar	£111,571	8.463	£4,192	0.297	Extendedly dominated by Secukinumab
Secukinumab	£112,125	8.791	£4,746	0.625	£7,597
Certolizumab pegol – with PAS	£115,344	8.678	£7,965	0.512	Secukinumab dominates
Adalimumab	£119,876	8.680	£12,497	0.514	Secukinumab dominates
Golimumab	£121,114	8.796	£13,736	0.630	£1,614,375
Infliximab biosimilar	£125,438	8.778	£18,059	0.612	Golimumab dominates
Infliximab	£127,650	8.778	£20,271	0.612	Golimumab dominates

ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life years

ERG comment: The programming errors found in the previous sections did not modify the results of the base case analysis. However, some of the assumptions of the company had changed in the analysis conducted by the ERG. The new ERG base case and its results will be further discussed in Section 5.3.

In addition, the ERG finds that the reduction factors (from Tables 5.13 and 5.27) used in the exploratory analyses which involved biologics in the second line may be speculative for biologics other than secukinumab. This is due to the fact that the reduction factors were derived from MEASURE 1 and 2 trials, and in these trials, the biologic experienced population in MEASURE 1 and 2 probably had predominantly received anti TNF-alphas in the previous lines (since secukinumab was not approved yet). Since secukinumab is a different class than the other biologics, the efficacy reduction of secukinumab applied after an anti TNF-alpha can be different from the efficacy reduction of an anti TNF-alpha applied after another anti TNF-alpha or anti TNF-alpha applied after secukinumab. For instance in the Danish registry DANBIO (Glintborg et al. 2013[69]), the relative reduction of anti TNF-alpha efficacy in 2nd and 3rd lines were calculated to be around 30%.

5.2.10 Sensitivity analyses

5.2.10.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analyses (PSA) were conducted only for the base case scenarios. The summary results of the PSA, which includes the mean and standard deviation of the costs, mean and

standard deviation of the QALYs and resultant ICERs for the analysis of the biologic naïve population are presented in Table 5.50.

Table 5.50: **Summary probabilistic base case results – biologic naïve population**

Treatment	Total mean costs (SD)	Total mean QALYs (SD)	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Secukinumab	£116,011 (£29,355)	10.494 (0.959)			
Etanercept	£120,471 (£35,462)	9.500 (0.959)	£4,459	-0.994	Dominated
Etanercept biosimilar	£120,614 (£34,936)	9.456 (0.953)	£4,602	-1.038	Dominated
Certolizumab pegol – with PAS	£127,032 (£32,659)	10.124 (0.989)	£11,020	-0.370	Dominated
Adalimumab	£131,609 (£31,241)	10.152 (0.952)	£15,598	-0.342	Dominated
Golimumab	£134,921 (£31,933)	10.465 (1.008)	£18,910	-0.029	Dominated
Infliximab biosimilar*	£156,555 (£42,181)	9.945 (1.052)	£40,544	-0.549	Dominated
Infliximab	£160,533 (£47,027)	9.865 (1.070)	£44,522	-0.629	Dominated

*Please note results for infliximab and etanercept biosimilars require separate PSA runs in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.
ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life years; SD = standard deviation

The scatter plots for the comparison of secukinumab to each comparator and the cost effectiveness acceptability curves (CEACs) for the biologic naïve patient population are presented in Figures 5.4 to 5.11.

Figure 5.4: Scatter plot for secukinumab vs. etanercept – biologic naïve population

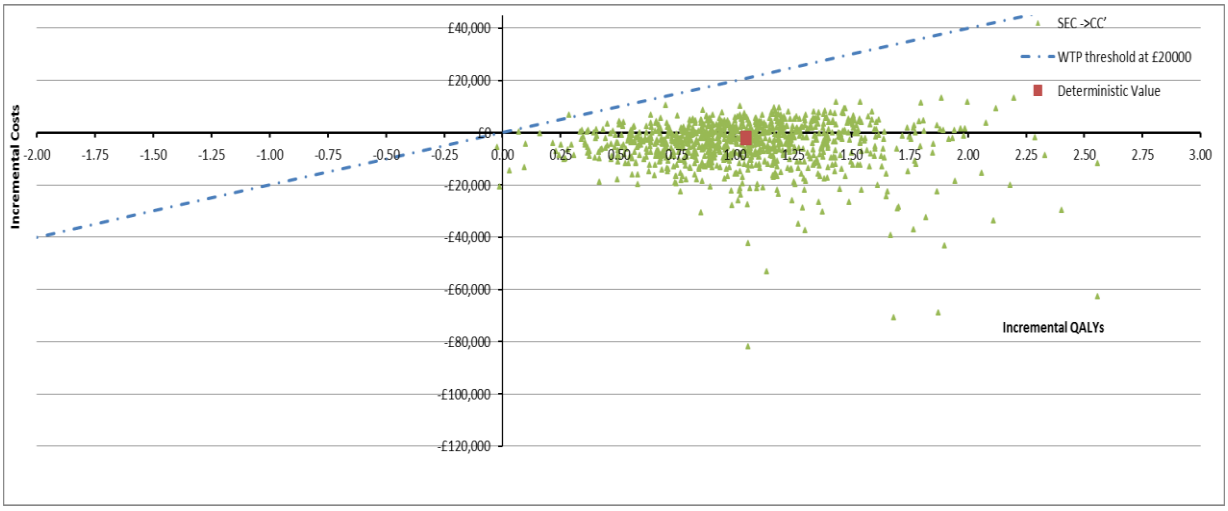


Figure 5.5: Scatter plot for secukinumab vs. etanercept biosimilar – biologic naïve population

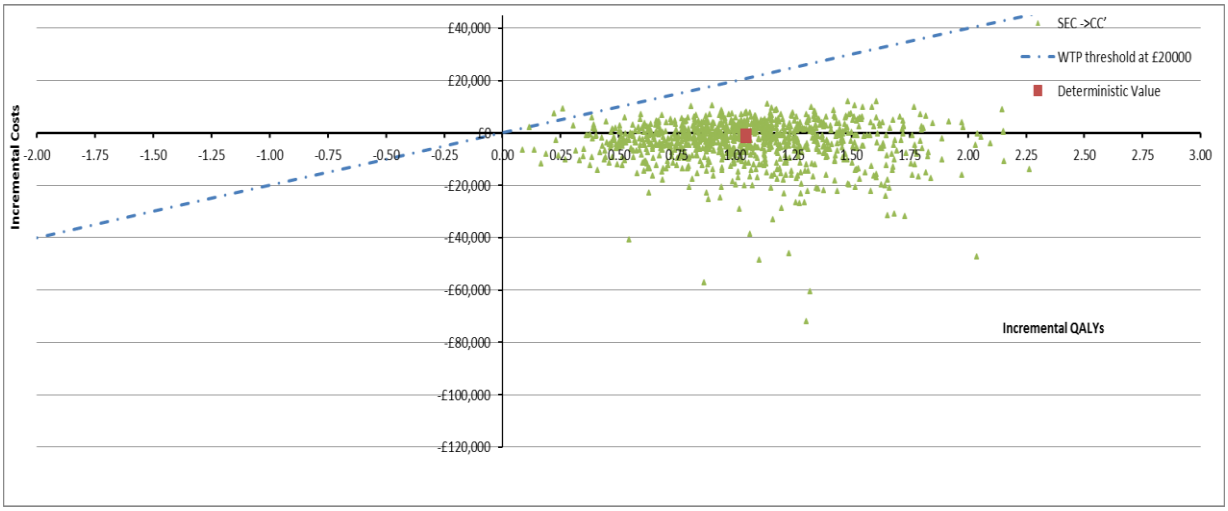


Figure 5.6: Scatter plot for secukinumab vs. certolizumab pegol – biologic naïve population

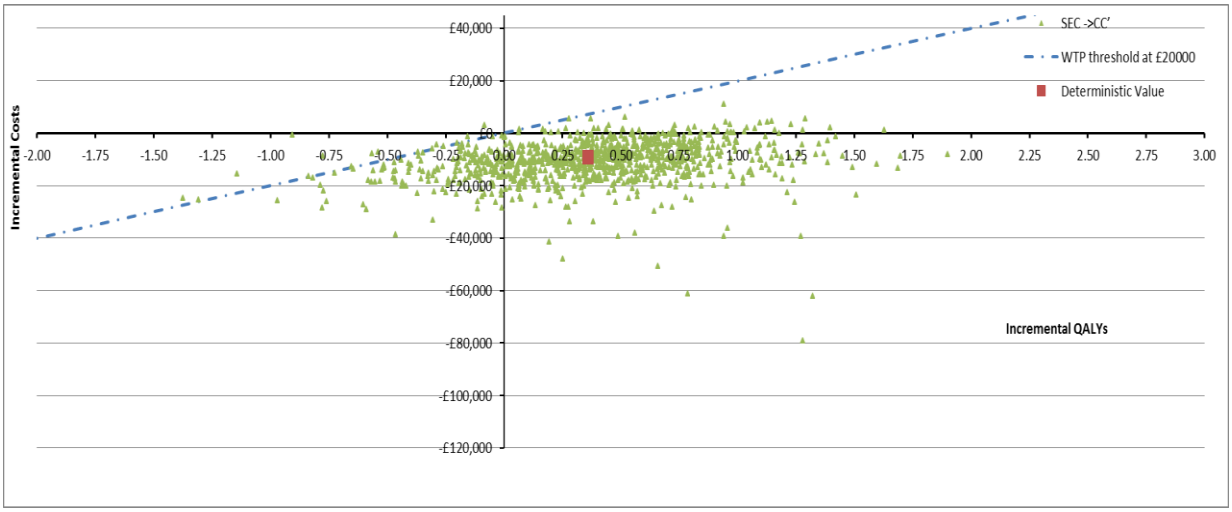


Figure 5.7: Scatter plot for secukinumab vs. adalimumab – biologic naïve population

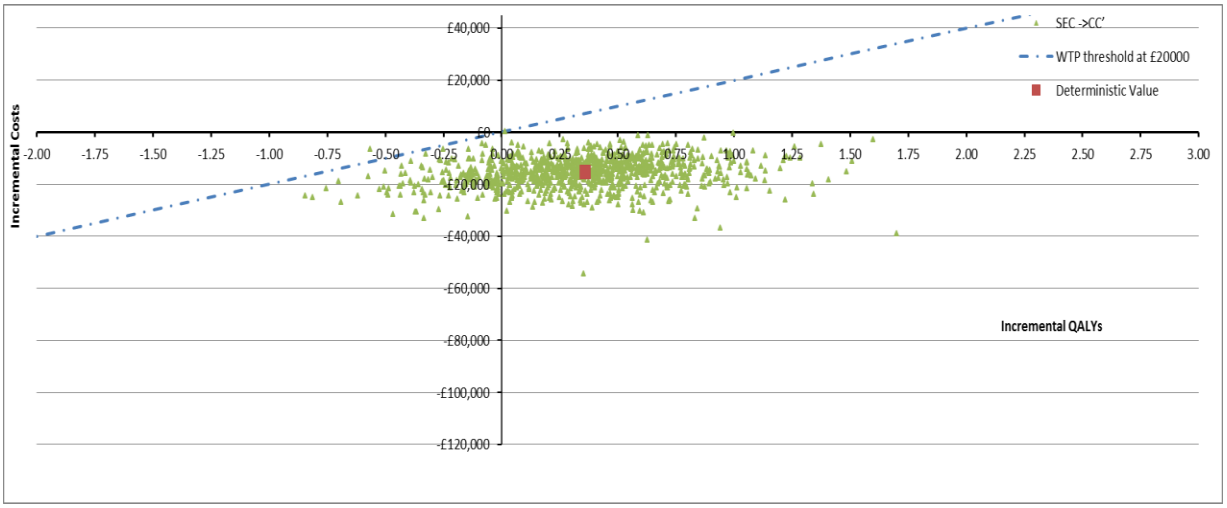


Figure 5.8: Scatter plot for secukinumab vs. golimumab – biologic naïve population

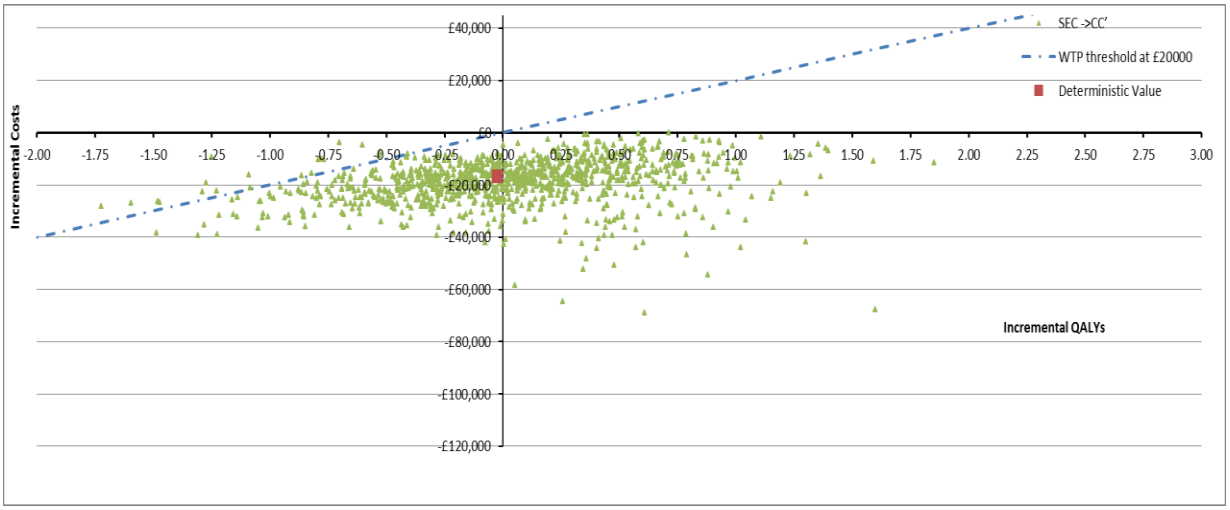


Figure 5.9: Scatter plot for secukinumab vs. infliximab – biologic naïve population

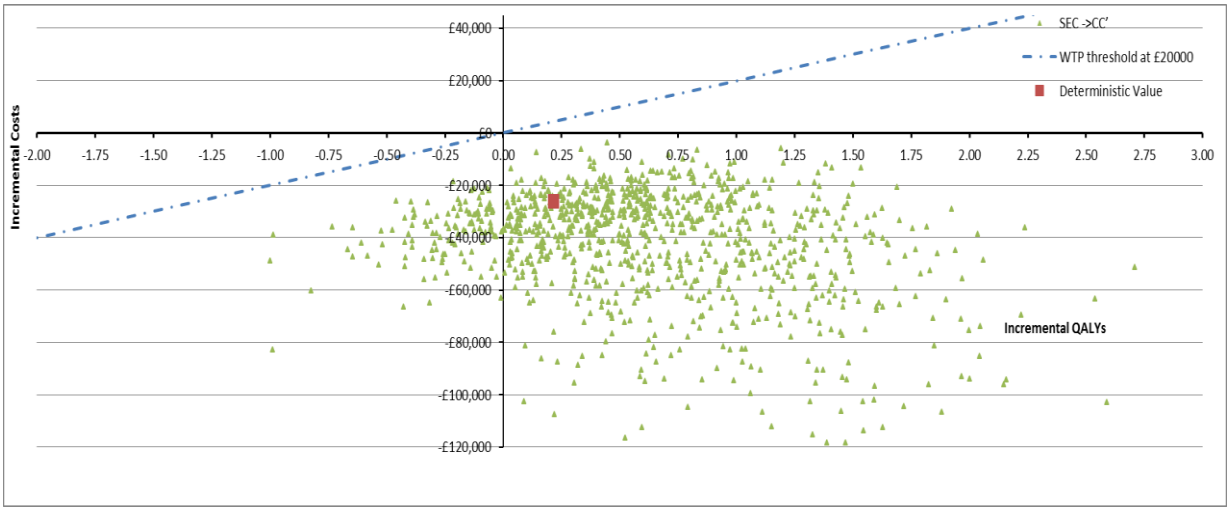
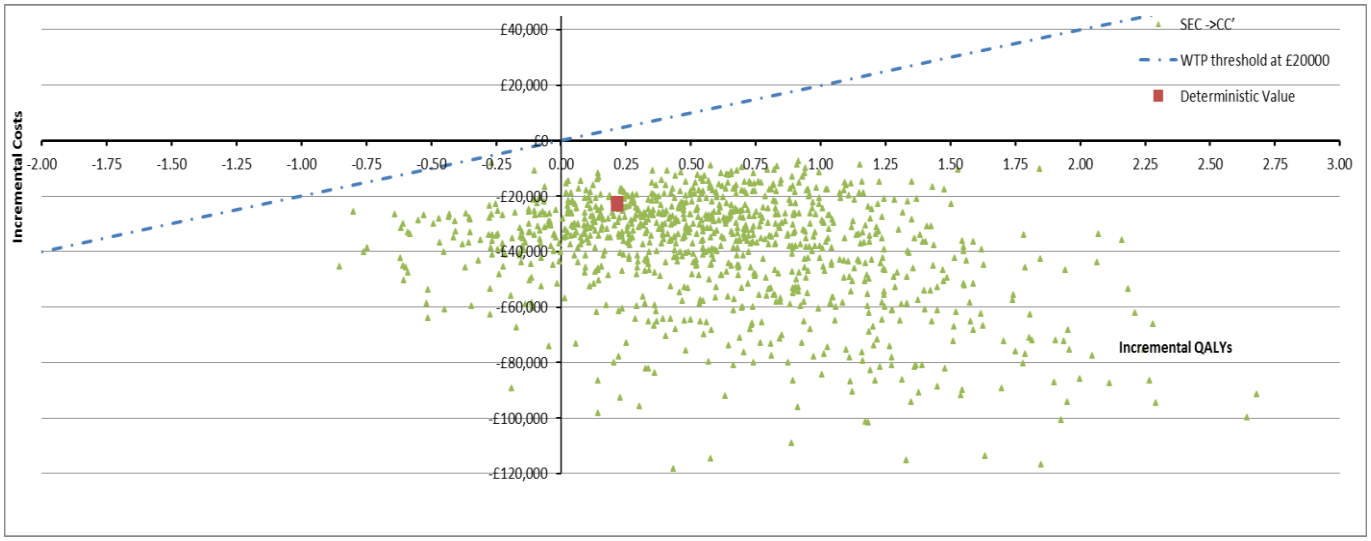
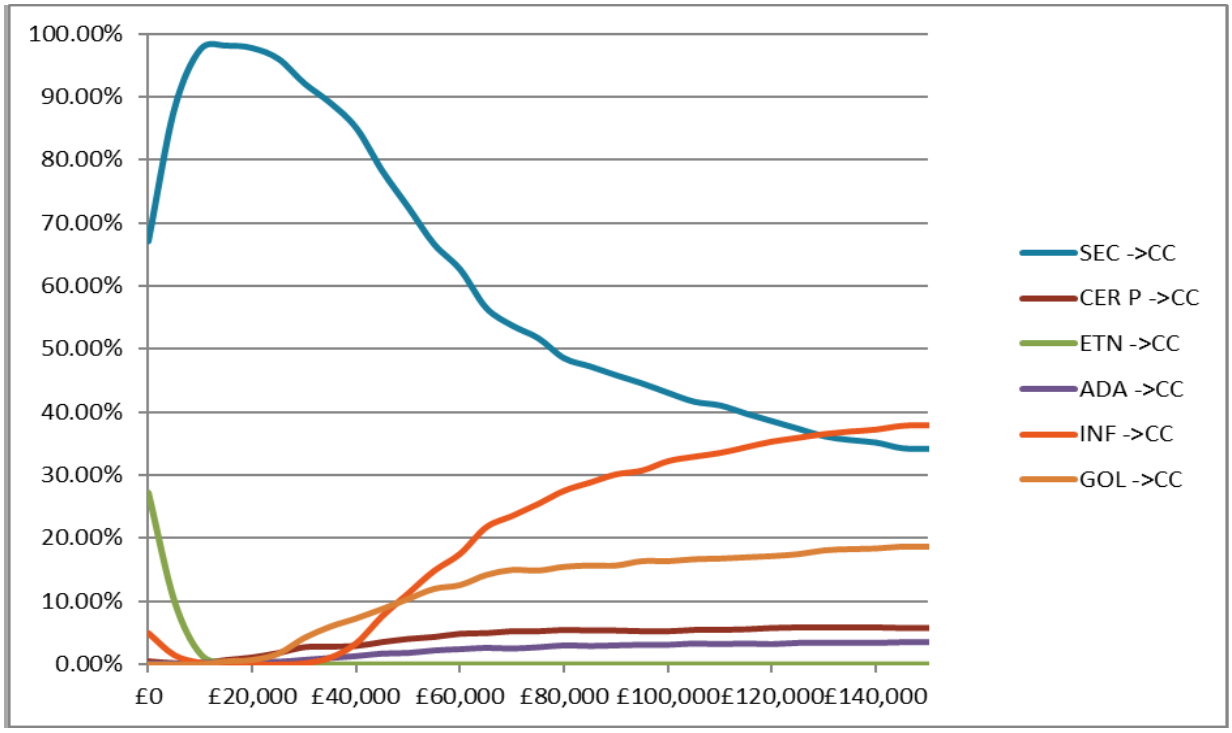


Figure 5.10: Scatter plot for secukinumab vs. infliximab biosimilar – biologic naïve population



*Please note results for infliximab biosimilar require a separate PSA run in the model but are nonetheless presented here alongside the original PSA run for simplification purposes.

Figure 5.11: CEAC for secukinumab versus comparators in the biologic naïve population



*The above chart combines results of two comparator CEAC results for secukinumab versus each comparator.

For the biologic experienced population, the ICERs derived from the probabilistic analysis are presented in Table 5.51. Then the scatter plot (Figure 5.12) and CEACs are presented (Figure 5.13).

Table 5.51: Summary probabilistic base case results – biologic experienced population

Treatment	Total mean costs (SD)	Total mean QALYs (SD)	Incremental mean costs versus baseline (£)	Incremental mean QALYs versus baseline	Mean probabilistic ICER (£/QALY) incremental
Conventional care	£111,974 (£36,811)	8.858 (0.972)			
Secukinumab	£113,433 (£32,639)	9.662 (1.016)	£1,458	£1	£1,815
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SD = standard deviation					

Figure 5.12: Scatter plot for secukinumab vs. conventional care – biologic experienced population

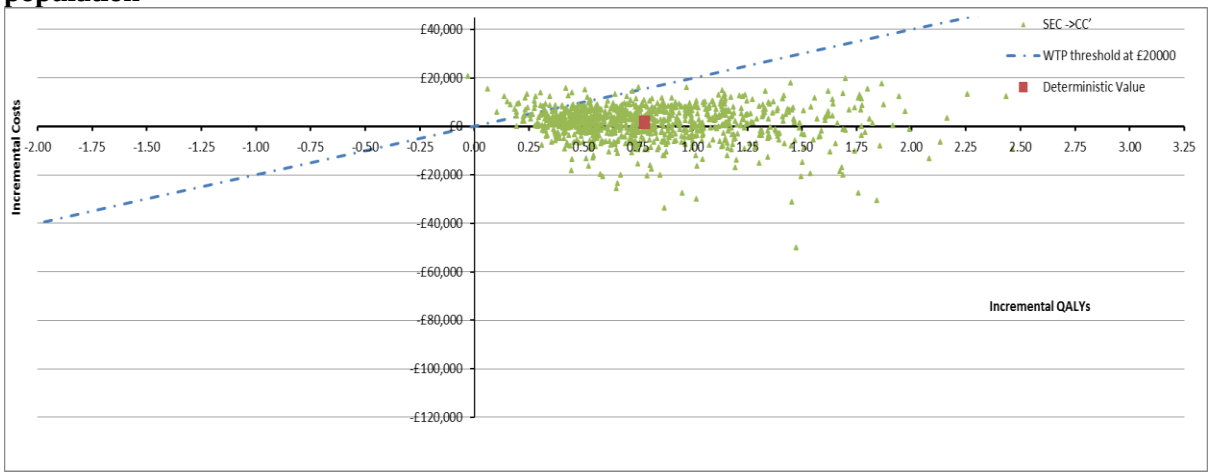


Figure 5.13: CEAC for secukinumab vs. conventional care – biologic experienced population

ERG comment: The ERG noticed that some of the model input parameters were not included in the PSA (e.g. relative risk of BASDAI 50 response for biologic experienced patients). The ERG asked for a justification from the company for the exclusion criteria that was applied to the input parameters for PSA. In their response to the clarification letter[6], it was admitted that inclusion of some of the parameters were was omitted in error and stated that these parameters were included in the PSA in the updated version of the model attached to the response to the clarification letter[6]. However, in the newer version of the excel model, the ERG still noticed that some input parameters were not included (like the response-conditional baseline BASDAI scores).

In the Excel model, the ERG realised that there was a big difference between the averages from probabilistic sensitivity analyses (PSA) and base case deterministic results, especially in QALYs. When the ERG asked for the reason underlying this difference, the company mentioned that this gap was due to a modelling error they had had in the original submission, and mentioned that in their new version which was submitted with the response to the clarification letter[6] this issue was handled. However, the ERG noticed that in the new model, the big gap between PSA averages and

deterministic base case still exists. Therefore, ERG went through the model and identified the following errors with remedy actions taken by the ERG below.

1. Beta distribution was used for the utility regression coefficients and it was not allowed for the regression coefficients change signs (coefficients are sampled from a normal distribution and they can switch signs).
2. It was possible to have a state utility value larger than one (a condition was activated in such a way that utility in a state can be maximum one).
3. In the model, if change from baseline for responders is larger than the baseline, negative scores for BASDAI and BASFI were not allowed. The average BASDAI/BASFI in a state under this condition, i.e. that the scores should be larger than 0, is not the same when this condition is applied to each sample and then the average of the scores are taken. The gap is obvious for infliximab especially, because in the base case the change from baseline is higher than the baseline (infliximab change from baseline effects are not varied)

These errors are corrected in the ERG model. There were other issues as well, such as the fact that the BASDAI, response and BASFI are sampled independently, even though there is an obvious correlation among them. Due to lack of data and time limitations, these issues were not corrected in the ERG model.

5.2.10.2 Deterministic sensitivity analysis

In the CS[1] and in the response to the clarification letter[6], tornado diagrams were presented to show the most impactful parameters that affected the net monetary benefit (with willingness to pay (WTP) £20,000 per QALY gained) for each comparison in the base case scenario of biologic naïve and experienced populations.

For the biologic naïve population, in each tornado diagram, following parameters were listed as the most impactful parameters:

- BASDAI 50 response of secukinumab at month 3
- Annual rate of mSASSS change for secukinumab
- Annual rate of mSASSS change for the comparator
- Regression coefficient for BASFI, which gives the background resource use cost estimate
- Baseline BASFI scores (response conditional) for secukinumab and its comparators
- Withdrawal of secukinumab after the first year
- Discount rate for the outcomes

For the biologic experienced population, tornado diagrams from the one way sensitivity analysis (OWSA) were similar and included all the parameters listed above.

5.2.10.3 Scenario analyses

Several scenario analyses were conducted to explore the structural uncertainties in the economic evaluation. The scenario analyses considered are listed as below:

1. Different time horizons
    a. 40 years
    b. 20 years
2. Alternative rebound assumption

In the base case it is assumed that after biologic discontinuation, BASFI deteriorates at an amount that is exactly equal to the response conditional BASFI improvement from baseline. In this scenario analysis, "*rebound to natural history*" the effects of a more pessimistic assumption were explored. After biologic discontinuation, it is assumed that the BASFI deteriorates to a level that a patient who had never received biologics would have had.

3. BASDAI and BASFI change from baseline not conditional on BASDAI 50 response.
   In the base case, it was assumed that the BASDAI and BASFI change from baseline were based on the BASDAI 50 response and responder/non-responder change from baseline ratios were applied to overall change from baseline estimates that were obtained from MTC. These response conditional changes from baseline estimates were then deducted from response conditional baseline values. In this scenario analysis, it is assumed that change from baseline estimates were the same for both responders and non-responders and this overall change from baseline estimate is deducted from overall baseline values. The overall baseline values that were used in this scenario are derived from MEASURE 1 and MEASURE 2 trials and are as below:

Table 5.52: Baseline BASDAI and BASFI scores pooled across MEASURE 1 and MEASURE 2 used in scenario 3

	Secukinumab 150 mg	Placebo
BASDAI	5.85	5.92
BASFI	6.47	6.61

BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; mg = milligram

4. Alternative source of biologic dropout rates
   In the base case dropout rates were derived independently for each biologic from corresponding clinical trials. In this scenario analysis, it is assumed that all biologics are associated with an annual withdrawal rate of 11%, which was applied to all biologics in the TA 383 York report[9]
5. Alternative definition of response
   Base case: response defined based on BASDAI 50 only, in this scenario, the following definition is used: BASDAI 50 or a fall of at least 2 units in BASDAI score
6. Alternative MTC scenario inputs (base case: MTC inputs using data from time points between weeks 12-16, using data from both MEASURE 1 and MEASURE 2)
   a. MTC inputs using data from time points between weeks 12-16, excluding MEASURE 1.
   b. MTC inputs using data only from time point weeks 12, using data from both MEASURE 2 and MEASURE 1
   c. MTC inputs using data only from time point weeks 12, excluding MEASURE 1.
7. Alternative utility models
   In the base case a utility model based on data from MEASURE 1 and MEASURE 2 data was used.
   a. Utility model from Wailoo et al. 2015[40]
   b. Utility model from Mcleod et al. 2007[32]
8. Alternative assumption around cost of intravenous infliximab administration

In the base case, an estimate (£326.46) derived from NHS reference costs 2014-2015 was used. In this scenario, an estimate that was derived from the costing template for adalimumab NICE submission in psoriasis (£1,453.48) was used.

9. Alternative assumption on the rate of radiographic progression (change in mSASSS) for secukinumab.
   In the base case, it was assumed that the rate of radiographic progression of secukinumab is same as the other biologics and equal to 0.42 per year. In this scenario, a lower rate with secukinumab is assumed compared to the biologic comparators, 0.15, based on findings from MEASURE 1 and MEASURE 2 trials.
10. In the base case, it was considered that the treatment effect on long-term BASFI changes manifests itself at treatment initiation. In this scenario, it was assumed that the treatment effect on long-term BASFI progression begins four years after treatment initiation.

The results of the scenario analyses for each biologic comparator versus secukinumab in the biologic naïve population are shown in Tables 5.53 to 5.54 below.

Table 5.53: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part a]

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case	£15,300	-0.359	SEC150 dominates	£9,202	-0.359	SEC150 dominates	£16,703	0.025	£674,914
Scenario 1a	£15,217	-0.354	SEC150 dominates	£9,092	-0.352	SEC150 dominates	£16,623	0.026	£632,894
Scenario 1b	£14,296	-0.260	SEC150 dominates	£8,441	-0.238	SEC150 dominates	£14,949	0.041	£361,558
Scenario 2	£16,025	-0.380	SEC150 dominates	£10,113	-0.386	SEC150 dominates	£16,923	0.018	£941,421
Scenario 3	£15,273	-0.291	SEC150 dominates	£9,216	-0.313	SEC150 dominates	£17,549	-0.063	SEC150 dominates
Scenario 4	£15,203	-0.120	SEC150 dominates	£10,671	-0.033	SEC150 dominates	£13,402	0.036	£374,910
Scenario 5	£23,265	-0.471	SEC150 dominates	£14,903	-0.474	SEC150 dominates	£25,783	0.029	£874,073
Scenario 6a	£17,762	-0.095	SEC150 dominates	£11,829	-0.133	SEC150 dominates	£19,009	0.318	£59,771
Scenario 6b	£17,318	0.086	£200,791	£10,361	0.062	£166,570	£16,205	0.358	£45,225
Scenario 6c	£11,280	-0.312	SEC150 dominates	£4,768	-0.367	SEC150 dominates	£9,880	-0.065	SEC150 dominates
Scenario 7a	£15,300	-0.369	SEC150 dominates	£9,202	-0.465	SEC150 dominates	£16,703	-0.065	SEC150 dominates
Scenario 7b	£15,300	-0.330	SEC150 dominates	£9,202	-0.331	SEC150 dominates	£16,703	0.022	£755,800
Scenario 8	£15,300	-0.359	SEC150 dominates	£9,202	-0.359	SEC150 dominates	£16,703	0.025	£674,914
Scenario 9	£16,581	-0.410	SEC150 dominates	£10,482	-0.409	SEC150 dominates	£17,984	-0.025	SEC150 dominates
Scenario 10	£15,344	-0.357	SEC150 dominates	£9,137	-0.353	SEC150 dominates	£16,606	0.028	£591,477

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SEC150 = secukinumab 150 mg

Table 5.54: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part b]

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
Base case	£2,033	-1.046	SEC150 dominates	£1,018	-1.046	SEC150 dominates	£26,223	-0.216	SEC150 dominates	£22,649	-0.216	SEC150 dominates
Scenario 1a	£1,828	-1.037	SEC150 dominates	£813	-1.037	SEC150 dominates	£26,104	-0.208	SEC150 dominates	£22,529	-0.208	SEC150 dominates
Scenario 1b	£1,171	-0.867	SEC150 dominates	£157	-0.867	SEC150 dominates	£25,658	-0.069	SEC150 dominates	£22,129	-0.069	SEC150 dominates
Scenario 2	£3,185	-1.086	SEC150 dominates	£2,171	-1.086	SEC150 dominates	£27,402	-0.250	SEC150 dominates	£23,827	-0.250	SEC150 dominates
Scenario 3	£1,227	-0.730	SEC150 dominates	£212	-0.730	SEC150 dominates	£22,643	-0.134	SEC150 dominates	£26,218	-0.134	SEC150 dominates
Scenario 4	£10,228	-0.367	SEC150 dominates	£8,344	-0.367	SEC150 dominates	£29,192	0.167	£174,456	£25,394	0.167	£151,759
Scenario 5	£1,792	-1.378	SEC150 dominates	£325	-1.378	SEC150 dominates	£37,686	-0.122	SEC150 dominates	£32,454	-0.122	SEC150 dominates
Scenario 6a	£4,029	-0.877	SEC150 dominates	£2,948	-0.877	SEC150 dominates	£30,252	-0.072	SEC150 dominates	£26,472	-0.072	SEC150 dominates
Scenario 6b	£3,265	-0.618	SEC150 dominates	£2,186	-0.618	SEC150 dominates	£27,711	0.231	£119,703	£24,046	0.231	£103,872
Scenario 6c	-£834	-1.056	£790*	-£1,796	-1.056	£1,701*	£20,730	-0.293	SEC150 dominates	£17,450	-0.293	SEC150 dominates
Scenario 7a	£2,033	-1.084	SEC150 dominates	£1,018	-1.084	SEC150 dominates	£26,223	-0.421	SEC150 dominates	£22,649	-0.421	SEC150 dominates
Scenario 7b	£2,033	-0.956	SEC150 dominates	£1,018	-0.956	SEC150 dominates	£22,649	-0.197	SEC150 dominates	£26,223	-0.197	SEC150 dominates
Scenario 8	£2,033	-1.046	SEC150 dominates	£1,018	-1.046	SEC150 dominates	£47,993	-0.216	SEC150 dominates	£44,419	-0.216	SEC150 dominates
Scenario 9	£3,313	-1.097	SEC150 dominates	£2,299	-1.097	SEC150 dominates	£27,504	-0.266	SEC150 dominates	£23,930	-0.266	SEC150 dominates
Scenario 10	£1,701	-1.028	SEC150 dominates	£686	-1.028	SEC150 dominates	£26,303	-0.214	SEC150 dominates	£22,729	-0.214	SEC150 dominates

* ICER estimate falls in the southwest quadrant
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SEC150 = secukinumab 150 mg

Table 5.55 presents the results of the scenario analyses in the biologic experienced population. In this case, results are expressed as ICERs for secukinumab versus conventional care. In the CS[1], it was mentioned that the scenarios 3, 6a-c and 8 were not relevant for the biologic experienced population since conventional care was the only comparator.

Table 5.55: Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population

	Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
Base case	£1,747	0.778	£2,245
Scenario 1a	£3,358	0.643	£5,223
Scenario 1b	£1,979	0.769	£2,574
Scenario 2	£8,556	0.601	£14,248
Scenario 3*	NA	NA	NA
Scenario 4	£1,363	0.654	£2,083
Scenario 5	£3,704	1.036	£3,574
Scenario 6a*	NA	NA	NA
Scenario 6b*	NA	NA	NA
Scenario 6c*	NA	NA	NA
Scenario 7a	£1,747	0.882	£1,979
Scenario 7b	£1,747	0.711	£2,455
Scenario 8*	NA	NA	NA
Scenario 9	£1,238	0.798	£1,551
Scenario 10	£2,173	0.762	£2,853

* These scenarios concern the biologic naïve population only.
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years

5.2.11 Model validation and face validity check

In the CS[1], it was mentioned that the face validity of the MTC results which informed the economic model had been checked by two clinical experts in rheumatology from UK. According to the CS[1], these experts deemed the results of the MTC to be in line with their clinical expectations.

For cross-validity, total costs predicted for TNF-alpha inhibitors and conventional care from the model submitted with the CS[1] were compared with those from the York model developed for TA383[9]. The model presented in the submission resulted in relatively similar costs compared to the York model for certolizumab pegol, adalimumab, golimumab and infliximab. However, for etanercept and conventional care, the total cost estimates between two models were different from each other (more than 10% relative difference).

As a final step, for external validation, it was discussed that, for patients on biologic treatment, the long term BASDAI and BASFI progression trends that the model generated were in agreement with the long term registry data from BSR Biologics Register in AS (BSRBR-AS), which acts as a source of UK-based real-world data on AS patients who have received biologic therapy.[70] The same

discussion was repeated for internal validation, this time comparing model generated trend with the follow-up data from MEASURE 1 and MEASURE 2.

ERG comment: For the cross-validity, the ERG requested the same type of model output comparison between submission model and the York MTA model for total QALYs. In the response to the clarification letter document, this requested comparison was provided in Table 71.[6] From this comparison, it was observed that the predicted total QALYs differ a great deal from each other between two models. Except for etanercept (7%), the relative difference between total QALYs predictions of York model and submission model was larger than 16% for all interventions. Note that the original submission model on which the cross validity checks for total costs were conducted included some errors, and a corrected model was provided in the response to the clarification letter document.[6] The ERG re-conducted the cross-validity exercise for costs with the updated submission model, and the results hardly changed.

For external validity, the ERG asked the company to provide figures that compare the average BASDAI and BASFI scores at different time points from the submission model with average BASDAI and BASFI scores at different time points from relevant clinical trials. In the response to the clarification letter [6], the company had provided such figures, comparing the average BASDAI and BASFI scores over time from relevant trials (ATLAS, Hu et al. 2012[71] and Huang et al. 2014[19], RAPID-ax SpA, Giardina et al. 2010[72], SPINE, ASSERT, GO-RAISE and MEASURE 1-2) - trials versus the average BASDAI and BASFI scores from cost effectiveness model.

The company mentioned that in general the model predicted lower BASDAI and BASFI scores than average scores observed in clinical trials. It was discussed that this underestimation was due to the model assumption which forced non-responders to discontinue biologic treatment, whereas within clinical trials non-responders continued biologic treatment.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

5.3.1 ERG base case analyses

Based on several remarks in Section 5.2 of this report the ERG defined a new base case analysis. This new ERG base case included the following adjustments:

Biologic naïve population:

- Errors confirmed and corrected by the company
- Programming/coding errors relating to the conversion factor estimates and other errors mentioned in Section 5.2 (these do not have an impact on the base case cost effectiveness analyses)
- Using MTC #3 for BASDAI 50 response rate and change from baseline estimates (MEASURE 1 and MEASURE 2, using week 12 data)
- Choice of MTC withdrawal rates from Corbett et al. 2014[9]

Biologic experienced population:

- Errors confirmed and corrected by the company
- Programming/coding errors relating to the conversion factor estimates (do not have an impact on the base case cost effectiveness analyses)
- Using week 12 response data instead of week 16 from MEASURE 1 and MEASURE 2. (14/61 for secukinumab and 5/62 for conventional care)

- Choice of MTC withdrawal rates from Corbett et al 2014[9]

The ERG decided to keep the other assumptions of the base case analyses from the updated model sent in the response to the clarification letter.[6] As explained in Section 5.2, even though the ERG has reservations especially regarding the model assumptions concerning treatment effectiveness, it was agreed to follow the base case and show the impact of the questionable assumptions in the scenario analyses.

The discounted results of the adjusted ERG base case are presented in Tables 5.56 and 5.57, for biologic naïve and biologic experienced populations, respectively. On top of these base case results, a table with the separate effect of all of these changes can be found in Section 6.

We observe that the ERG base case leads to substantially different results than the company base case, without materially changing the acceptability of secukinumab given the common threshold of £20,000 to £30,000 per QALY gained. Overall, secukinumab remains cost-saving, as was observed in the company base case. However, for some of the comparators, secukinumab no longer yields the higher QALYs, meaning that a trade-off needs to be made between cost-saving and loss of QALYs.

Table 5.56: Summary ERG base case results – biologic naïve population, discounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus secukinumab
Secukinumab	£111,662	9.185			
Etanercept biosimilar	£121,540	9.178	£9,879	-0.007	Secukinumab dominates
Certolizumab pegol – with PAS	£123,364	9.487	£11,702	0.302	£38,778
Etanercept	£123,555	9.178	£11,894	-0.007	Secukinumab dominates
Golimumab	£124,665	9.483	£13,003	0.298	£43,584
Adalimumab	£128,667	9.422	£17,006	0.237	£71,690
Infliximab biosimilar	£138,363	9.716	£26,702	0.531	£50,315
Infliximab	£142,258	9.716	£30,597	0.531	£57,654
ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme QALY = quality-adjusted life year					

Table 5.57: Summary ERG base case results – biologic experienced population, discounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£107,395	8.164			
Secukinumab	£109,016	8.893	£1,620	0.729	£2,223
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

In addition, the undiscounted results of the adjusted ERG base case are given in Tables 5.58 and 5.59, as well. For the biologic naïve population, we see that without discounting, the ICERs change only

slightly, which is to be expected in a disease where costs and QALYs are accumulated at the same rate over time. For the biologic experienced population, the impact of not discounting on costs is not large, but does cause the incremental costs to change into cost savings. As a result, without discounting secukinumab is the dominant treatment over conventional care, rather than the highly cost-effective treatment it was with discounting.

Table 5.58: Summary ERG base case results – biologic naïve population, undiscounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus secukinumab
Secukinumab	£211,834	15.533			
Etanercept biosimilar	£224,670	15.522	£12,835	-0.011	Secukinumab dominates
Etanercept	£227,197	15.522	£15,362	-0.011	Secukinumab dominates
Certolizumab pegol – with PAS	£227,219	15.925	£15,385	0.392	£39,203
Golimumab	£228,239	15.921	£16,404	0.388	£42,274
Adalimumab	£232,999	15.851	£21,164	0.318	£66,483
Infliximab biosimilar	£244,707	16.218	£32,872	0.686	£47,944
Infliximab	£249,536	16.218	£37,701	0.686	£54,987
ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme QALY = quality-adjusted life year					

Table 5.59: Summary ERG base case results – biologic experienced population, undiscounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£210,768	14.048			
Secukinumab	£208,641	15.113	-£2,127	1.065	Secukinumab dominates
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year					

5.3.2 Exploratory analyses with biologics as second line

In line with the CS[1], the ERG conducted exploratory analyses allowing for a second line biologic treatment after secukinumab for the biologic naïve population and including other biologics as possible comparators to secukinumab in the biologic experienced population. The results of these analyses are given in Tables 5.60 and 5.61. For the biologic naïve population, we see that including the option of a second line treatment with another biologic has little impact on the results; both costs and effects increase somewhat whilst all ICERs are slightly lower (approximately £1,000).

Table 5.60: Summary ERG exploratory case results – biologic naïve population; discounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus secukinumab
Secukinumab→mixed Tx	£121,281	9.420			
Etanercept biosimilar→ mixed Tx	£130,420	9.415	£9,139	-0.005	Secukinumab dominates
Certolizumab pegol – with PAS→ mixed Tx	£132,039	9.705	£10,758	0.286	£37,666
Etanercept→ mixed Tx	£132,757	9.415	£10,977	-0.005	Secukinumab dominates
Golimumab→ mixed Tx	£133,103	9.702	£11,822	0.283	£41,840
Adalimumab→ mixed Tx	£136,682	9.637	£15,401	0.218	£70,764
Infliximab biosimilar→ mixed Tx	£145,597	9.918	£24,316	0.498	£48,804
Infliximab→ mixed Tx	£149,667	9.918	£27,887	0.498	£55,971

ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year; Tx = Treatment

Table 5.61: Summary ERG exploratory case results – biologic experienced population; discounted

Treatment	Total costs (£)	Total QALYs	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus secukinumab
Secukinumab	£110,357	8.598			
Etanercept biosimilar	£115,624	8.595	£5,267	-0.003	Secukinumab dominates
Certolizumab pegol – with PAS	£115,950	8.691	£5,593	0.093	£60,029
Etanercept	£116,816	8.595	£6,459	-0.003	Secukinumab dominates
Golimumab	£117,745	8.688	£7,388	0.090	£81,710
Adalimumab	£119,950	8.673	£9,593	0.076	£126,880
Infliximab biosimilar	£126,982	8.818	£16,625	0.220	£75,553
Infliximab	£129,370	8.818	£19,013	0.220	£86,404

ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

5.3.3 Probabilistic sensitivity analyses

The summary results of the PSA for biologic naïve and biologic experienced patient population are given in Tables 5.62 and 5.63.

Table 5.62: Summary probabilistic base case results – biologic naïve population; discounted

Treatment	Total costs (SD)	Total QALYs (SD)	Incremental costs (£) versus baseline	Incremental QALYs versus baseline	ICER versus secukinumab
Secukinumab	£115,561 (£31,724)	9.199 (1.01)			
Etanercept biosimilar	£126,376 (£32,501)	9.198 (1.04)	£10,816	-0.001	Secukinumab dominates
Certolizumab pegol – with PAS	£128,232 (£32,289)	9.464 (1.03)	£12,672	0.295	£42,954
Etanercept*	£130,257 (£35,761)	9.199 (1.04)	£14,696	-0.001	Secukinumab dominates
Golimumab	£131,975 (£33,583)	9.439 (1.05)	£16,415	0.239	£68,550
Adalimumab	£132,215 (£31,277)	9.43 (1.00)	£16,655	0.231	£72,077
Infliximab biosimilar	£143,087 (£31,377)	9.677 (0.99)	£27,526	0.478	£57,608
Infliximab*	£149,037 (£34,115)	9.715 (0.95)	£33,476	0.516	£64,891

* Derived from separate PSA runs
ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year; SD = standard deviation

Table 5.63: Summary probabilistic base case results – biologic experienced population; discounted

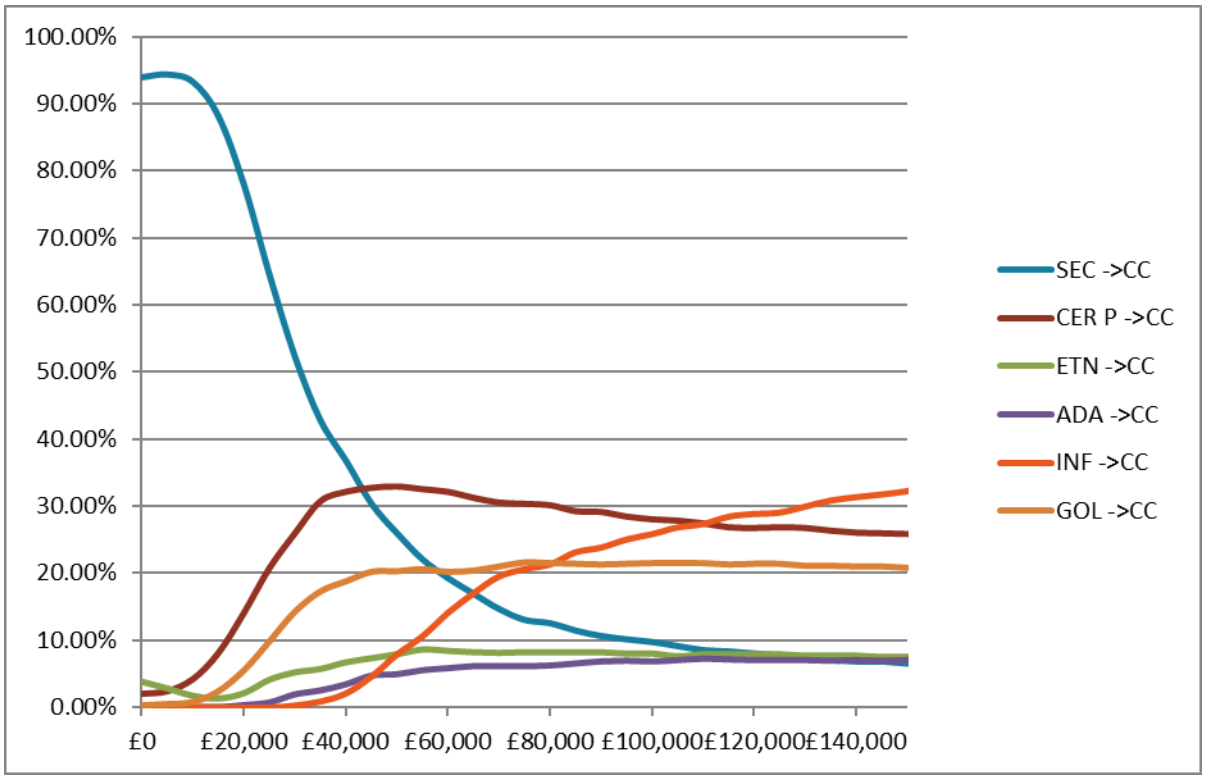
Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional care	£111,058 (£35,773)	8.847 (0.98)			
Secukinumab	£112,655 (£31,832)	9.546 (1)	£1,597	0.699	£2,286

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The cost-effectiveness acceptability curves (CEACs) related to the biologic naïve and experienced populations are given in Figures 5.14 and 5.15. Note that CEAC of the biologic naïve population only considered the biosimilar version of infliximab and etanercept.

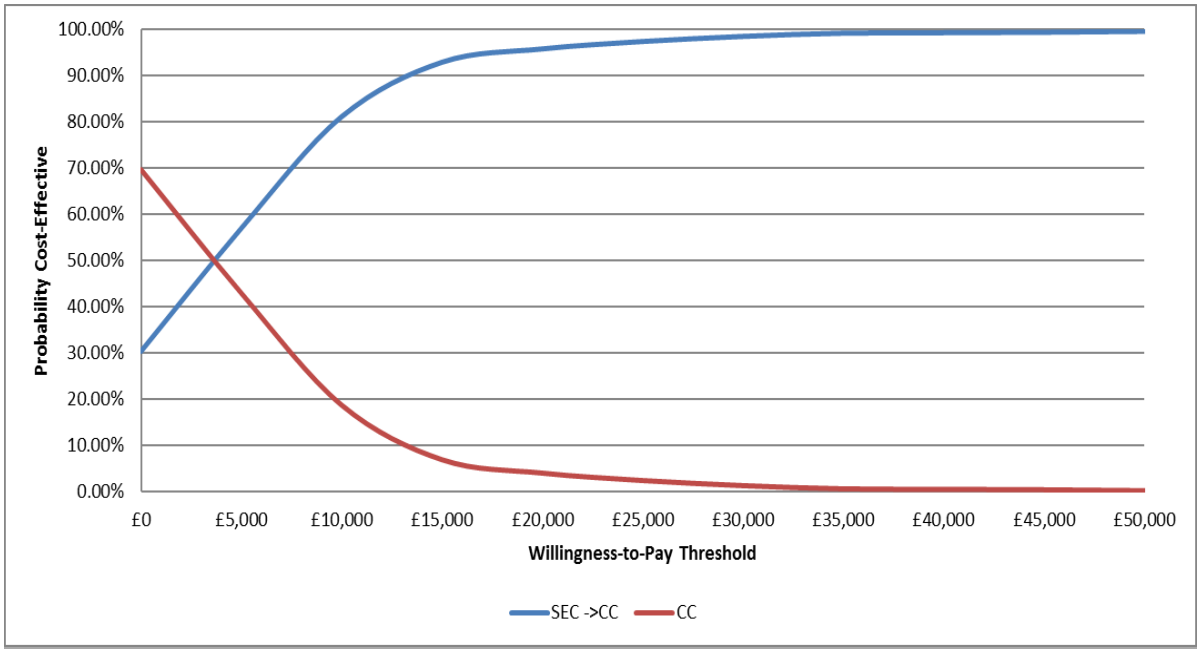
We observe that for the biologic naïve population, the probability that secukinumab is the most cost effective treatment is 81.3% for a threshold of £20,000 and 60.8% for a threshold of £30,000. For the biologic experienced population, the probability that secukinumab is acceptable given a threshold of £20,000 is 96% and given a threshold of £30,000 is 99%.

Figure 5.14: CEACs for biologic naïve population



ADA = Adalimumab 40 mg; CC = Conventional care; CER P = Certolizomab Pegol; ETN = Etanercept 50 mg; GOL = Golimumab 50 mg; INF = Infliximab 5 mg; SEC = secukinumab 150 mg

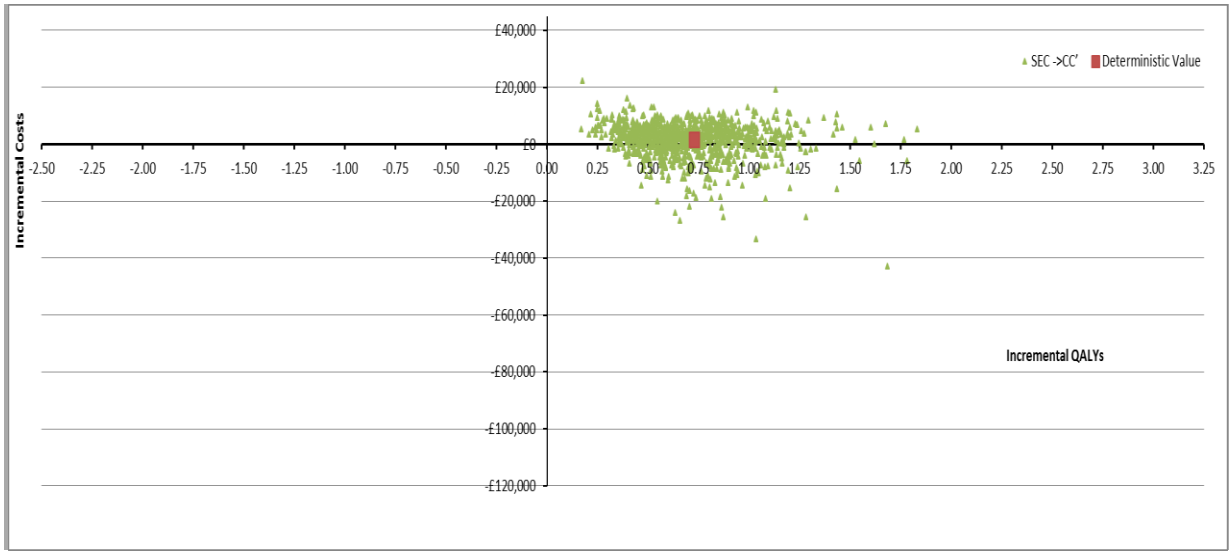
Figure 5.15: CEACs for biologic experienced population



CC = Conventional care; SEC = secukinumab 150 mg

The scatter plots for the biologic experienced population are given in Figure 5.16.

Figure 5.16: Scatter plot for biologic experienced population



5.3.4 Scenario analyses

Additional scenario analyses were conducted by the ERG to explore the structural uncertainties in the assumptions taken in the base case. Some of the scenarios are differing from those in the CS[1] and the response to the clarification letter[6]. Below is the list of scenarios explored.

1. Different time horizons (ERG base case life time)
    a. five years
    b. 20 years
2. Alternative rebound assumption
   In the ERG base case it is assumed that after biologic discontinuation, BASFI deteriorates at an amount that is exactly equal to the response conditional BASFI improvement from baseline. In this scenario analysis, "*rebound to natural history*" the effects of a more pessimistic assumption were explored. After biologic discontinuation, it is assumed that the BASFI deteriorates to a level that a patient who had never received biologics would have had.
3. Alternative definitions of response
   (ERG base case: response defined based on BASDAI 50 only)
    a. BASDAI 50 or a fall of at least two units in BASDAI score
    b. BASDAI 50 or (a fall of at least two units in BASDAI score and 2 cm improvement in VAS)
4. Alternative MTC scenario inputs
   (ERG base case: MTC inputs using data from time point weeks 12, using secukinumab data from both MEASURE 1 and MEASURE 2)
    a. MTC inputs using data only from time point week 12, excluding MEASURE 1.
    b. MTC inputs using data only from time points between week 12 and 16, using data from both MEASURE 2 and MEASURE 1.
5. Alternative utility models
   In the ERG base case a utility model based on data from MEASURE 1 and MEASURE 2 data was used.
    a. Utility model from Mcleod et al. 2007[32]
    b. Utility model from Wailoo et al. 2015[40]
6. Lower biosimilar prices

In this scenario, the ERG explored the impact of having lower biosimilar prices for etanercept and infliximab. In the ERG base case, list prices of these biosimilars were considered. The actual tender prices can be lower than these list prices. Therefore, in this scenario it is considered that the biosimilar prices are 25% lower than their list prices.

7. Same baseline BASDAI and BASFI scores for both responders and non-responders
   In the ERG base case, for the BASDAI and BASFI progression, the response-conditional baseline BASFI and BASDAI values from Table 5.16 were used. In this scenario, instead of using response-conditional BASDAI and BASFI scores, overall BASDAI and BASFI scores from Table 5.15 were used for both responders and non-responders.
8. Different assumptions on (responder/non-responder) change from baseline ratios
   In the ERG base case, different (responder/non-responder) change from baseline ratios for secukinumab, adalimumab and golimumab given in Tables 5.18 and 5.19 were used for BASDAI and BASFI. For all the others, the average BASDAI and BASFI ratios derived from the corresponding ratios of three (secukinumab, adalimumab and golimumab) interventions was assumed.
   a. the average BASDAI and BASFI ratios derived from the corresponding ratios of three (secukinumab, adalimumab and golimumab) interventions are assumed for all biologics
   b. The (responder/non-responder) ratios used in the York report for TA 383[9] were adopted. (-3.86/-1.64 = 2.354 for BASDAI and -3.08/-0.36=7 for BASFI, calculated from Table 82 from York report[9]). These ratios were derived from simulation that was based on the joint evidence synthesis modelling approach C.
9. Long term BASFI change effect
   In the base case, it was considered that the treatment effect on long-term BASFI changes manifests itself at treatment initiation. In this scenario, it was assumed that the treatment effects on long-term BASFI progression begins four years after treatment initiation.
10. Joint evidence synthesis for BASDAI 50, BASDAI and BASFI following York approach C
    In the response to the clarification letter document[6], the company provided the relevant treatment effectiveness estimates (i.e. BASDAI 50, BASDAI and BASFI change from baseline) from the joint evidence synthesis approach (approach C) from Corbett et al.[9]. Even though the applicability of these estimates was questionable (e.g. the MTC used mixed evidence from biologic naïve and biologic experienced population and it was not clear which time points of response assessment were used in each trial) the ERG conducted a scenario which uses the estimates from this joint evidence synthesis approach. In addition to the treatment effectiveness estimates provided in the response to the clarification letter document[6], the simulation-derived (responder/non-responder) change from baseline ratios from Corbett et al. 2014[9] mentioned in Scenario 8b were incorporated to the model.
11. No induction period for conventional care: In this scenario, it was assumed that there was no induction period for conventional care. This scenario concerns only the biologic experienced population. The handicaps of modelling an induction period for conventional care were discussed in the "ERG Comments" part of Section 5.2.3. Modifying the model in such a way that there is no induction period for conventional care was achieved by using the overall baseline BASFI and BASDAI values as in the scenario conducted in Section 5.3.3.7 and changing the response rate of conventional care to 0%
12. Alternative adverse events rate
    In this scenario, the average adverse event rate from all of the biologics calculated (0.3%). This average rate was assumed to hold for all TNF-alpha inhibitors, whereas for

secukinumab, twice of this average (0.6%) was assumed. Note that this scenario does not reflect any clinical expectation for the secukinumab safety profile, but rather represents the sensitivity of the incremental cost effectiveness analysis results to adverse event rates.

The results of the scenario analyses for each biologic comparator versus secukinumab in the biologic naïve population were shown in Tables 5.64 and 5.65 below.

The scenario analysis results show that etanercept (both original and biosimilar version) is associated with lower QALYs and higher costs versus secukinumab in all scenarios.

Infliximab (both original and biosimilar version) is associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for infliximab versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained.

Adalimumab, golimumab and certolizumab pegol are mostly associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for comparator versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained. For the scenarios which different treatment effectiveness inputs were used (e.g. from different MTCs), secukinumab dominates these treatments, i.e. secukinumab provides higher QALYs with lower costs.

Table 5.64: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part a]

	Adalimumab			Certolizomab Pegol			Golimumab		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
ERG Base case	£17,006	0.237	£71,690	£11,702	0.302	£38,778	£13,003	0.298	£43,584
Scenario 1a	£9,043	0.114	£79,335	£5,019	0.152	£32,988	£6,801	0.150	£45,224
Scenario 1b	£16,622	0.220	£75,396	£11,262	0.287	£39,292	£12,604	0.283	£44,489
Scenario 2	£17,009	0.240	£70,964	£11,704	0.303	£38,655	£13,005	0.299	£43,443
Scenario 3a	£26,681	0.314	£85,106	£19,627	0.395	£49,709	£20,413	0.389	£52,469
Scenario 3b	£22,847	0.283	£80,608	£16,488	0.358	£45,999	£17,472	0.355	£49,249
Scenario 4a	£11,783	-0.071	SEC150 dominates	£6,672	-0.035	SEC150 dominates	£8,013	-0.037	SEC150 dominates
Scenario 4b	£15,203	-0.120	SEC150 dominates	£10,671	-0.033	SEC150 dominates	£13,402	0.036	£374,910
Scenario 5a	£17,006	0.215	£79,252	£11,702	0.273	£42,924	£13,003	0.274	£47,537
Scenario 5b	£17,006	0.235	£72,423	£11,702	0.203	£57,649	£13,003	0.224	£57,993
Scenario 6	£17,006	0.237	£71,690	£11,702	0.302	£38,778	£13,003	0.298	£43,584
Scenario 7	£16,807	0.238	£70,551	£11,535	0.302	£38,174	£12,794	0.299	£42,824
Scenario 8a	£17,277	0.187	£92,548	£11,973	0.278	£42,993	£13,599	0.264	£51,416
Scenario 8b	£17,337	0.180	£96,057	£11,982	0.256	£46,845	£13,607	0.246	£55,277
Scenario 9	£17,274	0.228	£75,724	£11,786	0.298	£39,543	£13,075	0.295	£44,375
Scenario 10	£13,518	-0.012	SEC150 dominates	£11,776	-0.015	SEC150 dominates	£13,084	0.020	£663,864
Scenario 11	NA	NA	NA	NA	NA	NA	NA	NA	NA
Scenario 12	£16,869	0.237	£71,115	£11,471	0.302	£38,010	£12,878	0.298	£43,166

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years; SEC150 = Secukinumab 150 mg

Table 5.65: Incremental costs, incremental QALYs and ICERs for each comparator versus secukinumab in the biologic naïve population [Part b]

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER	Incr. Costs	Incr. QALYs	ICER
ERG base case	£11,894	-0.007	SEC150 dominates	£9,879	-0.007	SEC150 dominates	£30,597	0.531	£57,654	£26,702	0.531	£50,315
Scenario 1a	£6,037	-0.002	SEC150 dominates	£4,905	-0.002	SEC150 dominates	£18,000	0.270	£66,634	£15,717	0.270	£58,181
Scenario 1b	£11,355	-0.005	SEC150 dominates	£9,415	-0.005	SEC150 dominates	£29,664	0.506	£58,601	£25,904	0.506	£51,174
Scenario 2	£11,893	-0.007	SEC150 dominates	£9,878	-0.007	SEC150 dominates	£30,598	0.532	£57,548	£26,703	0.532	£50,223
Scenario 3a	£18,437	-0.009	SEC150 dominates	£15,421	-0.009	SEC150 dominates	£45,374	0.876	£51,798	£39,645	0.876	£45,258
Scenario 3b	£15,865	-0.008	SEC150 dominates	£13,243	-0.008	SEC150 dominates	£39,528	0.749	£52,786	£34,521	0.749	£46,100
Scenario 4a	£7,143	-0.344	SEC150 dominates	£5,369	-0.344	SEC150 dominates	£23,952	0.093	£257,216	£20,470	0.093	£219,827
Scenario 4b	£10,228	-0.367	SEC150 dominates	£8,344	-0.367	SEC150 dominates	£45,372	0.878	£174,456	£25,394	0.167	£151,759
Scenario 5a	£11,894	-0.006	SEC150 dominates	£9,879	-0.006	SEC150 dominates	£30,597	0.483	£63,304	£26,702	0.483	£55,245
Scenario 5b	£11,894	-0.018	SEC150 dominates	£9,879	-0.018	SEC150 dominates	£30,597	0.303	£100,980	£26,702	0.303	£88,163
Scenario 6	£11,894	-0.007	SEC150 dominates	£4,278	-0.007	SEC150 dominates	£30,597	0.531	£57,654	£17,938	0.531	£33,800
Scenario 7	£11,912	-0.007	SEC150 dominates	£9,897	-0.007	SEC150 dominates	£30,312	0.542	£55,913	£26,417	0.542	£48,729
Scenario 8a	£12,165	-0.030	SEC150 dominates	£10,150	-0.030	SEC150 dominates	£30,868	0.507	£60,834	£26,973	0.507	£53,158
Scenario 8b	£12,162	-0.033	SEC150 dominates	£10,147	-0.033	SEC150 dominates	£37,760	0.395	£95,687	£33,865	0.395	£85,817
Scenario 9	£11,845	-0.005	SEC150 dominates	£9,831	-0.005	SEC150 dominates	£30,646	0.527	£58,153	£26,751	0.527	£50,762

	Etanercept			Etanercept biosimilar			Infliximab			Infliximab biosimilar		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Scenario 10	£13,969	-0.064	SEC150 dominates	£11,762	-0.064	SEC150 dominates	£30,551	0.061	£500,177	£26,822	0.061	£439,125
Scenario 11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Scenario 12	£11,853	-0.007	SEC150 dominates	£9,838	-0.007	SEC150 dominates	£30,412	0.531	£57,306	£26,517	0.531	£49,967

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years; SEC150 = Secukinumab 150 mg

Table 5.66 presents the results of the scenario analyses in the biologic experienced population. In this case, results are expressed as ICERs for secukinumab versus conventional care. The scenarios 6, 8a-8b and 10 were not relevant for the biologic experienced population since conventional care was the only comparator.

Table 5.66: Incremental costs, incremental QALYs and ICERs for secukinumab versus conventional care in the biologic experienced population

	Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
ERG Base case	£1,620	0.729	£2,223
Scenario 1a	£3,917	0.298	£13,124
Scenario 1b	£3,323	0.635	£5,233
Scenario 2	£8,800	0.542	£16,240
Scenario 3a	£3,411	0.965	£3,536
Scenario 3b	£2,717	0.912	£2,981
Scenario 4a	-£2,323	1.042	SEC150 dominates
Scenario 4b	£1,747	0.778	£2,245
Scenario 5a	£1,620	0.667	£2,431
Scenario 5b	£1,620	0.831	£1,950
Scenario 6	NA	NA	NA
Scenario 7	£3,394	0.561	£6,054
Scenario 8a	NA	NA	NA
Scenario 8b	NA	NA	NA
Scenario 9	£2,196	0.709	£3,097
Scenario 10	NA	NA	NA
Scenario 11	£3,371	0.566	£5,959
Scenario 12	£1,696	0.729	£2,327

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years

In almost all of the scenarios for biologic experienced population, secukinumab is associated with higher QALYs and higher costs, with ICER values below £20,000 per QALY.

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope.

The ERG assessment indicated that the revised model (provided by the response to the clarification letter[6]) was generally well presented and reported. The major errors identified by the ERG in the original CS model[1] had already been corrected in the revised model, although the ERG still identified additional programming errors in the revised model, as well. These errors were minor and they mostly concerned the outcomes of the exploratory/scenario and probabilistic sensitivity analyses. They did not impact the estimates of the deterministic ICERs for the base case scenarios.

For the treatment naïve population, all anti TNF-alphas are considered as secukinumab's comparators, including available biosimilars of infliximab and etanercept. However, for the biologic experienced population, conventional care was the only comparator. The ERG finds other biologics should also have been considered as comparators to secukinumab in this population. An NHS and PSS perspective is adopted with a lifetime time horizon, in line with the final scope. Discount rates used for costs and QALYs were 3.5%

The cost effectiveness model was a decision tree representing the induction period embedded to a Markov model representing the post induction period. If a patient responds to a treatment s/he enters maintenance therapy, otherwise s/he receives conventional care. While the structure was similar for the biologic naïve and experienced populations, the input parameters used for these analyses were different. The model did not allow for comparing biologic treatment sequences, which is a limitation considering the increasing number of biologics available for this indication.

Treatment effectiveness was modelled via short/long term changes in BASDAI and BASFI scores and treatment response at the end of the induction period. Response conditional BASDAI and BASFI short term changes were applied on the response conditional baseline scores. It was assumed that after initial improvement, the BASDAI score remains constant whereas the BASFI score increases slowly. For patients on biologics, it is assumed that the annual rate of BASFI progression was smaller than for patients on conventional care. After biologic discontinuation, it is assumed that patients would lose all the initial BASFI improvements. The BASDAI and BASFI score per cycle are instrumental in calculating that cycle's state costs and QALY estimates.

Regression models (utility mapping model derived from MEASURE 1 and MEASURE 2 trials as the base case) and other published models in the literature were used to translate BASFI/ BASDAI to cost/QALY estimates. Unfortunately, the details of the utility mapping model and the model selection procedure were not provided by the company despite the request from the ERG.

Data from the MEASURE 1 and 2 trials were used for secukinumab effectiveness. In MEASURE 1, secukinumab was administered intravenously whereas it was licensed to be administered subcutaneously. Therefore, the company provided analyses where they used data only from the MEASURE 2 trial for secukinumab effectiveness. Comparative effectiveness estimates of secukinumab with other biologics in terms of BASDAI 50 and BASDAI/BASFI change from baseline were obtained via separate MTCs. In these MTCs, two possible options were available for selecting response assessment time points (strictly week 12 or between week 12-16). In addition to these, some conversion factors were derived from MEASURE 1 and 2 trials to transform response probability and change from baseline estimates for different response definitions.

In the modelling of the BASFI and BASDAI progression, response conditional baseline scores were used. In many of the baseline scores, it was observed that the responders had lower (better) baseline scores than non-responders. This might imply that patients at a better condition (with lower BASDAI/BASFI scores) would benefit more from the treatment than the patients at a worse condition (with higher BASDAI/BASFI scores). This implication was criticised by the appraisal committee of the NICE TA383.[7]

In addition, the response conditional baseline values and the conversion factors used in transforming effectiveness parameters (e.g. in between different response definitions) were all calculated based on

MEASURE 1 and 2 trial data collected from a fixed time point (week 12 or week 16). Hence, these values remain unchanged when MTC approaches with different time point assumptions were selected.

The ERG considers the independent evidence synthesis approach for BASDAI, BASFI baseline and change from baseline estimates and BASDAI 50 not plausible. These parameters are highly correlated which is overlooked in the independent synthesis approach followed by the company. Due to this independent approach, the model sometimes generates unreasonable estimates, e.g. change from baseline estimates that are higher than the baseline scores, a response conditional BASDAI change from baseline which is less than 50% of the baseline BASDAI even though response was defined as "BASDAI 50" etc.

To overcome this issue, the ERG requested results from the joint modelling approach based on the York model.[9] However the results provided in the response to the clarification letter[6] used data from a mixed population (biologic naïve and experienced) and the time point(s) when the response was measured were not reported. Therefore, the ERG could not base the base case analysis on the provided results from the joint evidence synthesis results. In spite of the limitations of the joint evidence synthesis results, the ERG conducted a scenario analysis, in which the treatment effectiveness of the biologics and secukinumab were based on these results.

In the company base case, "BASDAI 50" was chosen as response definition. MTC inputs synthesising data from time points between weeks 12-16, using data from both MEASURE 1 and MEASURE 2, were used to measure secukinumab effectiveness. The ERG thinks using MTC inputs based on time points between week 12 and week 16 would be inconsistent with the economic model, because the induction period was strictly 12 weeks. Furthermore, this would create a bias against interventions which had effectiveness evidence coming only from week 12, as these interventions would lack the additional effectiveness benefit that the other interventions have from the extra weeks of treatment after week 12. Therefore, the ERG opted for the inputs from MTCs that use data coming from strictly week 12. The other questionable input choice was how the withdrawal rates were selected in the original CS base case. The ERG was in favour of using the same withdrawal rate derived in the York MTA report[9] for all biologics instead of using separately derived withdrawal rates for each intervention as in the CS[1]. These updated input choices: selecting the MTC using strictly week 12 end point and the uniform withdrawal rates defined the ERG base case.

A similar issue also arose for the adverse event rates, since the adverse event rates were derived separately for each intervention. However, the ERG decided not to update the CS base case rates considering the limited impact on incremental results as explored in Section 5.3.4.

Note that the MTCs do not produce results for all of the comparators in the biologic naïve population. For example, treatment effectiveness of certolizumab pegol was assumed to be the average of other anti TNF-alpha treatments, since there is no trial for certolizumab pegol that reports its effectiveness in biologic naïve patient populations. Even though this approach was approved by the clinical experts from the UK, it should be kept in mind while interpreting the cost effectiveness results.

In the company base case for the biologic naïve population, secukinumab dominated all anti TNF-alpha agents except for golimumab (which had an ICER of £674,914 per QALY). In the ERG base case, only etanercept (both original and biosimilar versions) was dominated by secukinumab. All other anti TNF-alpha agents were associated with higher QALYs gained and higher costs, with ICERs compared to secukinumab ranging from £38,000 to £72,000 per QALY gained in the base case.

For the biologic experienced population, the ICER estimates (around £2,200 per QALY gained) are more or less the same for the original submission model and for the ERG model.

Besides the base case scenarios, two exploratory analyses were conducted. The first one was to estimate the impact of allowing for a second line biologic treatment for biologic naïve patients. The second analysis focused on the comparison of secukinumab with other anti TNF-alpha agents for biologic experienced population. Both of the analyses resulted in similar ICERs the base case ICER for the biologic naïve population, because in both of the exploratory analyses, the treatment effectiveness data for the biologics used in the second line originated from the same MTC results used in the base case for the biologic naïve population. The only difference is that the efficacy reduction factors derived from the MEASURE 1 and 2 trials were applied. Therefore, these exploratory analyses were not very informative.

Another ambiguity concerning the reduction factors from MEASURE 1 and 2 should be noted: These factors may reflect the reduction in secukinumab effectiveness when secukinumab was applied after an anti TNF-alpha. However, it is questionable to assume that anti TNF-alpha effectiveness would reduce with the same proportion after secukinumab or after another anti TNF-alpha, since these are different drug classes.

To assess parameter uncertainty, probabilistic sensitivity analyses were conducted. The ERG found some errors in the PSA code of the original model, which was causing the average PSA results to differ from base case deterministic results substantially. The ERG has corrected these errors in the PSA code, which lead to more plausible average PSA results. Even though average PSA results are comparable to the deterministic base case results after corrections from the ERG, using PSA results may still be misleading, since the existing correlation between baseline BASDAI/BASFI, BASDAI/BASFI change from baseline and BASDAI 50 inputs were not reflected as they were sampled independently.

Several scenario analyses were conducted to assess structural uncertainty. The ERG conducted some new scenarios that were not conducted in the company submission, i.e. testing the impacts of having a uniform baseline for all patients, of using alternative assumptions between responder/ non-responder change from baseline ratios, using the exact response definition from BSR, using treatment effectiveness estimates from joint evidence synthesis approach from the York MTA[9]. In all scenarios, etanercept was dominated by secukinumab. Infliximab (both original and biosimilar version) was associated with higher QALYs and higher costs compared to secukinumab: leading to ICERs higher than the conventional threshold of £20,000 - £30,000 per QALY gained.

Adalimumab, golimumab and certolizumab pegol are mostly associated with higher QALYs and higher costs versus secukinumab: in all such cases the ICER for comparator versus secukinumab falls above the conventional threshold of £20,000 - £30,000 per QALY gained. For the scenarios for which different treatment effectiveness inputs were used (e.g. from different MTCs), secukinumab dominates these treatments (i.e. secukinumab provides higher QALYs with lower costs).

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The errors confirmed by the company were already corrected and a new model provided with the response to the clarification document[6]. Tables 6.1 and 6.2 show how each individual change of the ERG base case impacts the ICER plus the combined effect of all changes simultaneously for the biologic naïve and biologic experienced populations.

Table 6.1: Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG for the biologic naïve population analysis [Part a]

	Secukinumab vs. Adalimumab			Secukinumab vs. Certolizomab Pegol			Secukinumab vs. Golimumab		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from the CS sent with the response to the clarification letter[6]	**£15,300**	**-0.359**	**SEC150 dominates**	**£9,202**	**-0.359**	**SEC150 dominates**	**£16,703**	**0.025**	**£674,914**
Programming errors (only effects scenario/ explanatory analyses)	£15,217	-0.354	SEC150 dominates	£9,092	-0.352	SEC150 dominates	£16,623	0.026	£632,894
Using results from the week 12 analysis using both MEASURE 1 & 2 trials	£17,318	0.086	£200,791	£10,361	0.062	£166,570	£16,205	0.358	£45,225
Using withdrawal rates from Corbett et al. 2014[9]	£17,006	0.237	£71,690	£11,702	0.302	£38,778	£13,003	0.298	£43,584
ERG revised base case	**£17,006**	**0.237**	**£71,690**	**£11,702**	**0.302**	**£38,778**	**£13,003**	**0.298**	**£43,584**

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years; SEC150 = secukinumab 150 mg

Table 6.2: Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG for the biologic naïve population analysis [Part b]

	Secukinumab vs. Etanercept			Secukinumab vs. Etanercept biosimilar			Secukinumab vs. Infliximab			Secukinumab vs. Infliximab biosimilar		
	Incr. Costs	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**	**Incr. Costs**	**Incr. QALYs**	**ICER**
Base case from the CS sent with the response to the clarification letter[6]	**£2,033**	**-1.046**	**SEC150 dominates**	**£1,018**	**-1.046**	**SEC150 dominates**	**£26,223**	**-0.216**	**SEC150 dominates**	**£22,649**	**-0.216**	**SEC150 dominates**
Programming errors (only effects scenario/ explanatory analyses)	£2,033	-1.046	SEC150 dominates	£1,018	-1.046	SEC150 dominates	£26,223	-0.216	SEC150 dominates	£22,649	-0.216	SEC150 dominates
Using results from the week 12 analysis using both MEASURE 1 & 2 trials	£3,265	-0.618	SEC150 dominates	£2,186	-0.618	SEC150 dominates	£27,711	0.231	£119,703	£24,046	0.231	£103,872
Using withdrawal rates from Corbett et al. 2014[9]	£11,894	-0.007	Dominated	£9,879	-0.007	Dominated	£30,597	0.531	£57,654	£26,702	0.531	£50,315
ERG revised base case	**£11,894**	**-0.007**	**SEC150 dominates**	**£9,879**	**-0.007**	**SEC150 dominates**	**£30,597**	**0.531**	**£57,654**	**£26,702**	**0.531**	**£50,315**

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years; SEC150 = secukinumab 150 mg

Table 6.3: Revised base case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG for the biologic experienced population analysis

	Secukinumab vs. Conventional care		
	Incr. Costs	**Incr. QALYs**	**ICER**
Base case from the CS sent with the response to the clarification letter[6]	£1,747	0.778	£2,245
Programming errors (only effects scenario/ explanatory analyses)	£1,747	0.778	£2,245
Using week 12 response data instead of week 16	£2,068	0.873	£2,368
Using withdrawal rates from Corbett et al. 2014[9]	**£1,620**	**0.729**	**£2,223**
ERG revised base case	**£1,620**	**0.729**	**£2,223**

CS = company submission; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; NA = not available; QALY = quality-adjusted life years

7 END OF LIFE

The ERG considers this intervention does not meet the end of life criteria. As discussed in Section 2, secukinumab is indicated for active AS patients who do not necessarily have a short life expectancy.

8 OVERALL CONCLUSIONS

There were some sources of potential heterogeneity in the submitted evidence on clinical effectiveness which may have introduced bias in the results. There was a difference in the method of secukinumab administration between the MEASURE 1 and MEASURE 2 studies. Secukinumab is delivered intravenously in MEASURE 1 and subcutaneously in MEASURE 2. This limitation was recognised by the company and explored in a sensitivity analysis as part of the MTC. In principle differences in the effectiveness of secukinumab when delivered by different methods could increase the uncertainty in the MTC results however the sensitivity analysis showed that this had minimal impact in practice.

The primary endpoint in both MEASURE 1 and MEASURE 2 was assessed at 16 weeks. This is longer than the majority of other studies in ankylosing spondylitis which typically report outcomes after 12 weeks. The 12 week time point reflects clinical practice as this is when a decision is typically made to continue with the current treatment or switch to an alternative treatment. In general patients treated for longer would be more likely to respond to treatment than those treated for a shorter time. The 16 week time point in the two MEASURE studies may therefore introduce a bias in favour of secukinumab compared to other treatments for AS measured after only 12 weeks of treatment. As part of the MTC the company carried out a sensitivity analysis using only data reported after 12 weeks for all studies including MEASURE 1 and MEASURE 2. In this analysis the effectiveness of secukinumab relative to all other treatments was reduced compared to the base case across all outcomes. The difference in the effectiveness estimates between the base case and the sensitivity analysis is unlikely to be large enough to substantially alter the ICER given the low cost of secukinumab compared to other treatments for AS.

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope.

In the company base case for the biologic naïve population, secukinumab dominated all anti TNF-alpha agents except for golimumab (which had an ICER of £674,914 per QALY). In the ERG base case, only etanercept (both original and biosimilar versions) was dominated by secukinumab. All other anti TNF-alpha agents were associated with higher QALYs gained and higher costs, ICERs ranging from £38,000 to £72,000 per QALY gained in the base case.

The various sensitivity analyses revealed that the ICER is relatively robust against changes in most input values although it was quite sensitive to changes in the treatment effectiveness estimates, i.e. by the MTC approach selected. Nevertheless, secukinumab would remain cost effective at a threshold of £30,000 per QALY in all scenarios.

8.1 Implications for research

MTC allows the indirect comparison of alternative treatments for a condition when direct evidence is lacking. The lack of direct evidence meant that all comparisons of secukinumab versus alternative treatments for AS had to be based on indirect comparisons via placebo. There is a need for large, well designed, randomised clinical trials which directly compare secukinumab against alternative active treatments for AS using robust, well-defined outcomes assessed at clinically relevant time points.

Furthermore, the ERG feels there is considerable uncertainty surrounding prevalence estimates and that this is an area for future research.

Clinical effectiveness and cost effectiveness for the treatment sequences in AS should be explored. In the current MEASURE 1 and MEASURE 2 studies, the biologic experienced population are probably only anti TNF-alpha experienced patients. Instead of a basket of treatments approach for second line biologics, evidence should be collected to compare the effectiveness of all relevant secukinumab anti TNF-alpha, anti TNF-alpha-secukinumab and anti TNF-alpha- anti TNF-alpha sequences

9 REFERENCES

[1] Novartis. *Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*: Novartis, 2016. 265p.

[2] National Institute for Health and Care Excellence. Clinical Knowledge Summary (CKS): ankylosing spondylitis, background, prevalence [Internet]. 2013 [accessed 11.3.16]. Available from: http://cks.nice.org.uk/ankylosing-spondylitis#!backgroundsub:1

[3] Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E, et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev* 2015;4:CD005468.

[4] Novartis. *Data on file: MEASURE 2 clinical study report – week 52 analysis*, n.d.

[5] National Institute for Health and Care Excellence. *Adalimumab, etanercept and infliximab for ankylosing spondylitis [TA143]*, 2008

[6] Novartis. *Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719] – Response to request for clarification from the ERG*: Novartis, 2016. 163p.

[7] National Institute for Health and Care Excellence. *TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. Technology appraisal guidance TA383 [Internet]*, 2016 [accessed 24.2.16]. 70p. Available from: https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077

[8] Emery P. Optimizing outcomes in patients with rheumatoid arthritis and an inadequate response to anti-TNF treatment. *Rheumatology (Oxford)* 2012;51 Suppl 5:v22-30.

[9] Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E, et al. *TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of technology appraisal 143 and technology appraisal 233*. York: CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, 2014. 371p.

[10] National Institute for Health and Care Excellence. *Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. Single Technology Appraisal: Final Scope [Internet]*: NICE, 2015 [accessed 6.4.16]. 4p. Available from: https://www.nice.org.uk/guidance/GID-TAG517/documents/final-scope

[11] National Institute for Health and Care Excellence. *TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233). Equality impact assessment - guidance document [Internet]*, 2016 [accessed 24.2.16]. 5p. Available from: https://www.nice.org.uk/guidance/TA383/documents/equality-impact-assessment-guidance-development

[12] Canadian Agency for Drugs and Technologies in Health. *CADTH peer review checklist for search strategies [Internet]*. Ottawa: CADTH, 2013 [accessed 17.7.13]. 3p. Available from: http://www.cadth.ca/en/resources/finding-evidence-is

[13] National Institute for Health and Care Excellence. *Single Technology Appraisal: specification for manufacturer/sponsor submission of evidence [Internet]*. London: NICE, 2012 [accessed 8.4.16]. 76p.

Available from: http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Specification-for-manufacturer-sponsor-submission-of-evidence-June-2012.doc

[14] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 23.3.16]. 93p. Available from: http://publications.nice.org.uk/pmg9

[15] Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions [Internet]*. Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011 [accessed 23.3.11]. Available from: http://www.cochrane-handbook.org/

[16] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[17] National Institute for Health and Care Excellence. *Single Technology Appraisal: user guide for company evidence submission template [Internet]*. London: NICE, 2015 [accessed 8.4.16]. 66p. Available from: https://www.nice.org.uk/article/pmg24/resources/non-guidance-single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf

[18] Novartis. *Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy [ID719]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): appendices*: Novartis, 2016. 304p.

[19] Huang F, Gu J, Zhu P, Bao C, Xu J, Xu H, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. *Ann Rheum Dis* 2014;73(3):587-94.

[20] Novartis. *Secukinumab for the treatment of active ankylosing spondylitis in adults who have responded inadequately to conventional therapy – Response to request for clarification from the ERG [ID719] - Addendum*: Novartis, 2016. 163p.

[21] Dougados M, Braun J, Szanto S, Combe B, Geher P, Leblanc V, et al. Continuous efficacy of etanercept in severe and advanced ankylosing spondylitis: results from a 12-week open-label extension of the SPINE study. *Rheumatology (Oxford)* 2012;51(9):1687-96.

[22] Novartis. *Data on file: MEASURE 2 - week 104 analysis tables*, n.d.

[23] Novartis. *Data on file: MEASURE 1 clinical study report – week 52 analysis*, n.d.

[24] Jin JF, Zhu LL, Chen M, Xu HM, Wang HF, Feng XQ, et al. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. *Patient Prefer Adherence* 2015;9:923-42.

[25] Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in ankylosing spondylitis. *N Engl J Med* 2015;373(26):2534-48.

[26] Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009;338:b1147.

[27] Ara RM, Reynolds AV, Conway P. The cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in the UK. *Rheumatology (Oxford)* 2007;46(8):1338-44.

[28] Armstrong N, Joore M, van Asselt T, Misso K, Manning N, Tomini F, et al. Golimumab for the treatment of ankylosing spondylitis: a NICE single technology appraisal. *Pharmacoeconomics* 2013;31(5):415-25.

[29] Botteman MF, Hay JW, Luo MP, Curry AS, Wong RL, van Hout BA. Cost effectiveness of adalimumab for the treatment of ankylosing spondylitis in the United Kingdom. *Rheumatology (Oxford)* 2007;46(8):1320-8.

[30] Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). *Rheumatology (Oxford)* 2004;43(9):1158-66.

[31] Kobelt G, Sobocki P, Sieper J, Braun J. Comparison of the cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in the United Kingdom based on two different clinical trials. *Int J Technol Assess Health Care* 2007;23(3):368-75.

[32] McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess* 2007;11(28):1-158, iii-iv.

[33] Scottish Medicines Consortium. *Etanercept 25mg vial of powder for subcutaneous injection (Enbrel) (No. 212/05) [Internet]*: SMC, 2005 [accessed 11.3.16]. 7p. Available from: http://www.scottishmedicines.org.uk/files/etanercept__Enbrel___for_ank_spond__212-05_.pdf.

[34] Scottish Medicines Consortium. *Golimumab 50mg solution for injections prefilled pen (auto-injector) or prefilled syringe (Simponi) (no. 721/11) [Internet]*: SMC, 2011 [accessed 11.3.16]. 8p. Available from: https://www.scottishmedicines.org.uk/files/advice/golimumab_Simponi_FINAL_August_2011_for_website.pdf.

[35] Scottish Medicines Consortium. *Certolizumab pegol 200mg/mL solution for injection in pre-filled syringe (Cimzia®) (no. 960/14) [Internet]*: SMC, 2014 [accessed 11.3.16]. 10p. Available from: https://www.scottishmedicines.org.uk/files/advice/certolizumab_pegol_Cimzia_FINAL_April_2014_for_website.pdf.

[36] Scottish Medicines Consortium. *Adalimumab, 40mg/0.8mL, solution for injection (Humira®) (no. 858/13) [Internet]*: SMC, 2013 [accessed 11.3.16]. 8p. Available from: https://www.scottishmedicines.org.uk/files/advice/adalimumab_Humira_FINAL_March_2013_for_website.pdf.

[37] Scottish Medicines Consortium. *Infliximab, 100mg, powder for concentrate for solution for infusion (Remsima®) (no. 1006/14) [Internet]*: SMC, 2015 [accessed 11.3.16]. 10p. Available from: https://www.scottishmedicines.org.uk/files/advice/infliximab_Remsima_FINAL_November_2014_amended_240205_for_website.pdf.

[38] Scottish Medicines Consortium. *Infliximab, 100mg, powder for concentrate for solution for infusion (Inflectra®) (no. 1007/14) [Internet]*: SMC, 2015 [accessed 11.3.16]. 10p. Available from: https://www.scottishmedicines.org.uk/files/advice/infliximab_Infectra_FINAL_November_2014_Amended_240215_for_website.pdf.

[39] Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011(2):CD008794.

[40] Wailoo A, Hernandez M, Philips C, Brophy S, Siebert S. Modeling Health State Utility Values in Ankylosing Spondylitis: Comparisons of Direct and Indirect Methods. *Value Health* 2015;18(4):425-31.

[41] Keat A, Barkham N, Bhalla A, Gaffney K, Marzo-Ortega H, Paul S, et al. BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. *Rheumatology (Oxford)* 2005;44(7):939-47.

[42] European Medicines Agency (EMA). Cosentyx 150 mg powder for solution for injection. Summary of Product Characteristics [Internet]. 2016 [accessed 12.1.16]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf

[43] European Medicines Agency (EMA). Humira 40 mg/0.8 ml solution for injection. Summary of Product Characteristics [Internet]. 2015 [accessed 15.12.15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf

[44] European Medicines Agency (EMA). Enbrel 25 mg powder and solvent for solution for injection. Summary of Product Characteristics [Internet]. 2015 [accessed 15.12.15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf

[45] European Medicines Agency (EMA). Simponi 50 mg solution for injection in pre-filled pen. Summary of Product Characteristics [Internet]. 2015 [accessed 15.12.15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000992/WC500052368.pdf

[46] European Medicines Agency (EMA). Remicade 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics [Internet]. 2015 [accessed 12.1.16]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf

[47] European Medicines Agency (EMA). Cimzia 200 mg solution for injection. Summary of Product Characteristics. Summary of Product Characteristics [Internet]. 2015 [accessed 15.12.15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf

[48] Revicki DA, Luo MP, Wordsworth P, Wong RL, Chen N, Davis JC, Jr. Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS). *J Rheumatol* 2008;35(7):1346-53.

[49] Landewe R, Dougados M, Mielants H, van der Tempel H, van der Heijde D. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. *Ann Rheum Dis* 2009;68(6):863-7.

[50] Ramiro S, Stolwijk C, van Tubergen A, van der Heijde D, Dougados M, van den Bosch F, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. *Ann Rheum Dis* 2015;74(1):52-9.

[51] Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis Rheum* 2013;65(10):2645-54.

[52] Novartis. *Data on file: MEASURE 1 - clinical study report – week 104 analysis*, n.d.

[53] Sieper J, Landewe R, Rudwaleit M, van der Heijde D, Dougados M, Mease PJ, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis: results from a phase III randomized trial. *Arthritis Rheumatol* 2015;67(3):668-77.

[54] Navarro-Sarabia F, Fernandez-Sueiro JL, Torre-Alonso JC, Gratacos J, Queiro R, Gonzalez C, et al. High-dose etanercept in ankylosing spondylitis: results of a 12-week randomized, double blind, controlled multicentre study (LOADET study). *Rheumatology (Oxford)* 2011;50(10):1828-37.

[55] Sieper J, van der Heijde D, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Ann Rheum Dis* 2012;71(5):700-6.

[56] van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52(2):582-91.

[57] Braun J, Deodhar A, Dijkmans B, Geusens P, Sieper J, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period. *Arthritis Rheum* 2008;59(9):1270-8.

[58] Deodhar A, Braun J, Inman RD, van der Heijde D, Zhou Y, Xu S, et al. Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Ann Rheum Dis* 2015;74(4):757-61.

[59] Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Ann Rheum Dis* 2011;70(11):1921-5.

[60] European Medicines Agency (EMA). Inflectra 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics [Internet]. 2015 [accessed 12.1.16]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002778/WC500151489.pdf

[61] European Medicines Agency (EMA). Remsima 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics [Internet]. 2015 [accessed 12.1.16]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002576/WC500150871.pdf

[62] Personal Social Services Research Unit. *Unit Costs of Health and Social Care [Internet]*. Canterbury: University of Kent, 2015 [accessed 30.3.16]. 284p. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php

[63] Department of Health. *NHS reference costs 2014-2015 [Internet]*. London: Department of Health, 2015 [accessed 30.3.16] Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.

[64] National Institute for Health and Care Excellence. *Adalimumab for the treatment of adults with psoriasis. TA146. Costing template [Internet]*: NICE, 2008 [accessed 19.1.16] Available from: https://www.nice.org.uk/guidance/ta146/resources

[65] National Institute for Health and Care Excellence. *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Technology Assessment Report For NICE MTA [Internet]*: NICE, 2009 [accessed 19.1.16]. 387p. Available from: https://www.nice.org.uk/guidance/TA199/documents/psoriatic-arthritis-etanercept-infliximab-adalimumab-review-acd-assessment-report3

[66] Boonen A, van der Heijde D, Landewe R, Guillemin F, Rutten-van Molken M, Dougados M, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. *Ann Rheum Dis* 2003;62(8):732-40.

[67] Department of Health. *NHS reference costs 2013-2014. National schedule of reference costs: the main schedule. [Internet]*. London: Department of Health, 2014 [accessed 19.1.16] Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015

[68] Cooksey R, Husain MJ, Brophy S, Davies H, Rahman MA, Atkinson MD, et al. The Cost of ankylosing spondylitis in the UK using linked routine and patient-reported survey data. *PLoS One* 2015;10(7):e0126105.

[69] Glintborg B, Ostergaard M, Krogh NS, Tarp U, Manilo N, Loft AG, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor alpha inhibitor therapy: results from the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2013;72(7):1149-55.

[70] University of Aberdeen. British Society for Rheumatology Biologics Registers: Ankylosing Spondylitis (BSRBR-AS) [online presentation] [Internet]. 2012 [accessed 14.4.16]. Available from: http://www.rheumatology.org.uk/includes/documents/cm_docs/2012/1/1130_inbank_bsr_registers_and_the_new_information_age.pdf

[71] Hu Z, Xu M, Li Q, Lin Z, Liao Z, Cao S, et al. Adalimumab significantly reduces inflammation and serum DKK-1 level but increases fatty deposition in lumbar spine in active ankylosing spondylitis. *Int J Rheum Dis* 2012;15(4):358-65.

[72] Giardina AR, Ferrante A, Ciccia F, Impastato R, Miceli MC, Principato A, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. *Rheumatol Int* 2010;30(11):1437-40.

[73] Boonen A, van der Heijde D, Severens JL, Boendermaker A, Landewe R, Braun J, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. *Ann Rheum Dis* 2006;65(2):201-8.

[74] Tran-Duy A, Boonen A, van de Laar MA, Franke AC, Severens JL. A discrete event modelling framework for simulation of long-term outcomes of sequential treatment strategies for ankylosing spondylitis. *Ann Rheum Dis* 2011;70(12):2111-8.

[75] Tran-Duy A, Boonen A, van de Laar MA, Severens JL. Simultaneously forecasting burden of illness and cost-effectiveness: The case of tumour necrosis factor-alpha antagonist for ankylosing spondylitis in the dutch society. *Ann Rheum Dis* 2013;71(Suppl 3).

[76] Gonzalez Alvarez A, Gomez Barrera M, Borras Blasco J, Giner Serret EJ. [Analisis of the budget impact of adalimumab and etanercept in rheumatoid arthritis and spondyloarthropathies]. *Farm Hosp* 2013;37(3):192-7.

[77] Ji X, Joshi A, Vidal Pérez-Campoamor S, Sanchez Hernandez R, Botteman M, Bao Y. A cost-effectiveness model of adalimumab (ADA) in non-radiographic axial spondyloarthritis in Spain. *Ann Rheum Dis* 2014;73(Suppl 2):122-123.

[78] Kobelt G, Sobocki P, Mulero J, Gratacos J, Collantes-Estevez E, Braun J. The cost-effectiveness of infliximab in the treatment of ankylosing spondylitis in Spain. Comparison of clinical trial and clinical practice data. *Scand J Rheumatol* 2008;37(1):62-71.

[79] Scaccabarozzi L. Cost-minimization analysis of anti-Tnf biologics in the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis under the Brazilian private health care system perspective. *Value Health* 2014;17(3):A229.

[80] Zavada J, Uher M, Sisol K, Forejtova S, Jarosova K, Mann H, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. *Ann Rheum Dis* 2016;75(1):96-102.

[81] Kobelt G, Andlin-Sobocki P, Maksymowych WP. The cost-effectiveness of infliximab (Remicade) in the treatment of ankylosing spondylitis in Canada. *J Rheumatol* 2006;33(4):732-40.

[82] Fautrel B, Benhamou M, Breban M, Roy C, Lenoir C, Trape G, et al. Cost effectiveness of two therapeutic regimens of infliximab in ankylosing spondylitis: economic evaluation within a randomised controlled trial. *Ann Rheum Dis* 2010;69(2):424-7.

[83] Neilson AR, Sieper J, Deeg M. Cost-effectiveness of etanercept in patients with severe ankylosing spondylitis in Germany. *Rheumatology (Oxford)* 2010;49(11):2122-34.

[84] Codreanu C, Mogosanu C, Joita M, Purcaru O. Cost-effectiveness of certolizumab pegol in the treatment of active rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis in Romania. *Value Health* 2014;17(7):A379.

[85] Ivakhnenko O, Rebrova O, Avxentyeva M, Khachatryan G. Three TNF-a-inhibitors for treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Value Health* 2013;16(7):A564.

Appendix 1: ERG Search Strategies

No additional ERG searches were conducted.

Appendix 2: Summary list of UK-based economic evaluations and HTA reports identified in the systematic literature review

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
Ara 2007 [27]	UK; NR	Mathematical model using patient-level data from phase 3 RCTs to inform clinical effectiveness and HRQoL changes in the model.	This study aimed to provide evidence on the potential costs and benefits associated with long-term (25-year) etanercept treatment for patients with severe AS in the UK in accordance with the BSR guidelines.	25 years	All patients had active AS and were assumed to have tried and failed to respond to at least two consecutive NSAIDs and have a BASDAI measurement ≥40 (scale 0–100) prior to entering the model. The mean age of patients in these studies ranged from 39.5 to 42 years.	Breakdown of costs and time horizons incurred for a cohort of 1,000 patients over 4 time periods			
						2 years			
						Etanercept plus NSAIDs	£13,041,740	1,185	£27,594
						NSAIDs alone	£2,889,706	817	—
						5 years			
						Etanercept plus NSAIDs	£26,389,802	2,646	£23,649
						NSAIDs alone	£7,109,054	1,831	—
						15 years			
						Etanercept plus NSAIDs	£51,415,277	5,739	£22,580
						NSAIDs alone	£18,596,422	4,286	—
						25 years			
						Etanercept plus NSAIDs	£62,516,684	7,285	£22,704
						NSAIDs alone	£26,538,439	5,700	—
Arm-	UK; NR	Initial	HTA	20 years in	Adults with	Base-case results			

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
strong 2013[28]		decision tree and then a Markov model	submission	the base case. Lifetime in the ERG analysis.	severe, active AS whose response to conventional therapy has been inadequate. Average age: NR.	Golimumab	Total=£93,786 Incremental = £5,119	Total=6.8506 Incremental = 0.1925	£26,597 vs. conventional
						Etanercept	Total=£93,782 Incremental = £5,115	Total=6.8504 Incremental = 0.1923	NA (extendedly dominated)
						Adalimumab	Total = £93,601 Incremental = £4,934	Total = 6.8426 Incremental = 0.1845	NA (extendedly dominated)
						Conventional treatment	£88,667	Total = 6.6581	Reference
						ERG analysis			
						Golimumab	Total = £99,361 Incremental = £4,134	Total = 8.0296 Incremental = 0.1534	NA (extendedly dominated)
						Etanercept	Total = £108,347 Incremental = £52	Total = 8.3712 Incremental = 0.0029	£26,505 vs. conventional
						Adalimumab	Total = £108,295 Incremental = £8,934	Total = 8.3683 Incremental = 0.3387	NA (extendedly dominated)

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						Conventional treatment	Total = £95,227	Total = 7.8762	Reference
Botte-man 2007[29]	UK; 2004	The analysis was based on pooled data from 2 phase 3 studies of adalimumab in patients with active AS. A micro-simulation model was used to simulate individual histories of patients enrolled in 2 adalimumab clinical trials.	This study evaluated the cost-effectiveness of adalimumab vs. conventional therapy in patients with active AS.	1, 5, and 30 years	A total of 397 patients with active AS were enrolled. 354 met the spinal pain VAS and BASDAI criteria at baseline, and 315 met both criteria at baseline and pre-baseline and therefore were included in the simulation. Compared with the trial patient population,	1 year (48 weeks)			
						Adalimumab	Total costs = £9,857 AS-specific costs = £3,668 ADA therapy = £6,189 (drug costs = £5,233, monitoring costs = £905, AE costs = £51)	0.5529	£47,083
						Conventional therapy	Total cost = £4,832 AS-specific costs = £4,832	0.4461	—
						5 years			
						Adalimumab	Total costs = £36,802 AS-specific costs = £18,136 ADA therapy =	2.6653	£26,332

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
					those included in the simulation were very comparable in average baseline age (42.0 years old vs.42.2 years old, respectively), sex (76% vs.75% male, respectively) and race (96% vs. 95% white, respectively).		£18,666 (drug costs=£16,566, monitoring costs=£1,929, AE costs=£171)		
						Conventional therapy	Total cost=£23,529 AS-specific costs=£23,529	2.1613	—
						30 years			
						Adalimumab	Total costs=£115,937 AS-specific costs=£81,330 Adalimumab therapy = £34,607 (drug costs = £30,999, monitoring = £3,230, AE costs = £378)	9.2220	£23,097
						Conventional therapy	Total costs=£92,080	8.1891	—

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							AS-specific costs=£92,080		
Kobelt 2004[30]	UK; 2002	Cost-effectiveness of infliximab was modelled using an individual simulation based on a 3-month placebo-controlled clinical trial with open, 1-year extension in 70 patients, over a total time frame of 2 years. The effect of long-term treatment	The aims of this study were to investigate the cost of AS in the UK, focusing on the influence of disease severity on cost and QoL, and to construct a disease model to estimate the cost-effectiveness of infliximab in patients with active,	Main cost-effectiveness model = 2 years. Hypothetical Markov model = 30 years	All patients had confirmed and active AS. The economic analysis included the open extension to 54 weeks for the intervention group; while for the purpose of comparison, patients from the placebo group were assumed to receive standard treatment	Infliximab	Main model		
						Base case, societal perspective (incremental vs. placebo)	£6,214	0.175	£35,400
						Base case, only health care costs included (incremental vs. placebo)	£12,844	0.175	£73,300
						Infliximab	Hypothetical long-term model		
						Base case, societal perspective (incremental vs. placebo)	£25,200	2.62	£9,600
						Base case, only health care costs included (incremental vs.	£87,700	2.62	£33,500

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		was evaluated in a hypo-thetical Markov model over 30 years based on epidemiolog ical data to illustrate potential long-term treatment and compliance with treatment.	unremitting disease.		after 12 weeks.	placebo)			
Kobelt 2007[31]	UK; 2005	Combined decision tree with a subsequent Markov model.	To compare the cost-effectiveness of the treatment of AS with infliximab in the UK	Lifetime	The first trial by Braun et al. 2002 randomised 70 patients with active AS. The mean age	Infliximab (5 mg/kg every 6 weeks) compared to standard treatment.	Incremental cost (£)	QALY gain	ICER
							BRAUN trial		
							No progression while on treatment Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
			over a lifetime, estimated from 2 different clinical trials and adjusted for clinical practice guidelines.		was 39.0 and 40.1 years in the placebo and the infliximab groups, respectively. ASSERT included 279 patents with active AS. The mean age in this trial was 41 and 40 years in the placebo and the infliximab groups, respectively. Resource utilisation and cost data were based		£–16,862	1.28	Dominance
							£36,378	1.28	£28,332
							50% progression while on treatment Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		
							£–3,975	1.01	Dominance
							£35,756	1.01	£35,332
							Same progression in both groups Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		
							£12,156	0.81	£15,045
							£39,336	0.80	£49,417
							ASSERT		
							No progression while on treatment Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		
							£–15,927	1.27	Dominance
							£33,920	1.27	£26,751

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
					on a cross-sectional retrospective survey that included 1,413 patients with a mean age of 57 years.		50% progression while on treatment Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		
							£–5,233	1.01	Dominance
							£34,408	1.01	£34,067
							Same progression in both groups Top value=societal perspective, all costs Bottom value=NHS and Personal Social Services costs only		
							£10,540	0.88	£11,937
							£39,242	0.86	£46,167
McLeod 2007[32]	UK; NR	Exploratory economic modelling. A simple spread-sheet model was developed and combined life-table–adjusted mortality	To assess the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab	12 months (short-term model); 20 years (long-term model extension).	Cohort of males aged 40 years with initial mean BASDAI/ BASFI scores of 6.5 and 5.6, respectively.	Short-term model baseline costs (£):			
						Conventional therapy	All costs: £213	Mean utility: 0.531 Total QALYs: 521.7	
						Adalimumab	All costs: £5,860 Drug acquisition = £5,453;	Mean utility: 0.631 Total QALYs: 620.3 Incremental all	Incremental cost per QALY gained: £57,258

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		rates with Markov-like transitions between TNFα inhibitor treatments.	for the treatment of AS. It was commissioned by the National Coordinating Centre of Health Technology Assessment on behalf of NICE.				Drug administration = £0; Therapy monitoring = £92; TB testing = £89; TB treatment=£8; AEs = £173; Disease-related=£173	costs: £5,647 Incremental QALYs per patient: +0.099	
						Etanercept	All costs: £5,680 Drug acquisition = £5,454; Drug administration = £0; Therapy monitoring = £92; TB testing= £89;	Mean utility: 0.631 Total QALYs: 620.3 Incremental all costs: £5,647 Incremental QALYs per patient: +0.099	Incremental cost per QALY gained: £57,261

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							TB treatment = £8; AEs = £173; Disease-related = £173		
						Infliximab	All costs: £12,059 Drug acquisition = £9,856; Drug administration = £1,796; Therapy monitoring = £92; TB testing = £89; TB treatment = £8; AEs = £173; Disease-related = £173; Incremental costs = £11,845	Mean utility: 0.631 Total QALYs = 620.3 Incremental QALYs per patient = 0.099 Incremental all costs: £11,845 Incremental QALYs per patient: 0.099	Incremental cost per QALY gained: £120,109

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-2 costs (£)			
						Conventional therapy	All costs: £425	Total QALYs: 1,015.6	
						Adalimumab + etanercept	All costs: £9,425 Drug acquisition = £8,750; Drug administration= £0; Therapy monitoring = £162; TB testing = £89; TB treatment = £13; AEs = £58; Disease-related = £354; Accumulated incremental costs = £9,000	Total QALYs: 1,186.9 Accumulated increment-al costs: 9,000 Accumulated increment-al QALYs: 0.171	Incremental cost per QALY gained: £52,534

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-3 costs (£)			
						Conventional therapy	All costs: £632	Total QALYs: 1,489.2	
						Adalimumab + etanercept	All costs: £12,411 Drug acquisition = £11,479; Drug administration = £0; Therapy monitoring = £220; TB testing = £89; TB treatment = £16; AEs = £69; Disease-related = £539	Total QALYs: 1711.7 Accumulated increment-al costs: 11,780 Accumulated incremental QALYs: 0.223	Incremental cost per QALY gained: £52,932
						Infliximab	All costs: £22,779 Drug	Total QALYs: 1,711.7	Accumulated incremental costs: 22,147

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							acquisition=£18,544; Drug administration = £3,301; Therapy monitoring = £220; TB testing = £89; TB treatment = £16; AEs = £69; Disease-related = £539		Accumulated incremental QALYs: 0.223 Increment-al cost per QALY gained: £99,516
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-5 costs (£)			
						Conventional therapy	All costs: £1,033	Total QALYs: 2,378.6	
						Adalimumab + etanercept	All costs: £12,411 Drug acquisition = £15,791; Drug	Total QALYs: 2,662.5 Accumulated increment-al costs: 11,780 Accumulated	Incremental cost per QALY gained: £56,976

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							administration = £0; Therapy monitoring = £311; TB testing = £89; TB treatment = £23; AEs = £86; Disease-related = £913	incremental QALYs: 0.284	
						Infliximab	All costs: £30,969 Drug acquisition = £25,113; Drug administration = £4,435; Therapy monitoring = £311; TB testing=£89; TB treatment=£23;	Total QALYs: 2662.5	Accumulated incremental costs: 29,936 Accumulated incremental QALYs: 0.284 Increment-al cost per QALY gained: £105,423

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							AEs=£86; Disease-related=£913		
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-10 costs (£)			
						Conventional therapy	All costs: £1,962	Total QALYs: 4,292.3	
						Adalimumab + etanercept	All costs: £25,675 Drug acquisition = £23,146; Drug administration = £0; Therapy monitoring = £468; TB testing = £89; TB treatment = £33; AEs = £115; Disease-related = £1,823	Total QALYs: 4624.2 Accumulated increment-al costs: 23,713 Accumulated increment-al QALYs: 0.332	Incremental cost per QALY gained: £71,454

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						Infliximab	All costs: £44,573 Drug acquisition = £35,782; Drug administration = £6,262; Therapy monitoring = £468; TB testing = £89; TB treatment = £33; AEs = £115; Disease-related = £1,823; Accumulated incremental costs=£42,610	Total QALYs: 4624.2	Accumulated incremental costs: 42,610 Accumulated incremental QALYs: 0.332 Incremental cost per QALY gained: 128,399
						LRiG model (2-20 years discounted at 3.5% for costs and outcomes): year 0-20 costs (£)			
						Conventional	All costs:	Total QALYs:	

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						therapy	£3,546	7,009.0	
						Adalimumab + etanercept	All costs: £36,705 Drug acquisition=£32,339; Drug administration = £0; Therapy monitoring = £665; TB testing = £89; TB treatment = £46; AEs = £153; Disease-related=£3,413	Total QALYs: 7344.2 Accumulated incremental costs: 33,159 Accumulated incremental QALYs: 0.335	Incremental cost per QALY gained: £98,910
						Infliximab	All costs: £62,213 Drug acquisition = £49,284; Drug	Total QALYs: 7344.2	Accumulated incremental costs: £58,667 Accumulated incremental

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							administration = £8,563; Therapy monitoring = £665; TB testing = £89; TB treatment = £46; AEs = £153; Disease-related = £3,413		QALYs: 0.335 Incremental cost per QALY gained: £175,000
SMC 2005[33]	Scotland; Unclear	Individual patient-based cost-utility model.	HTA submission	15 years	Patients with active AS who had shown an inadequate response to 2 NSAIDs were included.	Etanercept (25 mg twice a week)	£9,296 per year	NR	The result of the base-case model was an incremental cost per QALY ratio of £11,700 at 15 years.
						Infliximab (5 mg/kg every 6-8 weeks)	£10,894-£14,525 per year (£14,665-£17,877 in first year for patients weighing 60 kg-80 kg; for those weighing < 60 kg, annual costs would be	NR	

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
							£8,170-£10,894 [£10,999-£13,408 in first year]).		
SMC 2006[36]	Scotland; 2006	Cost utility, micro-simulation model.	HTA submission	30 years	Data to populate the model was taken from 2 clinical trials which included adults with severe, active AS who had an inadequate response to 2 or more NSAIDs.	Adalimumab (40 mg every 2 weeks)	£9,295 per year	NR	The cost per QALY in the baseline analysis was £23,000, rising to £26,000 if a 5-year time horizon was used or £47,000 if a 48-week horizon was taken.
						Infliximab (5 mg/kg every 6 to 8 weeks)	£10,910-£14,547 per year (£14,687-£17,903 in first year for patients weighing 60 kg to 80 kg patient; for those weighing < 60 kg, annual costs would be £8,183-£10,910 [£11,015-£13,428 in first year])	NR	
						Etanercept (25 mg twice weekly or 50 mg	£9,295 per year	NR	

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
						weekly)			
						Conventional therapy	NR	NR	
SMC 2011[34]	Scotland; 2011	CUA, a decision tree and Markov model was used to assess treatment effect at 12 week cycles CMA was also presented in response to a request from SMC.	HTA submission	20 years	Adults with severe, active AS who had responded inadequately to 2 conventional therapies.	Golimumab (50 mg once monthly as a s.c. injection)	£9,156 per year	NR	If 5% of patients were assumed to require the 100-mg dose of GOL, the cost per QALY vs. conventional DMARDs was £32,546, which was less cost-effective than ADA or ETN.
						Adalimumab (40 mg every 2 weeks as a s.c. injection)	£9,156 per year	NR	
						Etanercept (25 mg twice weekly or 50 mg weekly as a s.c. injection)	£9,295 per year	NR	
						Conventional therapy	NR	NR	
SMC 2014[35]	Scotland; 2014	The company submitted a CUA for AS and used a dual	HTA submission	Lifetime	Data from the RAPID-axSpA study were used which involved	Certolizumab pegol (200 mg s.c. every 2 weeks or 400 mg every 4 weeks)	£9,295 per year	NR	NR

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
		structure for the model with a decision tree, followed by a Markov structure for the longer-term impact on the disease. CMA was provided in response to a request from SMC reviewers.			patients with active AS.	Golimumab (50 mg or 100 mg s.c. once monthly)	£9,156-£18,311 per year	NR	NR
						Etanercept (25 mg s.c. twice weekly or 50 mg s.c. once weekly)	£9,295 per year	NR	NR
						Adalimumab (40 mg s.c. every other week)	£9,156 per year	NR	NR
SMC 2015[37]	(Scotland, UK, 2014)	Cost-minimisation analysis	HTA submission	1 year	Data from the PLANETRA study were used. As infliximab (Remsima®) is a biosimilar	Infliximab (Remicade®) (3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion	First year £10,071 Subsequent years £7,553 to £8,812 (6 to 7 doses)	NR	NR

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
					medicine, the conclusion of clinical equivalence based on this study was assumed to extrapolate to the other indications for the reference product.	doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter)			
SMC 2015[38]	(Scotland, UK, 2014)	Cost-minimisation analysis	HTA submission	1 year	Data from the PLANETRA study were used. As infliximab (Remsima®) is a biosimilar medicine, the conclusion of clinical equivalence based on this	Infliximab (Inflectra®) (3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter)	First year £9,064 Subsequent years £6,798 to £7,931 (6 to 7 doses)	NR	NR

Author (Year)	Country; Cost-year	Analysis or Model Type	Purpose of the Study	Time Frame	Patient Population	Intervention(s) and comparator(s)	Cost	QALYs	ICER
					study was assumed to extrapolate to the other indications for the reference product.	Infliximab (Remicade®) (3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter)	First year £10,071 Subsequent years £7,553 to £8,812 (6 to 7 doses)	NR	NR

ADA = Adalimumab 40 mg; AE = Adverse event; AS = Ankylosing spondylitis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BSR = British Society for Rheumatology; CMA = cost minimisation analysis; CUA = cost-utility analysis; DMARD = Disease modifying anti-rheumatic drug; ERG = Evidence Review Group; GOL = Golimumab; HRQoL = Health-related Quality of Life; HTA = Health Technology Assessment; ICER = Incremental cost-effectiveness Ratio; kg = kilogram; LRiG = Liverpool Reviews and Implementation Group; mg = milligram; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; NSAID = Non-steroidal anti-inflammatory drug; QALY = Quality-adjusted Life Year; RCT = randomised controlled trial; s.c. = subcutaneous; TB = tuberculosis; UK = United Kingdom

Appendix 3: Summary list of nonUK-based economic evaluations and HTA reports identified in the systematic literature review

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
Boonen 2006[73]	The Netherlands 2002	A Markov model over 5 years with cycle times of 3 months was computed.	To estimate the incremental cost utility of ETN and INF compared with usual care in patients with active AS.	5 years	A Markov model was chosen because it takes into account changes over time by redistributing the patient cohort after each cycle over the health states distinguished. The time horizon of 5 years was chosen because modelling beyond that time would not be realistic in the absence of empirical data.	Patients entering the model had active AS defined as BASDAI ≥ 4.The mean ages of the patients in the cohort study were 47 and 45 years for the BASDAI score of < 4 and ≥ 4, respectively.	Patients in the model could be treated either with INF, 5 mg/kg every 6 weeks, after the usual loading dose at weeks 0, 2, and 6; or with ETN 25 mg twice weekly; or with usual care, comprising NSAIDs or physiotherapy or both.		Total costs over 5 years	Total QALYs over 5 years	€ per QALY
								INF	€62,047	3.11	€189,564
								ETN	€52,137	3.16	€118,022
								Usual care	€21,261	2.89	Reference
Tran-Duy 2011[74]	The Netherlands;	Discrete-event	The general	The simulation	In AS, the long-term	An initial population of	Two strategies were		Mean annual cost	Mean QALYs per patient	ICER (95% CI)

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
	NR	simulation	purpose of this study was to develop a modelling framework which can simulate long-term QALYs and societal costs as affected by drug treatment strategies for AS.	was run until death of the patients.	relationships among disease measures, treatments, costs and health utility are complex. Therefore, discrete-event simulation was considered the most appropriate modelling tool as it can overcome limitations of a decision-tree and a Markov model. Rationale for time frame not reported.	13,000 patients was used for both first and second-order uncertainty analyses. Simulated baseline characteristics of the patients (mean age, 32.8; male, 69.9%; mean BASDAI, 3.4; mean BASFI, 4.1) agreed well with the empirical data.	compared: strategy 1: 5 NSAIDs available in a random order for each patient; strategy 2: the same as strategy 1 plus 2 TNFα inhibitor agents available also in a random order for each patient. Following the ASAS recommendations, a next treatment was considered when a drug failed and BASDAI was ≥ 4.		per patient	since AS diagnosis until death	
								Strategy 1 (5 available NSAIDs)	Year 1: €6,765; Year 70: €2,243	19.48	-
								Strategy 2 (same available NSAIDs as in strategy 1 plus 2 TNFα inhibitor agents)	Year 1: €7,738; Year 70: €2,337	19.97	€35,186 (€24,815 to €55,130)
Tran-Duy 2013[75]	The Netherlands; NR	Discrete-event modelling framework.	To develop a simulation model to	The prevalent AS cohort was	To date, modelling strategies in health	Patients with AS in the Dutch population were used. The	In Scenario 1, 5 NSAIDs were available.	Scenario 2 vs. Scenario 1	The use of anti-TNFαs would result in an	The use of anti-TNFαs would result in an increase	Incremental costs per QALY gained of

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			forecast impact of treatment strategies for a chronic disease in a real society on patient and population health, budgets, and cost-effectiveness at specific points in calendar time.	identified on 1 January 2012 and the incident AS cohorts in the subsequent 20 years; the model created an actual number of AS patients. Data on patient characteristics, treatments and cumulative costs, and QALYs were calculated at discrete time points until death or end of the simulation time.	economic evaluations fail to provide comprehensive information expected by decision makers, such as actual numbers of patients in a society receiving a new technology and health burden and expenditure at different points in calendar time. Simultaneously, forecasting burden of illness and cost-effectiveness of complex treatment strategies for rheumatic	predicted size of prevalent AS in the Dutch society varied from 69,350 to 70,540, with 31%-33% of the patients receiving anti-TNFαs over the period 2012-2032 (age: NR).	In Scenario 2, 5 NSAIDs and 2 anti-TNFαs were available.		increase in annual total drug costs (€86.1-€146.3 million), but a decrease in annual total productivity cost (€18.2-€40.3 million) and in annual total costs of health care categories other than drugs (€2.1-€5.8 million).	in annual total QALYs (677-1,786)	Scenario 2 against Scenario 1 on 1 January 2017 and 2032 would be €130,700 and €86,700, respectively.

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
					diseases in a real context of a society has not yet been done.						
González Álvarez 2013[76]	Spain; 2012	Budget-impact analysis (health care perspective; only direct costs)	A BIM was developed to estimate the economic impact that would have widening the usual administration intervals of ADA and ETN. Scenario A: ADA, 40 mg every 2 weeks and ETN, 50 mg weekly. Scenario B: ADA,	2 years (2011-2013)	NR	ETN (n=26): average age: 60.1 (SD: 12.9); AS (n=6) ADA (n=45); average age: 55.8 (SD: 12.7); AS (n=19)	NA	ETN ADA	Monthly mean cost[a]: AS = €24,262	NA	NA

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			40 mg every 3 weeks, and ETN, 50 mg every 2 weeks.								
Ji 2014[77]	Spain; NR	CEA using a cohort Markov model; uncertainty was addressed via scenario, univariate, and probabilistic sensitivity analyses.	To evaluate, from the Spanish NHS perspective, the cost-effectiveness of ADA vs. conventional care in the licensed population when used according to existing	40 years	Model was primarily based on the ABILITY-1 trial data and supplemented with literature	Used patients from the ABILITY-1 trial.	Patients were categorised into ASAS 40 responders and non-responders at week 12. Over time, responders were further categorised among those who stayed on therapy and those who discontinued, based on modelled	ADA (40 mg every other week)	€146,463 The use of ADA resulted in higher drug (€16,865), initiation (€439), and monitoring costs (€972) and lower axSpA-related costs (-€6,080 and €128,187 vs. €134,267).	10.34 QALYs	ADA resulted in an ICER of €22,787 per QALY In scenario analyses, the ICER ranged from €17,878 per QALY to €53,924 per QALY, depending on assumptions. In probabilistic

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			international treatment guidelines. ADA was recently been approved by the European Medicines Agency for the treatment of adults with severe axSpA.				discontinuation curves.	Conventional care	€134,267	9.80 QALYs	sensitivity analyses, the ICER was ≤ €31,450 in 95% of runs.
Kobelt 2008[78]	Spain 2005	The model combined a decision tree representing the clinical trial period with a Markov model representing	To estimate the cost-effectiveness of treating AS with INF in Spain for up to 40	40 years	This study was an adaptation of earlier cost-effectiveness models based on a double-blind trial to Span.	The main analysis for effectiveness used a double-blind trial that included 70 patients with confirmed AS and active disease	In the models, only responders, defined as patients achieving an improvement in BASDAI of > 50% or > 2 points, were		Incremental cost (€)	Incremental effect	Incremental cost per QALY (€)
								Double-blind trial			
								50% of natural disease progression while on treatment			
								All costs included	–198 637	2.255	Dominant
								Health care costs only	50,780	2.255	22,520
								No progression while on treatment			

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
		the open-extension periods and beyond.	years.			(BASDAI ≥ 4). The second analysis for effectiveness used an open, multicentre clinical trial in Spain that included 42 patients with refractory spondylo-arthropathies. For cost and utility, a cross-sectional burden-of-illness study in 601 patients in Spain was used. The mean age in the sample was 48 years; 80% were male and 91% were less than 65 years old. The mean age of patients	allowed to continue treatment. Non-responders continued on standard treatment.	All costs included	–248,092	2.959	Dominant
								Health care costs only	44,836	2.959	15,152
								No effect of treatment on progression			
								All costs included	–137,142	1.824	Dominant
								Health care costs only	57,859	1.824	31,721
									Incremental cost (€)	Incremental effect	Increment-al cost per QALY (€)
								Spanish trial			
								50% of natural disease progression while on treatment			
								All costs included	–634,731	2.705	Dominant
								Health care costs only	23,982	2.705	8,866
								No progression while on treatment			
								All costs included	–710,659	3.077	Dominant
								Health care costs only	16,331	3.077	5,307
								No effect of treatment on progression			
								All costs included	–541,979	2.429	Dominant

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
						in the decision tree was 40.		Health care costs only	33,177	2.429	13,659
Scaccabarozzi 2014[79]	Brazil; NR	CMA (published literature shows no difference in safety and efficacy between the anti-TNFαs).	To compare the treatment cost of TNFα inhibitor biologics indicated simultaneously for the treatment of RA, AS, and PsA from the Brazilian public health care system perspective.	NR	A CMA was performed as presented by Morais et al. at ISPOR 18th Annual Meeting (reference not given).	Patients with RA, AS, or PsA	NR	ADA, ETN, INF, and GOL	GOL had the lowest cost of treatment across the biologics in all indications, at R$17,703 per patient per year. GOL treatment cost remained unchanged across indications or years of treatment, as loading dose is not required. For AS and PsA treatments, due to	NR	NR

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
									higher dosing of INF, the average cost per patient is R$24,418, similar to the cost with ADA and ETN. Using deterministic sensitivity analysis, cost of treatment with INF for AS and PsA can reach up to R$30,522, assuming a patient weight of 100 kg.		

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
Zavada 2014[80]	Czech Republic NR	Type of CUA of dosing approaches, assuming other direct and indirect costs were equal in both groups.	To critically assess the technique of tailoring reduced doses of anti-TNFαs that many physicians are prescribing in the light of clinical experience and funding restrictions. Tailored	1 year	Time frame chosen for practical reasons.	The authors used propensity score methodology to identify 2 cohorts of patients matched for relevant baseline characteristics that were treated with either standard or reduced doses of TNFα inhibitors. Standard TNFα inhibitor dosing group included 83 patients (ETN=31, ADA=19,	NA		Mean (SD)	Mean (SD) QALY, area under the curve	Mean (95% CI)[b]
								Standard TNFα inhibitor dosing	€12,000 (NR) Mean net monetary benefit (95% CI) of standard-dosing group was –€3,354 (–€4,989 to –€1,666)	0.78 (0.12)	Incremental cost: Mean (95% CI)= €4,214 (€3,701 to €4,707) Incremental effective-ness: Mean (95% CI) =0.020 (−0.016 to 0.057) ICER (95% CI undefined)= €211,426

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			reduced dosing is compared with standard TNFα inhibitor dosing.			INF=33) (mean age=39.5 years) patients. The reduced-dosing group included 53 (ETN=25, ADA=11, INF=17) (mean age=41.0 years) patients.		Reduced TNFα inhibitor dosing	€7,784 (2,254)	0.76 (0.14)	Reference
Kobelt 2006[81]	Canada; 2004	A Markov model. The model combines patient-level data from the 12 week double-blind period of a clinical trial and a Markov model with annual cycles, using group data from the open extension of the trial.	Previous economic models have been conducted in the UK with INF, due to high costs but increased efficiency. This model assessed the cost-effectiveness of INF in the treatment	30 years	A previously published disease model based on functional capacity and disease activity was adapted to the Canadian setting.	The effectiveness data were from a clinical trial with open extension in 70 patients with confirmed AS and active disease who were randomised to 5 mg/kg INF every 6 weeks, with a loading dose at 2 weeks, or to placebo. After the double-blind phase, all patients were	Disease progression in the model was expressed with changes in BASFI. During the double-blind period, BASDAI and BASFI scores for each period between the measurements in the trial (baseline, 6, and 12 weeks) were assigned to patients	Cost per QALY gained over 30 years, using the treatment regimen of the double-blind trial (5 mg/kg of INF every 6 weeks vs. placebo)			
								INF	Incremental cost (Can$)	QALY gain	ICER (Can$/ QALY)
								No progression while on treatment			
								All costs included	110,822	2.96	37,491
								All direct costs	119,416	2.96	40,399
								Health care costs only	135,283	2.96	45,767
								50% progression while on treatment			
								All costs included	116,250	2.58	45,121
								All direct costs	123,599	2.58	47,973
								Health care costs only	138,441	2.58	53,733
								Same progression in both groups			
								All costs included	122,993	2.27	54,137
								All direct costs	128,882	2.27	56,729

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			of AS in Canada over the long term, with both international and Canadian treatment regimens.			offered treatment with INF. For resource utilisation and cost data, 545 completed questionnaires were included and involved community and academic rheumatologists in the city of Edmonton.	continuing treatment. At the end of the double-blind period, patients who did not respond adequately to treatment discontinued treatment. For the extension period, patients were entered in the Markov model in 1 of 3 states: "on treatment", "off treatment", and "dead". Patients withdrawing from treatment during the extension reverted to the	Health care costs only	142,641	2.27	62,785
								Treatment of all patients beyond 12 weeks			
								All costs included	164,786	1.95	84,642
								All direct costs	169,819	1.95	87,228
								Health care costs only	187,374	1.95	96,245
								Cost per QALY gained over 30 years, using the treatment regimen of the Canadian trial (75% at 3 mg/kg every 8 weeks, 15% at 3 mg/kg every 6 weeks, and 10% at 5 mg/kg every 8 weeks)			
								No progression while on treatment			
								All costs included	30,341	2.96	10,264
								All direct costs	38,935	2.96	13,172
								Health care costs only	54,802	2.96	18,540
								50% progression while on treatment			
								All costs included	35,769	2.58	13,883
								All direct costs	43,118	2.58	16,735
								Health care costs only	57,960	2.58	22,496
								Same progression in both groups			
								All costs included	42,512	2.27	18,712
								All direct costs	48,401	2.27	21,304

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
							mean scores of the no-treatment group over a period of 12 weeks.	Health care costs only	62,160	2.27	27,360
Fautrel 2010a[82]	France, 2006	Cost-effectiveness analysis	To determine the ICERs of 2 therapeutic regimens of INF for AS.	1-year	NR	230 patients with active AS who were participating in a RCT comparing two INF (5 mg/kg) infusion modalities, every 6 weeks and on demand.	NA		Mean (95% CI) Year 1 Total Costs	Mean Effectiveness (95% CI)	Base-case scenario, ICER of every 6 weeks to on demand (95% CI)
								INF every 6 weeks INF on demand	€22,388 (€21,242-€23,863)	Utility gain=0.30 (0.25-0.35) QALYs	€50,760/ QALY (€17,963-€216,452)
										ASAS20 response at year 1=75.9% (67.3%-82.7%)	€15,841/ ASAS20 response (€6,925-€37,910)
										ASAS partial remission at year 1=27.6% (20.3%-36.3%)	€23,296/ ASAS partial response (€9,580-€61,000)
									€17,596 (€16,114-	Utility gain=0.20	-

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
									€19,032)	(0.16-0.25) QALYs	
										ASAS20 response at year 1=45.6% (36.8%-54.8%)	-
										ASAS partial remission at year 1=7.0% (3.6%-13.2%)	-
Neilson 2010a[83]	Germany; 2007	A similar methodology to that employed in the UK economic model of ETN in severe AS was used to simulate the health care costs and benefits of 1,000 hypothetical patients.	To estimate the cost-effectiveness of ETN plus usual care (including NSAIDs) compared with usual care alone (including NSAIDs) in patients with severe AS in Germany.	25-year	Adaptation of existing model, previously applied to the UK setting (Ara et al.2007)	AS patients enrolled in a European RCT with an average age of 39.5, 41.7 and 39.7 in placebo (n=51), ETN 1x 50 mg (n=155) and ETN 2 × 25 mg (n=150) respectively.	The current model follows the BSR guidelines. The model assumed that all patients have tried and failed to respond to at least 2 consecutive NSAIDs and had a BASDAI measurement ≥ 40 before entering the model. To		Total discounted costs (25 years)	Total discounted QALYs (25 years)	Incremental cost per QALY
								ETN	SHI perspective: €148,142,209 Societal perspective: €291,300,065	6882	SHI perspective: €54,815/ QALY Societal perspective: €22,147/ QALY
								Comparator	SHI perspective: €67,314,541 Societal perspective: €258,642,475	5408	NA

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
							continue on treatment with ETN, patients must respond to treatment. On withdrawal of treatment, it was assumed that patients continued to receive NSAIDs.				
Codreanu 2014[84] (abstract only)	Romania; 2013	Cost-utility models, using a Markov structure, were developed for each condition.	To evaluate the cost-effectiveness of CZP vs. other s.c. anti-TNFαs currently licensed and reimbursed in Romania (ETN and ADA) in the	Lifetime	Followed the EULAR, ASAS, and NICE guidelines.	Adult patients with active RA, axSpA (AS and nr-axSpA) and PsA. No other details were reported.	NR	CZP, ETN, and ADA	CZP dominated ADA and ETN; total costs were lower by RON48,499.73 and RON8,350.28 than for ADA and ETN, respectively	CZP dominated ADA and ETN; QALYs gains were 0.098 and 0.021 vs. ADA and ETN, respectively	NR

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
			treatment of adult patients with active RA, axSpA (AS and nr-axSpA) and PsA.								
Ivakhnenko 2013[85]	Russia; NR	CMA (indirect comparison demonstrated that compared drugs have similar efficacy and safety)	To compare the cost for 1-year treatment with GOL, ADA, and INF in doses according to the approved recommendations.	2 years	NR	Number of patients to be treated with TNFα inhibitors was calculated based on state statistical data and data on the percentages of patients who did not respond to therapy with synthetic DMARDs and first-line biologic DMARDs from clinical trials.	Assumed that INF is used in the first-line therapy during 1 year and ADA or GOL in the second-line therapy during the second year.	INF	1-year treatment costs = €24,319 for AS	NR	NR
								GOL	€16,544 per year	NR	NR
								ADA	€24,243 per year	NR	NR

Author (Year)	Country; Cost-year	Analysis/ Model Type	Study purpose	Analysis Time Frame	Rationale for Design/ Time Frame	Patient Population (Average Age)	Study design	Interventions/ Comparators	Cost	Outcome	ICER
ADA = Adalimumab 40 mg; AS = Ankylosing spondylitis; ASAS = Assessment of Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BIM = budget impact model; CEA = cost effectiveness analysis; CI = confidence interval; CMA = cost minimisation analysis; CUA = cost-utility analysis; CZP = Certolizumab pegol; ETN = Etanercept; EULAR = European League Against Rheumatism; GOL = Golimumab; HTA = Health Technology Assessment; ICER = Incremental cost-effectiveness Ratio; INF = Infliximab; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; kg = kilogram; mg = milligram; NA = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; NSAID = Non-steroidal anti-inflammatory drug; PsA = Psoriatic arthritis; QALY = Quality-adjusted Life Year; RA = rheumatoid arthritis; SD = standard deviation; SHI = Statutory health insurance; TNF = Tumour Necrosis Factor; UK = United Kingdom										

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Secukinumab for treating ankylosing spondylitis after inadequate response to non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors

You are asked to check the ERG report from **Kleijnen Systematic Reviews (KSR)** to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 27th April 2016** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccurate descriptions of MEASURE 1 and MEASURE 2 study numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 13: "MEASURE1….which recruited 371 adults…'' and "MEASURE2….which recruited 222 adults…"	Please amend to: "MEASURE1….which ***randomised*** 371 adults''' and "MEASURE 2….which ***randomised*** 222 adults'''	Correction to study description.	Changes were made accordingly (page 13).

Issue 2 Inaccurate references to data requested at clarification and not provided

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 17: "In spite of an ERG request, the company did not provide comparable 12 week effectiveness data for all outcomes specified in the scope." Page 22: "In its clarification letter, the ERG requested that the company provide data separately for all outcomes specified in the scope (after 12 and 16 weeks), for both of the MEASURE trials." Page 64: "The company did not provide 12 week data in a format comparable to the 16 week data in the CS…for all outcomes specified in the scope, as requested."	Please amend as follows: Page 17: "the company did not provide comparable 12 week effectiveness data for all outcomes specified in the scope" Page 22: Delete sentence Page 64: "The company did not provide 12 week data in a format comparable to the 16 week data in the CS…for all outcomes specified in the scope"	The only 12 week data requests included in the clarification questions referred to sub-groups (defined by mild, moderate and severe at A1, and by response to other treatments at A8 and A9). Both of these were challenging to provide; for A1 due to reasons described in our response, and for A8 and A9 due to extensive post-hoc data analysis requirements. Had a request been made for 12 week data in the full cohorts it would have been simple to provide, but no such request was received. In addition please note 12 week MEASURE 1 data is publicly available in the supplementary appendix of the MEASURE 1 & 2 publication (Baeten D. et al. 2015)[1]	Changes were made accordingly (pages 17, 22 and 64)

Issue 3 Inaccurate description of MEASURE 1 dosing

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 19: "In MEASURE 1, secukinumab was administered intravenously" Page 64: "The ERG note that MEASURE 1 is based on intravenous administration of secukinumab…" Page 104: "in MEASURE 1 secukinumab was administered as an intravenous therapy different from its SmPC" Page 113: "In the MEASURE 1 study secukinumab was administered intravenously"	Page 19: "In MEASURE 1, ***loading doses of*** secukinumab were administered intravenously" Page 64: "The ERG note that MEASURE 1 ***loading doses*** are based on intravenous administration of secukinumab…" Page 104: "in MEASURE 1 ***loading doses of*** secukinumab were administered as an intravenous therapy different from its SmPC" Page 113: "In the MEASURE 1 study ***loading doses of*** secukinumab were administered intravenously"	As currently written, the text is misleading as it suggests that secukinumab was administered intravenously throughout the MEASURE 1 study. This is not accurate since only three loading doses were administered intravenously; maintenance doses were administered subcutaneously as per the licensed posology.	Changes were made accordingly (pages 19, 64, 104 and 113)

Issue 4 Misleading description of systematic review methods

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 17: "Firstly only one reviewer was used in the process" Page 22: "Only one reviewer, rather than a minimum of two, was used in data extraction and quality assessment	Whilst we acknowledge that the description supplied in the Novartis submission lacked clarity, we would like to re-assure the ERG that their interpretation is	The Novartis submission stated: "Data for included articles were extracted from full-text versions of studies, when these were available, by one reviewer. Abstracts or posters were only used for extraction when these were the terminal source document". The full SLR protocol stated "Data will be extracted from full-text versions of studies, where available, by one reviewer. After data	Not a factual error

processes” Page 38: “Only one reviewer was used in the process”	factually inaccurate.	extraction, RCTs will be evaluated for potential inclusion in the meta-analysis; data will be quality-checked by the statistician responsible for the meta-analysis.” Therefore, data extraction for all included records was quality checked by a team member not involved in the data extraction. We apologise that this was not clear in the Novartis submission.	

Issue 5 Inaccurate statement regarding comparability of clinical trial populations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 22: “Uncertainty surrounds the severity of patients between trials and within trials, which brings into question their comparability.” Page 19: “Some of the biologic comparators of secukinumab were licensed only for severely active AS, which may potentially create a bias if the effectiveness evidences of the biologics licensed for severely active AS reflect their licensed population.”	Please remove these sentences.	Table 201 of the Novartis submission indicates that the baseline disease activity of the populations included in all studies within the network meta-analyses was BASDAI ≥ 4 / 40 (when measured on scales from 0-10 and 0-100 respectively). This is aligned to the inclusion criteria for MEASURE 1 and MEASURE 2. Therefore the comparability of the included populations in terms of disease activity, is not uncertain.	Page 19, changed sentence to “The population of the cost effectiveness analysis seems to be broadly in line with the scope. Some of the biologic comparators of secukinumab were licensed only for severely active AS, which may potentially create a bias if their effectiveness is based on populations which include non severely active AS patients.” Not a factual error on page 22

Issue 6 Misleading reference to specification of relevant comparator for the biologic experienced population

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 22: "Lack of clarity on severity also means that there is a concern that switching between TNF inhibitors may have been inappropriately excluded from part of "established clinical management without secukinumab". Page 31: "One concern is that switching between TNF inhibitors has not been considered as part of *"established clinical management without secukinumab" …*difficult to assess the impact of omitting switching".	Please remove these sentences.	Switching between TNF inhibitors was not excluded from "established clinical management without secukinumab". Table 1 of the Novartis submission indicates that TNF-α inhibitors were considered relevant comparators for the biologic experienced population. The lack of robust randomised clinical data to support use of the TNFα inhibitors in this population, as acknowledged by the York Assessment Group, and supported by the systematic literature reviews presented in Section 4.1 of the Novartis submission, were the reason why comparisons versus TNFα inhibitors were presented as exploratory rather than base cases analyses.	Removed sentences on pages 22 and 31 as suggested.

Issue 7 Clarification on description of abstracts and posters as data sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 17: "secondly abstracts or posters were only used when	"abstracts or posters were only used when no full text paper was	The Novartis submission stated: "Data for included articles were extracted from full-text versions of studies, when these were available, by one reviewer. Abstracts or	Not a factual error

these were the terminal source" Page 22: "abstracts or posters were only used when no full text paper was available. Therefore, there is a chance that relevant data might have been missed or extracted incorrectly."	available." (please delete subsequent sentence).	posters were only used for extraction when these were the terminal source document". The process followed was to start by extracting from the primary publication (generally a full-text publication). After extracting the primary publication, secondary publications were checked to see if they reported any additional endpoints/baseline data. The secondary publications could be either abstracts or full-texts. Sometimes abstracts present additional safety data or PRO data which was not available in the primary publication, or sometimes they present follow-up data at later time points. However, for outcomes reported in both an abstract and a full-text, data from the full-text was used as it was assumed to be the final, peer-reviewed data.	

Issue 8 Misleading reference to TA383 Equality impact assessment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 22 and page 31: "The ERG notes that, according to the equality impact assessment for TA 383, "people with severe disease are currently not allowed to switch to second TNF-alpha inhibitor if their disease does not respond to their first TNF-alpha inhibitor". However, the ERG is not aware that this guidance applies to patients with non-severe forms of the	Please remove these sentences.	The Equality Impact Assessment for TA383 mentions that "People with severe disease are currently not allowed to switch to second TNF-alpha inhibitor if their disease does not respond to their first TNF-alpha inhibitor" is an issue that was raised ***during the appraisal scoping process***. The ERG presents this as if it is ***guidance***, which is factually incorrect. The final guidance states "Treatment with another tumour necrosis factor (TNF)–alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response." The final guidance makes no	Pages 22 and 31, changed text to: "The ERG notes that the Equality Impact Assessment for TA383 mentions, as part of the appraisal scoping process, that *"people with severe disease are currently not allowed to switch to second TNF-alpha inhibitor if their disease does not respond to their first TNF-alpha inhibitor"*. However, the ERG is not aware that this applies to patients with non-severe forms of the condition."

condition."		reference to disease activity.	

Issue 9 Inaccurate description of the cause of implausible comparator efficacy estimates

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 22: "This approach may overlook the correlations between the treatment effectiveness parameters and generates implausible outcomes such as having a BASDAI decline from the baseline higher than the baseline itself."	"This approach may overlook the correlations between the treatment effectiveness parameters and ***may contribute to*** implausible outcomes such as having a BASDAI decline from the baseline higher than the baseline itself."	The main factor leading to implausible changes from baseline for infliximab, is the need to make assumptions about the ratio of responder to non-responder changes from baseline, as outlined in response to clarification question B6. The lack of correlation between efficacy inputs may contribute to this result, but is not the sole causal factor.	Changes were made accordingly (page 22)

Issue 10 Inaccurate presentation of manufacturer's response to clarification questions

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 33: "In response to a clarification request, the company stated that the databases were searched from inception to the search dates above. No specific database spans were provided after clarification." Page 34: "The database hosts for each database and the date search conducted were listed, however a specific date span for each database was not provided. As with the clinical effectiveness SLR, no specific	Amend to read "In response to a clarification request, the company stated that the databases were searched from inception to the search dates above; database inception dates for PubMed, EMBASE and BIOSIS were provided."	Database inception dates were provided for PubMed, EMBASE and BIOSIS in response to question A4 of the clarification questions (these dates are noted at the bottom of the response). The databases within the Cochrane Library do not have inception date as such, and therefore this information was not provided.	Changes were made accordingly (pages 33 and 34).

database spans were provided after clarification."			

Issue 11 Incorrect PAS price

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 32: The PAS price is quoted incorrectly	The PAS price should be corrected	Correction	Not a factual error (see page 28 of the CS)

Issue 12 ERG preferred base case NMA presented as a matter of fact rather than judgement

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 80: "The argument that data were taken from the primary endpoint of each study is not a sound justification for pooling data across time points" Page 113: "It is essential that all studies have the same time point (12 weeks) for the response assessment"	Page 80: "Although this is an approach that has been employed in previous NICE appraisals, the ERG prefers the NMA scenarios employing 12 week secukinumab analyses, in order to keep the measurement time point consistent across comparators." Page 113: "The	A range of time points has been used frequently in previous NICE appraisals of rheumatic diseases such as ankylosing spondylitis and psoriatic arthritis, including; • 10-16 weeks in the MTA of TNFα inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (TA383; see page 25, Table 7 and Table 9 of the Assessment Group report) • 12-16 weeks in the STA of ustekinumab for psoriatic arthritis (TA340; see page 62 of the ERG report available here: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0003/98094/ERGReport-12-58-01.pdf) • 12-14 weeks in the MTA of adalimumab, etanercept and infliximab for psoriatic arthritis (TA199; see Assessment team assumptions in Table 5.20, page 74 of the Assessment Group report) Furthermore, the MEASURE 1 and MEASURE 2 studies were powered to detect differences between secukinumab and placebo at week 16, not at week 12.	Not a factual error.

	ERG considers it important that all studies have the same time point (12 weeks) for the response assessment"		

Issue 13 Inaccurate summary of the impact of using 12 week rather than 16 week data for secukinumab in MTC

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pages 17 & 86: "The sensitivity analysis reported in the CS which limited analysis to only data reported at 12 weeks showed reduced effectiveness for secukinumab across all outcomes."	The sensitivity analysis reported in the CS which limited analysis to only data reported at 12 weeks showed reduced effectiveness for secukinumab ***for most*** outcomes.	Table 4.23 indicates that in the biologic naïve population ASAS20 and ASAS40 outcomes improve in the sensitivity analysis versus the base case. Table 4.24 indicates that in the whole population BASDAI change from baseline improves in the sensitivity analysis versus the base case. Therefore the statement as currently written is factually inaccurate.	Changes were made accordingly (pages 17 and 86). Furthermore, two typos (double instead of single minus signs) were corrected in table 4.24 (page 84).

Issue 14 Incorrect representation of Novartis submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 60: "Results at 16 weeks were not provided for MEASURE 2 but were available for MEASURE 1." Page 64: "The ERG was not able to assess significant adverse event profile for	Removal of sentence and addition of table detailing deaths, other serious or clinically significant adverse events or related discontinuations – up to week 16 (Safety set) – MEASURE 2.	This data were included in Table 60 of the Novartis submission.	Changes were made accordingly: Text on pages 59 and 61, new Table 4.18, numbering of subsequent tables as well as table of tables

MEASURE 2 and week 16 because results were not available."			updated.

Issue 15 Misleading representation of the Novartis submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 64: "The ERG also notes that evidence from MEASURE 1 and MEASURE 2 is favourable towards secukinumab in relation to placebo for pain and health related quality of life (although this is not clearly stated by the company)."	Removal of the clause "although this is not clearly stated by the company" in relation to the results of health related quality of life.	The company submission clearly states the following: "The AS quality of life measure, ASQoL, demonstrated that the secukinumab 150 mg arm experienced significant improvements in quality of life compared to placebo controls in both trials" (followed by presentation of the relevant data), on page 24 of the Novartis submission. With similar text included on page 42 and page 92 of the Novartis submission.	The statement on page 64 now reads: "The ERG also notes that evidence from MEASURE 1 and MEASURE 2 [redacted]".

Issue 16 Misleading references to "mapping" algorithms

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Throughout the report there are several references to "utility mapping" / "mapping algorithm" (e.g. page 18, 19, 94, 95, 136, 183). We consider the term mapping to be misleading in this context and would suggest the descriptions refer instead to	Change text to refer to utility regression analysis / models.	The term "mapping" is understood to "development and use of an algorithm (or algorithms) to predict health-state utility values using data on other indicators or measures of health".[2] For example, mapping can be used to estimate generic health outcomes from condition-specific measures. As stated in Section 5.4.2 of the Novartis	Not a factual error. Utility mapping terms were used in the CS (page 28) and the definition from DSU describe the approach taken by the company.

regression analysis. On page 95 the phrase "Even though HRQoL was measured in the trial, in the model a mapping algorithm is used." Suggests a non-standard approach has been used.		submission, "Given that the MEASURE 1 and 2 trials collected the EQ-5D health utility instrument, no mapping of other health-related quality of life measures was considered necessary in order to derive utility values from this trial to inform the model." Standard linear regression analysis, using the same covariates as other published utility models in ankylosing spondylitis, was carried out on the MEASURE 1 and MEASURE 2 trial data, to estimate utilities as a function of BASDAI, BASFI, age and gender.	

Issue 17 Error in description of economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 92: "In the Markov model four health states are distinguished"	Change to "In the Markov model ***three*** health states are distinguished"	Correct reporting of the model structure.	Changes were made accordingly (page 92)

Issue 18 Unclear text

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 98: "In this exploratory analysis, for secukinumab or other biologics, when a patient did not respond to the first line treatment at week 12 or when s/he withdrew from the first line treatment given in the maintenance therapy state of the	"In this exploratory analysis, for secukinumab or other biologics, when a patient did not respond to the first line treatment at week 12 or when s/he withdrew from the first line treatment given in the maintenance therapy state of the Markov model, that patient would enter another decision tree model with the same	As it currently stands the text suggests that only 75% of patients enter the decision-tree for second line therapy. In fact all patients enter the decision tree, within which there is a 75% probability of receiving a second line biologic and a 25% probability of receiving conventional care.	Not a factual error

Markov model, that patient would enter another decision tree model with the same structure as depicted in Figure 5.1 with a probability of 75% (whilst moving to the conventional care state with 25% probability).”	structure as depicted in Figure 5.1 with a probability of 75% ***of receiving a second line biologic*** (whilst moving to the conventional care state with 25% probability).		
Page 114: “In the Excel model provided, only the results for modelling approach A3 …, A4 … and A5…were incorporated”	“In the Excel model provided, the results for modelling approach A3 …, A4 … and A5…were incorporated”	As discussed in later paragraphs, we also provided an attempt at B4 and C4. Therefore the word “only” is misleading.	Changes were made accordingly (page 114)
Page 128: “In Table 5.22, it can be seen that the change from baseline given BASDAI 50 response estimates [redacted] for BASDAI and from [redacted] for BASFI”	“In Table 5.22, ***for secukinumab*** it can be seen that the change from baseline given BASDAI 50 response estimates range from [redacted] for BASDAI and from [redacted] for BASFI”	The current text is not clear that these are the secukinumab estimates.	Changes were made accordingly (page 128)
Page 170: “It was discussed that this underestimation was due to the model assumption which forced non-responders to discontinue biologic treatment, whereas within clinical trials non-responders received another biologic treatment.”	“It was discussed that this underestimation was due to the model assumption which forced non-responders to discontinue biologic treatment, whereas within clinical trials non-responders ***continued*** biologic treatment.”	The text as it currently stands suggests that non-responders are switching onto alternative biologic treatments within clinical trials, which is not the case. Clinical trials do not employ stopping rules; both responders and non-responders are permitted to continue biologic treatment, in line with product licenses.	Changes were made accordingly (page 170)

Issue 19 Misunderstanding of the Appraisal Committee's concerns in TA383

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 99: "…the baseline BASDAI and BASFI scores of responders and non-responders were different. In the final appraisal document for TA383, the committee expressed concerns over this assumption, mentioning that this difference may imply that patients with more severe disease (higher baseline values) may not benefit as much from the biologics as patients with less severe disease. Page 183: "This might imply that patients at a better condition (with lower BASDAI/BASFI scores) would benefit more from the treatment than the	Delete or re-phrase as follows: Page 99: "…the baseline BASDAI and BASFI scores of responders and non-responders were different. In the final appraisal document for TA383, the committee expressed concerns over this assumption, mentioning that ***the differences predicted by the York Assessment Group's extended synthesis model*** may imply that patients with more severe disease (higher baseline values) may not benefit as much from the biologics as patients with	Paragraph 4.61 of TA383 states: "The Committee heard that in the Assessment Group's model, 'responders' had lower baseline BASDAI and BASFI scores compared with 'non-responders' (a difference that was reduced in scenario 2). The Committee noted that this assumption implied that people with more severe disease did not benefit as much from TNF-alpha inhibitors as people with less severe disease, because someone with more severe disease (higher baseline scores) must have larger absolute improvements than someone with less severe disease to achieve a BASDAI 50 response." The TA383 Assessment Group report illustrates that a difference in baseline BASDAI and BASFI scores between responders and non-responders is to be expected; "While it is natural to consider that conditional change in BASDAI scores differ between respondents and non-respondents, differences in the baseline of respondents and non-respondents may be less intuitive. These are, however, natural." However, a disparity between responder / non-responder baselines observed in patient level analysis of clinical trials versus those predicted by the extended synthesis approach, was acknowledged by the Assessment Group: "there appeared a disparity in the magnitude of the difference in the conditional baseline scores estimated from the extended synthesis model compared to the differences reported by those manufacturers who provided additional data on request. Specifically, the difference between responders and non-responders appeared higher in our extended synthesis compared to the direct data reported by manufacturers." Comparison of Tables 77 and 78 in the Assessment Group report for TA383 reveals that the extended synthesis approach resulted in a substantially greater difference between responder and non-responder	Not a factual error TA383 is about the assumptions and implications from the York Assessment Group's model which were followed by the company

patients at a worse condition (with higher BASDAI/BASFI scores). This implication was criticised by the appraisal committee of the NICE TA383"

less severe disease.

Page 183: "This might imply that patients at a better condition (with lower BASDAI/BASFI scores) would benefit more from the treatment than the patients at a worse condition (with higher BASDAI/BASFI scores). This implication ***of the York Assessment Group's extended synthesis model*** was criticised by the appraisal committee of the NICE TA383"

baselines than was observed in either the available adalimumab or golimumab trial data. For ease, a summary of the comparisons is provided in Tables 1 & 2 below.

Table 1: Comparison of conditional baseline BASDAI scores predicted by the TA383 Assessment Group extended synthesis model versus those observed in trials

Baseline BASDAI scores	AG synthesis model	Adalimumab IPD	Golimumab IPD
BASDAI50 responders: control group	3.83	6.31	6.52
BASDAI50 non-responders: control group	6.31	6.37	6.63
BASDAI50 responders: treatment group	4.76	6.14	6.25
BASDAI50 non-responders: treatment group	7.03	6.35	6.69

Table 2: Comparison of conditional baseline BASFI scores predicted by the TA383 Assessment Group extended synthesis model versus those observed in trials

Baseline BASFI scores	AG synthesis model	Adalimumab IPD	Golimumab IPD
BASDAI50 responders: control group	3.42	4.50	3.56
BASDAI50 non-responders: control group	5.43	5.91	5.39

		BASDAI50 responders: treatment group	4.17	4.53	4.45	
		BASDAI50 non-responders: treatment group	6.02	5.78	5.48	
		In scenario 2, "the difference in the conditional baselines was based on a pooled estimate of the differences across the trials provided by manufacturers rather than those estimated by the extended synthesis model". Since scenario 2 is mentioned as reducing the difference that led to the Committee's concern, we believe their concern lay with use of the Assessment Group's extended synthesis model to inform baseline BASDAI/BASFI scores of responders / non-responders, rather than with use of individual patient level data from relevant trials.				

Issue 20 Inaccurate description of ASSERT primary endpoint

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 106: "e.g. for the ASSERT trial, week 12 BASDAI 50 data are used because the primary endpoint of ASSERT trial was 18 weeks"	e.g. for the ASSERT trial, week 12 BASDAI 50 data are used because the primary endpoint of ASSERT trial was 24 weeks	From the van der Heijde et al. 2005 abstract: "The primary end point in this study was the proportion of patients with a 20% improvement response according to the ASAS International Working Group criteria (ASAS20 responders) at week 24."[3]	Changes were made accordingly (page 106)

Issue 21 Inconsistency between Table 5.6 and Table 5.8

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 5.8, Page 108	Table 5.8 needs to change to say	Table 5.6 labels MTC #5 as being at Week	Changes were made

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	Week 12-16 in rows 10 and 11 for MTC #5	12-16 (correctly), whereas Table 5.8 suggests MTC #5 was conducted at the week 12 timepoint only and therefore needs to be corrected	accordingly (Table 5.8, page 108)

Issue 22 Lack of confidentiality highlighting

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 63; mSASSS change from baseline in the placebo-secukinumab 150mg arm	"…and [redacted] in the placebo-secukinumab 150mg arm."	These figures are not publically available and have been marked as academic in confidence in the Novartis submission.	Changes were made accordingly (page 63)
Page 107 & 112; values of the predefined conversion constant	Page 107: [redacted] for conventional care and [redacted] for all other biologic treatments Page 112: [redacted] for conventional care and [redacted] for secukinumab and other biologics	These figures are not publically available and have been marked as academic in confidence in the Novartis response to clarification questions and elsewhere in the ERG report.	Changes were made accordingly (pages 107 and 112)

Issue 23 Inaccurate description of second-line conditional baseline BASFI scores

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 117: "The conditional baseline BASDAI and BASFI scores applied in the post-induction states representing	"The conditional baseline BASDAI scores applied in the post-induction states representing second line biologic	The text is correct in relation to BASDAI, but incorrect in relation to BASFI. Second line conditional baseline BASFI scores are based on the median cycle of first line	Changes were made accordingly (page 117)

second line biologic post-induction period were assumed to be the same conditional baseline scores of the first line."	post-induction period were assumed to be the same conditional baseline scores of the first line."	discontinuation (as discussed in the subsequent paragraph of the ERG report). It is therefore incorrect to state that they were the same as the first line conditional baseline scores.	

Issue 24 Unclear description of comparator short-term BASDAI and BASFI data source

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 118: "For the other comparators (etanercept, infliximab, certolizumab pegol and conventional care), the average ratio of change from baseline was derived from the other comparators and used."	"For other comparators (etanercept, infliximab, certolizumab pegol and conventional care), the average ratio of change from baseline was derived from secukinumab and the other comparators and used."	Referring to the average ratio being derived from "other comparators" only is not clear that this also included secukinumab data.	Text was changed to "For the other comparators (etanercept, infliximab, certolizumab pegol and conventional care), the average ratio of change from baseline was derived from the other biologics and used" (page 118).

Issue 25 Clarification on data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 127	The ERG report states that inputs used in the MTCs from Huang *et al.* were not provided. This statement should be removed.	Although not provided as part of the clarification response in which the biologic naïve networks were revised to include Huang *et al.*, the data inputs from the Huang *et al.* study were provided in the appendices of the original company submission (Table 202). In this original submission the Huang *et al.* inputs were labelled as being from the whole population but have since been clarified to be from the biologic naïve population.	Not a factual error Updated NMA input tables for the newly conducted MTC were not provided in the response to the clarification letter document.

Issue 26 Errors in reporting of conditional changes from baseline

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 128: Reporting error: "adalimumab from [redacted] for BASDAI and [redacted] for BASFI" Data not marked AIC: "from [redacted] (BASDAI) and [redacted] (BASFI) for secukinumab" Reporting error: [redacted] (BASDAI) and [redacted] (BASFI) for certolizumab-pegol	"adalimumab from [redacted] for BASDAI and [redacted] for BASFI" "from [redacted] (BASDAI) and [redacted] (BASFI) for secukinumab" "[redacted] (BASDAI) and [redacted] (BASFI) for certolizumab-pegol"	Correct reporting of MTC results. Correct marking of academic in confidence data. Correct reporting of MTC results	Changes were made accordingly (page 128)

Issue 27 Different value presented as an error, when it is due to rounding in ERG calculations

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 128: "In the economic model, the conversion factor for BASFI change from baseline for non-responders is slightly different from what had been reported (i.e. 1.145 is used in the model instead of 1.138 reported in Table 5.24)"	Remove this paragraph.	The figure of 1.145 as inputted to the economic model by Novartis is correct. To 4 decimal places the calculation is 0.006635/0.05795 which yields 1.145, as entered.	Not a factual error These values are provided by the company, rounding is not in ERG calculations.

Issue 28 Incorrect reporting of data inputs to economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Pages 146-148, Table 5.37; incorrect standard error for BASDAI change from baseline in biologic experienced responders to conventional care	Correct value from 0.613 to 0.669	Correct reporting of parameter uncertainty applied in probabilistic sensitivity analyses.	Changes were made accordingly (page 146)
Page 150, Table 5.37; incorrect number of doses for certolizumab pegol at months 1-3	Correct value from 9.78 to 0, since the manufacturer provides the first 12 weeks of (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.	To reflect the patient access scheme in place for certolizumab pegol, the number of doses in the first model cycle was reduced to zero in the final version of the model submitted to the ERG.	Changes were made accordingly (page 150)

Issue 29 Unspecific wording around input parameters not included in the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 163: "However, in the newer version of the excel model, the ERG still noticed that some input parameters were not included (like the response-conditional baseline BASDAI scores)."	"However, in the newer version of the excel model, the ERG still noticed that some input parameters ***for baseline characteristics*** were not included (like the response-conditional baseline BASDAI scores)."	Differences in baseline characteristics are often considered to reflect heterogeneity rather than parameter uncertainty, and are therefore not varied in probabilistic sensitivity analyses. Had the ERG provided a rationale for including baseline characteristics in the PSA with the clarification questions, this change would have been made.	Not a factual error In the CS, the reason for not including the parameters should have been given.

Issue 30 Incorrect reporting of cost-effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 172, Table 5.58; the undiscounted incremental costs of certolizumab with PAS versus secukinumab are £15,385, not £12,835 as stated.	Correct undiscounted incremental costs for certolizumab with PAS versus secukinumab to £15,385.	Correct reporting of cost-effectiveness results.	Changes were made accordingly (page 150, Table 5.58)
Page 180, Table 5.65 in full report, Table 5.2 in subsequent correction; incremental costs for infliximab versus secukinumab have been duplicated in the ICER column.	Correct the ICER for infliximab versus secukinumab to £57,654 (as correctly reported in Table 5.56)		Changes were made accordingly (page 180, Table 5.65)
Page 180, Table 5.65 in full report, Table 5.2 in subsequent correction; Scenario 4b: Incremental costs and QALYs for infliximab are incorrect Scenario 5b: ICER for infliximab is incorrect Scenarios 1b, 3b & 7: Novartis calculated very slightly different incremental costs and ICERs – the differences are less than £5 so are not reported here. Scenarios 8b & 12: Differences of <2% in ICERs were obtained for adalimumab, certolizumab, golimumab and etanercept in Scenario 8b and for all comparators in Scenario 12 (not reported here). More substantial differences were found in results of infliximab (and infliximab biosimilar) versus secukinumab in scenario 8b. Novartis is unable to determine how scenario 10 has been implemented by the ERG. The York Model C approach generates an estimate of % BASDAI 50 responders which is constant across comparators, as	Correct incremental costs for infliximab versus secukinumab in scenario 4b to £29,192 Correct incremental QALYs for infliximab versus secukinumab in scenario 4b to 0.167 Correct ICER for infliximab versus secukinumab in scenario 5b to £101,023 Novartis results for infliximab versus secukinumab in scenario 8b: • Inc. costs = £41,545 • Inc. QALYs = 0.287 • ICER = £144,720 Novartis results for infliximab biosimilar versus secukinumab in scenario 8b: • Inc. costs = £37,650 • Inc. QALYs = 0.287		Changes in scenarios 4b, 5b and 12 were made accordingly. Results of the other mentioned scenarios were double checked and no factual errors were found. For scenario 10, overall change from baseline estimates from York Model C are transformed to response specific change from baseline estimates by using 2.354 for BASDAI (responder/non responder) ratio and using 7 for BASFI (responder/non

well as changes from baseline in BASDAI and BASFI which are specific to each drug but represent overall changes from baseline across the total cohort (both responders and non-responders). With both of these parameters fixed for a given treatment, and following the logic outlined on page 119 of the ERG report, Novartis is uncertain how specific ratios (from the Corbett et al. 2014 report) of responder change from baseline to non-responder change from baseline can be implemented.	• ICER = £131,153 The ERG is kindly requested to check the implementation of scenario 10 and provide further detail on this.		responder) ratio like in Scenario 8b.
Page 173, Table 5.61; incremental costs for certolizumab pegol are incorrect, and total QALYs for infliximab and infliximab biosimilar are incorrect	Correct incremental costs for certolizumab pegol to £5,593. Correct total QALYs for infliximab and infliximab biosimilar to 8.818		Changes were made accordingly (page 173, Table 5.61)

Issue 31 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 18: BASDI rather than BASDAI Page 183: BASDI rather than BASDAI	Page 18 & 183: "Comparative effectiveness estimates of secukinumab with other biologics in terms of BASDAI 50 and ***BASDAI***/BASFI change from baseline were obtained via separate MTCs"	Accurate description of outcome measure.	BASDI has been corrected to BASDAI (pages 18 and 183)
Table 5.9, page 110	Alter commas to decimal points in this table	For consistency	Decimal points were included in the last two columns of table 5.9 (page 110)
Page 124, Table 5.23: Table sub-titles are misleading – should refer to BASDAI / BASFI change from baseline given no BASDAI	Row 2: "BASDAI change from baseline given ***no*** BASDAI 50 response" and "BASFI change from baseline ***no*** given BASDAI 50 response"	Correct description of table content.	Text was changed to "BASDAI change from baseline given no BASDAI 50 response" (row 2) and "BASFI change from

50 response.			baseline given no BASDAI 50 response" (row 10), respectively.
Page 166: "In this scenario, an estimate that was derived from the costing template for adalimumab NICE submission in psoriasis arthritis (£1,453.48) was used"	"In this scenario, an estimate that was derived from the costing template for adalimumab NICE submission in psoriasis (£1,453.48) was used"	Accurate description of assumption source.	Changes were made accordingly (page 166)

References

1. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med 2015a;373:2534-48.
2. Longworth L, Rowen D NICE DSU technical support document 10: the use of mapping methods to estimate health state utility values. London: NICE, 2011; nicedsu.org.uk.
3. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.