NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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Certolizumab pegol for the treatment of ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

September 2014

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Abbreviations

Abbreviation	Word/Phrase
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
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 MRI scoring system for disease activity
AST	Asparate aminotransferase
AWMSG	All Wales Medicines Strategy Group
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
BNF	British National Formulary
BSR	British Society for Rheumatology
CC	Conventional care
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
COX-2	Cyclooxygenase-2
CrI	Credible interval
CRP	C-reactive protein
CU	Cost utility
CZP	Certolizumab pegol
DIC	Deviance information criterion
DMARD	Disease-modifying anti-rheumatic drug
EQ-5D	EuroQoL Health Status Questionnaire [5 dimensions]
ETA	Etanercept
EULAR	European League Against Rheumatism
FAS	Full analysis set
GGT	Gamma glutamyltransferase
GOL	Golimumab
HCQ	Hydroxychloroquine
HLT	Higher level term
hsCRP	High-sensitivity C-reactive protein
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFX	Infliximab
IV	Intravenous
IXRS	Interactive voice/web response system
KOL	Key opinion leader
LOCF	Last observation carried forward
LOE	Loss of effect
LS	Least squares
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	Minimum clinically important difference
MCS	Mental component summary
mNY	Modified New York
MOS	Medical outcomes study

MRI	Magnetic resonance imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
mTSS	Modified total Sharp score
MTX	Methotrexate
NA	Not applicable
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NRI	Non-responder imputation
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology
OR	Odds ratio
OSA	One-way sensitivity analysis
PAS	Patient access scheme
PBO	Placebo
PCS	Physical component summary
PEG	Polyethylene glycol
PPD	Purified protein derivative
PRO	Patient-reported outcome
PsA	Psoriatic arthritis
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Pt-years	Patient-years
PtGADA	Patient's global assessment of disease activity
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QALY	Quality adjusted life year
RA	Rheumatoid arthritis
RCT	Randomised control trial
Rhs	Right-hand side
RR	Relative risk
RS	Randomised set
SAE	Serious adverse event
sc	Subcutaneous
SD	Standard deviation
sDMARD	Synthetic disease-modifying antirheumatic drug
SE	Standard error
SF-36	Short form 36
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SOC	System organ class
SpA	Spondyloarthritis
SPARCC	Sacroiliac Spondyloarthritis Research Consortium of Canada
SS	Safety set
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment-emergent adverse events
TNF	Tumour Necrosis Factor
VAS	Visual analogue scale
WPS	Work productivity survey

1 Description of Technology

Certolizumab pegol (CZP, Cimzia®) is a TNF inhibitor, consisting of a recombinant, humanised antibody Fab' fragment against tumour necrosis factor (TNF)-alpha, which is conjugated to polyethylene glycol (PEG). CZP therefore reduces the activity of TNF-alpha, which is a pro-inflammatory cytokine, and reductions in TNF-alpha levels are thought to reduce disease activity by reducing inflammation. CZP is the only PEGylated anti-TNF approved for the treatment of axSpA.[1]

1.1 Licensed indication

Rheumatoid arthritis

CZP, in combination with methotrexate (MTX), is indicated for the treatment of moderate-to-severe, active rheumatoid arthritis in adult patients where the response to disease modifying antirheumatic drugs (DMARDs), including MTX, has been inadequate. CZP can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. CZP has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.[1]

Axial spondyloarthritis

CZP is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:[1]

- Ankylosing spondylitis (AS)
  Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs)

- Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA)
  Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs

Psoriatic arthritis

CZP, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to DMARDs including methotrexate, has been inadequate.[1]
CZP can be given as monotherapy in case of intolerance to MTX or when continued treatment with methotrexate is inappropriate.[1]

For the above indications, available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.[1]

Posology

The recommended starting dose of CZP for adult patients with axial spondyloarthritis is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks.[1]

Table 1-1. Formulation, cost and dosing information of CZP

Pharmaceutical formulation	CZP is formulated as a solution for sc injection. Each pre-filled syringe (type I glass) with plunger stopper (bromobutyl rubber) contains 200 mg CZP in 1 mL. None of the components of the syringe contain latex. CZP is provided in a pack size of 2 pre-filled syringes and 2 alcohol wipes.
Acquisition cost (excluding VAT)	The list price per pack is £715, excluding VAT, which is equivalent to a net price of £357.50 per 200 mg pre-filled syringe.[2] Under the patient access scheme (PAS) agreed with the Department of health for the use of CZP in the treatment of RA, the first 12 weeks of CZP are provided free of charge which is equivalent to 10 vials at a total cost saved of £3,575 in Year 1 of treatment.[2] This approved PAS will be extended for the use of CZP in the treatment of axial spondyloarthritis. A Welsh PAS for CZP in this indication has already been accepted by the All Wales Medicines Strategy Group (AWMSG).
Method of administration	Sc injection. Suitable sites for injection would include the thigh or abdomen.
Recommended dose (for adult patients) and dosing frequency	For patients with axSpA, 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks thereafter.[1]
Course of treatment	Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.[1]

CZP is currently recommended by NICE as an option for the treatment of people with rheumatoid arthritis, if:[3]

- CZP is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130);
- The manufacturer provides the first 12 weeks of CZP (10 pre-loaded 200 mg syringes) free of charge to all patients starting treatment.

CZP is currently recommended by the Scottish Medicines Consortium (SMC) as an option for the treatment of adults:

- **Axial spondyloarthritis:** With severe active axial spondyloarthritis comprising ankylosing spondylitis ([AS] adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs) and axial spondyloarthritis without radiographic evidence of AS (nr-axSpA) (adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs);[4]
- **Rheumatoid arthritis:** In combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients when the response to disease modifying anti-rheumatic drugs, including methotrexate, has been inadequate;[5]
    - As monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
- **Psoriatic arthritis:** With active psoriatic arthritis whose disease has not responded to adequate trials of at least two standard DMARDs either individually or in combination.[6]
- These SMC advice are contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

In the present submission for the NICE MTA, CZP will be evaluated within its licensed indication, for the treatment of patients with severe active axSpA, comprising of patients with AS and with axSpA without radiographic evidence of AS.[1]

2 Executive Summary

- Certolizumab pegol (CZP) offers a clinically effective treatment option across the spectrum of axSpA, which is increasingly recognised as one disease, irrespective of radiographic evidence of sacroiliitis, with proven efficacy in both AS and nr-axSpA subpopulations up to 96 weeks.
    - The RAPID-axSpA study is the first registration trial to examine the efficacy of an anti-TNF therapy across the spectrum of axSpA disease, including patients AS and nr-axSpA who had comparable disease burden at study baseline.
    - CZP-treated patients in both AS and nr-axSpA subpopulations reported greater improvements in the signs and symptoms of disease, physical function, pain, fatigue, health-related quality of life (HRQoL) and workplace and household productivity than placebo-treated patients at Week 24, which were maintained to Week 96. These data demonstrate that irrespective of the presence or absence of evidence of radiographic damage in the sacroiliac joints, treatment with CZP results in meaningful and comparable benefits to patients in the management of disease.
    - No new safety signals were identified in this patient population as compared with the use of CZP in RA or PsA, or versus other anti-TNF therapies in AS or nr-axSpA patients.
- A systematic literature review and a mixed treatment comparison (MTC) were carried out to assess the relative efficacy of CZP compared to currently licensed anti-TNF therapies within the scope of the NICE MTA. In AS patients, CZP showed similar efficacy (with no significant difference) when compared to other anti-TNFs. In nr-axSpA patients, CZP showed numerically greater improvements, with significant differences noted for several outcomes, over other anti-TNFs. The MTC reported that treatment with anti-TNF therapies were superior to placebo in several efficacy outcomes and patient-reported outcomes in AS and nr-axSpA.
- The base case analyses indicated that with the patient access scheme (PAS), CZP is cost-effective against conventional care at a willingness-to-pay threshold of £20,000 per quality-adjusted life year, in both the AS and nr-axSpA subpopulations. In the AS subpopulation, the base case analysis indicated that CZP with the PAS dominates ADA, ETA and GOL and is cost-effective against IFX. In the nr-axSpA subpopulation, the base case analysis indicated that CZP with the PAS dominates both ADA and ETA.
- The base case of the budget impact analysis indicated that the introduction of CZP with the PAS as an alternative treatment for axSpA would lead to an estimated net budgetary saving for the NHS in England and Wales of £9,251,887 over a 5-year time horizon. Of this amount, £5,566,617 savings would arise in the treatment of patients with AS and £3,685,270 in the treatment of patients with nr-axSpA.
- Therefore, CZP is a valuable treatment option with an acceptable risk-benefit ratio for axSpA patients including patients with AS and axSpA without radiographic evidence of AS.

2.1 Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the axial skeleton (the sacroiliac joints and spine), with many patients experiencing symptoms of inflammatory back pain, stiffness and spinal disability. In addition, patients may also have extra-spinal involvement such as arthritis, enthesitis or uveitis. Onset of first symptoms typically occurs when patients are in their third decade,[7] meaning that the condition affects people of working age with the potential for substantial socioeconomic implications.[8-10] A diagnosis is typically based upon physical examination, magnetic resonance imaging (MRI) and X-rays of the sacroiliac joints and laboratory assessments, in addition to the presence or history of other related clinical features of the spondyloarthritides.[11]

Axial SpA describes a disease spectrum and patients with axSpA are classified as having AS or non-radiographic axSpA (nr-axSpA) by the presence or absence of evidence of sacroiliitis on plain X-rays (radiographs), which is typically the only differentiating clinical feature between these subpopulations.[12] Patients across the axSpA disease spectrum (encompassing both AS and nr-axSpA) suffer from pain, stiffness, decreased spinal mobility and function, fatigue, and disturbed sleep and work disability. These symptoms interfere with activities of daily life and result in a reduction in health-related quality of life (HRQoL) for the patients living with axSpA.[13, 14] This comparable disease burden, in addition to the observation that

not all axSpA patients will ever develop the radiographic symptoms required for the classification of AS, highlights that effective treatments are similarly warranted for patients across the axSpA spectrum.

There is also evidence that axSpA incurs a substantial economic impact on society and individual patients. These costs are driven mainly by the reduced capacity to work observed in this population of young, economically active patients.[8-10] The economic burden of axSpA has recently been estimated in the RAPID-axSpA study. At study baseline, there was a similarly high impact of disease on workplace and household productivity between AS and nr-axSpA patients that would lead to a large financial burden for patients and society. Many employed patients reported that their disease was detrimental to their ability to perform their paid work and household tasks, and this was again similar between the AS and nr-axSpA subpopulations.[15] Given the similarity in disease burden across AS and nr-axSpA patients, both conditions are similarly amenable to therapy. The lifelong nature of the disease means that the provision of effective new treatment options for axSpA patients will likely have an important impact on the wider societal costs of the disease.

Pharmacological therapy to manage patients' symptoms starts with non-steroidal anti-inflammatory drugs (NSAIDs), with progression to anti-tumour necrosis factor (TNF) therapies in the case of non-response or intolerance to optimised NSAIDs. Patients across the axSpA spectrum can fail a specific anti-TNF therapy for a number of reasons. With such limited treatment options in axSpA, alternatives would bring value, particularly a specific anti-TNF therapy. Alternative treatment options would therefore bring value, particularly for the treatment of nr-axSpA patients for whom there is currently no treatment options recommended in England.

2.2 Clinical Efficacy of CZP

RAPID-axSpA is the first randomised, placebo (PBO)-controlled, multicentre registration study to examine the efficacy of an anti-TNF therapy across the spectrum of axSpA patients rather than in individual AS and nr-axSpA subpopulations. The study allowed for a direct comparison of the burden of disease and efficacy of CZP treatment in AS and nr-axSpA patients, as classified by the Assessment of SpondyloArthritis International Society (ASAS) criteria.

In this ongoing registration study, recruited patients had a high and similar burden of disease across subpopulations. A wide range of patient relevant outcomes were collected in the RAPID-axSpA study allowing the evaluation of the benefits of CZP across a broader spectrum of outcomes. At study baseline, the burden of disease was high across the axSpA population and similar between the AS and nr-axSpA populations. HRQoL was assessed through the short form (SF)-36, which measures both physical and mental components of well-being, in addition to the AS quality of life (ASQoL), which is a validated disease-specific 18-item questionnaire for measuring HRQoL in subjects with AS,[16] and can also be used in axSpA patients.[8, 17]

CZP demonstrated efficacy across a range of pre-specified endpoints. Both maintenance dosing regimens tested resulted in statistically significant increases versus PBO in the proportion of ASAS20 responders at Week 12 (primary trial endpoint) and Week 24 (both $p<0.001$), and these responses were maintained through to Week 96.[18, 19] CZP was also superior to PBO at improving physical function (Bath ankylosing spondylitis functional index [BASFI]) and spinal mobility (Bath ankylosing spondylitis mobility index [BASMI] linear), and reducing disease activity (Bath ankylosing spondylitis disease activity index [BASDAI]).[18] CZP had a rapid onset of action, with significant and clinically meaningful changes in patient-reported outcomes (PROs) and clinical outcomes as early as Week 1 (eg. ASAS responses, change in BADAI, BASFI and BASMI). CZP also resulted in improvements in extra-articular and extra-spinal manifestations (enthesitis, peripheral arthritis and a reduction in the number of uveitis flares).[18, 20, 21] These improvements in disease activity translated into increased workplace and household productivity and increased participation in social, family and leisure activities from Week 4,[22] and through to Week 96 of the study,[23] which has important economic benefits.

No new safety signals were identified in this patient population as compared with the use of CZP in rheumatoid arthritis (RA) or psoriatic arthritis (PsA), or versus other anti-TNF therapies in AS or nr-axSpA patients.

Therefore, CZP offers a valuable alternative treatment option across the spectrum of axSpA, which is increasingly recognised as one disease spectrum, irrespective of radiographic evidence of sacroiliitis, with proven efficacy in both AS and nr-axSpA subpopulations up to 96 weeks.

2.3 Mixed Treatment Comparison

A systematic literature review and a meta-analysis were carried out to assess the relative efficacy of CZP compared to currently anti-TNF therapies that have marketing authorisation for the treatment of AS: adalimumab (ADA); etanercept (ETA); golimumab (GOL); and infliximab (IFX), or for the treatment of nr-axSpA: ADA; and ETA.[24-27] The analysis was performed for a number of key outcomes such as ASAS responses, BASFI, BASDAI and PROs. The analysis indicated that all five anti-TNF therapies were superior to PBO in both subpopulations. Furthermore, in the AS subpopulation, the primary MTC results indicated that CZP showed similar efficacy (with no significant differences) when compared to ADA, ETA, GOL and IFX at 24 weeks. In nr-axSpA patients, CZP showed numerically greater improvements over ADA and ETA at 12 weeks in most outcomes assessed, in terms of ASAS responses (ASAS20, 40, partial remission, 5/6), disease activity and physical function; significant differences were noted in changes in BASFI, BASDAI and PtGADA..

2.4 Cost-Effectiveness

A Markov model was used to evaluate the cost-effectiveness of CZP against conventional care (CC; primarily NSAIDs) and other anti-TNF therapies (ADA, ETA, GOL and IFX in AS, and ADA and ETA in nr-axSpA). The base case results indicated that CZP with the PAS (see Table 1-1) is cost-effective against CC and other available anti-TNF therapies.

The base case analyses indicated that with the PAS, CZP is cost-effective against CC at a willingness-to-pay threshold of £20,000 per quality-adjusted life year (QALY), in both the AS (ICER [incremental cost-effectiveness ratio] £16,647) and nr-axSpA (ICER £15,615) subpopulations.

In the AS subpopulation, the base case analysis indicated that CZP with the PAS dominates ADA, ETA and GOL and is cost-effective against IFX (ICER for IFX vs CZP: £114,097). In the nr-axSpA subpopulation, the base case analysis indicated that CZP with the PAS dominates both ADA and ETA.

One-way sensitivity analyses (OSA) in both the AS and nr-axSpA subpopulation showed that ICERs were most sensitive to the probability of achieving an ASAS20 response, discount factors for health outcomes and costs, and CZP drug acquisition cost. In the AS subpopulation, probabilistic sensitivity analyses (PSA) showed that CZP was similar to ADA, ETA and GOL in terms of costs and QALYs and that all anti-TNF therapies except IFX were similarly more effective and more costly than CC. Results also show that IFX is generally more costly and marginally more effective than CZP, ADA, ETA and GOL. In the nr-axSpA subpopulation, PSA showed that CZP had the highest probability of being the most cost-effective amongst all treatment options, including CC (74.2% at £20,000/QALY threshold) for the nr-axSpA subpopulation.

2.5 Budget Impact

Under the base case assumptions, the budget impact analysis indicated that the introduction of CZP with the PAS as an alternative treatment for axSpA would lead to an estimated net budgetary saving for the NHS in England and Wales of £9,251,887 over a 5-year time horizon. Of this amount, £5,566,617 savings would arise in the treatment of patients with AS and £3,685,270 in the treatment of patients with nr-axSpA.

Scenario sensitivity analyses tested assumptions about the prevalence of axSpA in England and Wales, the uptake of CZP from CC for the nr-axSpA subpopulation, discontinuation rates of anti-TNF therapy, and the potential introduction of IFX and ETA alongside CZP as alternative treatments for AS and nr-axSpA respectively. In these sensitivity analyses, the 5 year budget impact in the axSpA population (AS and nr-axSpA combined) ranged between net savings of £36,035,518 (assuming higher disease prevalence) and net increased budget of £4,205,185 (assuming greater number of patients come from CC).

3 Context

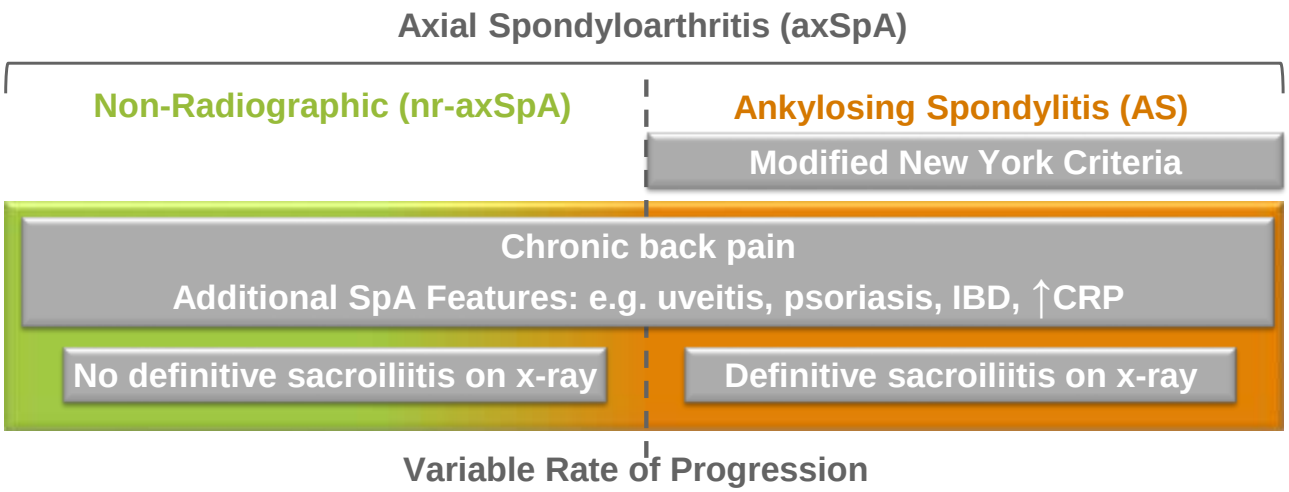
- Axial spondyloarthritis is a chronic inflammatory disease with a high and similar level of patient burden in both AS and nr-axSpA patients.
- Given the similar level of patient burden in patients with AS and nr-axSpA, the high level of economic burden reported from patients with AS is likely to all patients living with axSpA.
- Treatment for axSpA is focused on NSAIDs, with the addition of anti-TNFs in patients not responding to these therapies.
- For adults with severe active AS, the currently licensed comparators to CZP include adalimumab, etanercept, golimumab and infliximab. Adalimumab and etanercept are the only comparators for CZP that are licensed for the treatment of patients with severe axSpA without radiographic evidence of AS.

3.1 Disease Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the axial skeleton (the sacroiliac joints and spine), with many patients experiencing symptoms of inflammatory back pain, stiffness and spinal disability. In addition, patients may also have extra-spinal involvement such as arthritis and enthesitis or extra-articular involvement such as uveitis. Onset of first symptoms typically occurs when patients are in their third decade,[7] meaning that the condition affects people of working age with the potential for substantial socioeconomic implications.[8-10] A diagnosis is typically based on physical examination, MRI and X-rays of the sacroiliac joints and laboratory assessments as well as the presence or history of other related clinical features of the spondyloarthritides.[11]

Patients with axSpA are classified as having Ankylosing Spondylitis (AS) or non-radiographic axSpA (nr-axSpA) by the presence or absence of evidence of sacroiliitis on plain X-rays (radiographs) according to the modified New York (mNY) criteria for AS, which is typically the only differentiating clinical feature between these subpopulations (Figure 3-1).[12] The prevalence of axSpA is 0.9–1.4%, as reported by the NHANES (National Health and Nutrition Examination Survey) study using a population based in the US, with the prevalence of AS being 0.52–0.55%.[28] Recent studies have revealed that progression rates from nr-axSpA to AS are 11.6% over 2 years, and 24.3% over 5–10 years.[29, 30] Importantly, these data also suggest that not all patients with nr-axSpA progress to the point where radiographic sacroiliitis can be detected (AS). Elevated CRP or inflammation at the sacroiliac joint, as assessed by MRI, are significant risk factors for the progression to AS.[31]

Figure 3-1: The clinical spectrum of axSpA, adapted from ASAS[18, 19]



CRP: C-reactive protein; **IBD**: Inflammatory bowel disease; **mNY**: Modified New York criteria

Patients across the axSpA disease spectrum (encompassing both AS and nr-axSpA) suffer from pain, stiffness, decreased spinal mobility and function, fatigue, and disturbed sleep and work disability. Crucially, levels of pain and disease activity are high and similar between the AS and nr-axSpA subpopulations, as reported by various European and North American outpatient/hospital registry analyses and patient baseline characteristics of clinical trials of AS and/or nr-axSpA.[8-10, 15, 18, 32-34] All of these symptoms interfere with

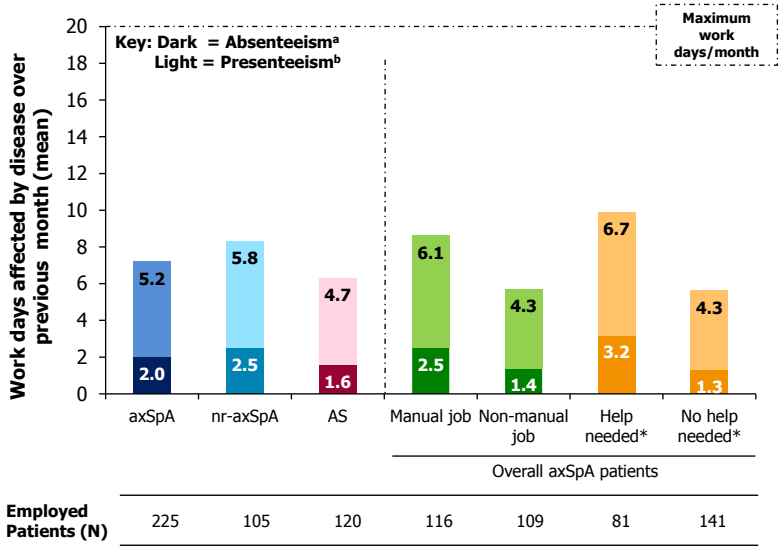
activities of daily life and result in a reduction in HRQoL.[13, 14] This comparable disease burden, in addition to the observation that not all axSpA patients will ever develop the radiographic symptoms required for the classification of AS, highlights that effective treatments are similarly warranted for patients across the axSpA spectrum.

3.2 Economic Burden of axSpA

There is evidence that axSpA incurs a substantial economic impact on society and individual patients. These costs are driven mainly by the reduced capacity to work observed in this population of young, economically active patients.[8-10] Given the similarity in disease burden across AS and nr-axSpA patients, both conditions are similarly amenable to therapy.

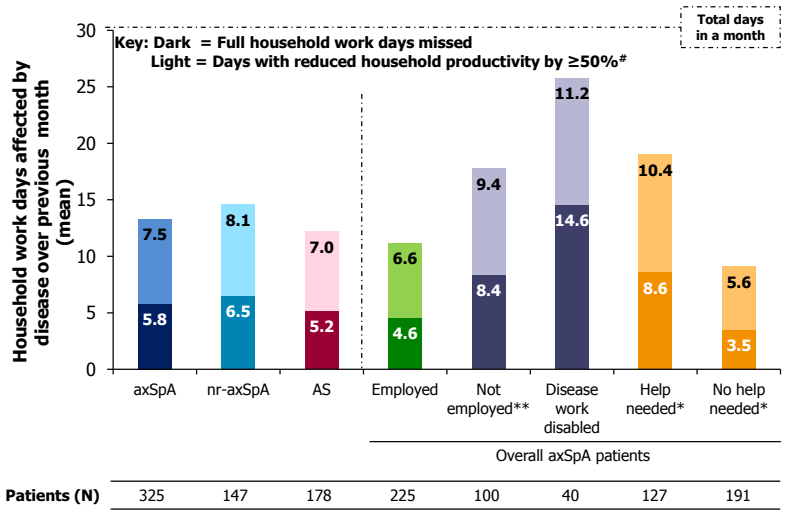
The economic burden of axSpA has recently been estimated using the arthritis-specific Work Productivity Survey (WPS) in the RAPID-axSpA study. At study baseline, there was a similarly high impact of disease on workplace and household productivity between AS and nr-axSpA patients that could lead to a large financial burden for patients and society. Employment rates outside the home were 69.2% of axSpA patients, 67.4% AS and 71.4% nr-axSpA.[35] Many of these employed patients reported that their disease was detrimental to their ability to perform their paid work and household tasks, and this was again similar between the AS and nr-axSpA subpopulations (Figure 3-2 and Figure 3-3). In addition, 39.1% of axSpA patients reported that they needed regular assistance from relatives, friends or paid caregivers in their activities of daily living because of their disease, which was comparable between the two subpopulations (42.1% in AS compared with 35.4% in nr-axSpA).[35]. This indicates that as well as the burden on the patients themselves, axSpA disease may represent a burden on wider society as families and friends of patients give up their time to provide the additional help and support that axSpA patients require. Although the disease burden was high in both groups, greater productivity losses due to axSpA at both the workplace and within the household, and in social participation, were reported by those patients who needed regular assistance compared to those who did not.[35]

Figure 3-2: Burden of axSpA on workplace productivity at study baseline in employed patients in RAPID-axSpA[15]



[a]Absenteeism = work days missed due to arthritis over previous month; [b]Presenteeism = days with work productivity reduced by ≥50% due to arthritis over previous month (does not include days counted in absenteeism);
*Need of regular assistance from relatives/friends or paid caregivers in usual activities due to axSpA
Data correspond to the randomised set, observed data

Figure 3-3: Burden of axSpA on household work productivity at study baseline in RAPID-axSpA[15]



#Does not include days counted in full household work days missed; *Need of regular assistance from relatives/friends or paid caregivers in usual activities due to axSpA; **Not employed included unable to work due to arthritis, retired, homemaker, student and other non-employed status
Data correspond to the randomised set, observed data

Available evidence suggests that the economic burden of axSpA to the UK healthcare system and wider economy is substantial. A UK secondary care rheumatology unit revealed that annual direct healthcare costs for patients living with AS were a mean of £1,852 per year (median £892 per year).[36] However, these costs only represent a minor proportion of the total economic burden of the disease. A subsequent analysis across 10 rheumatology centres in the UK reported total three month costs of £2,802 (median £1,160) for AS patients, with direct healthcare costs contributing to just 15% of this burden. The majority of costs were reported to due to unemployment (63.2%) and presenteeism (reduced productivity whilst at work [19.0%]), whilst absenteeism (absence from work) contributed a further 1.4% to total costs.[37] Additionally, direct and indirect costs were found to escalate steeply with worsening disease activity.[36, 37]

Given the similarity in disease burden, employment status and frequency of presenteeism and absenteeism between patients with AS and nr-axSpA, it is likely that the economic burden of AS extends to all patients suffering from axSpA. Therefore, the lifelong nature of the disease means that effective treatments for axSpA that improve patient function and prevent disability have great potential to relieve the high costs and wider societal impact associated with this disease, especially in those patients with high disease activity.

3.3 Current Clinical Practice

A number of national and international professional bodies have issued guidelines and recommendations for the treatment of axSpA and its subpopulations of AS or nr-axSpA. The international ASAS and European League against Rheumatism (EULAR) guidelines, as detailed in Appendix 11.1.1, are the most commonly followed set of clinical guidelines for the management or treatment of axSpA.

3.4 Comparators

Axial spondyloarthritis
There are limited treatment options that cover the spectrum of axSpA disease, compared to other diseases with a similar burden of disease such as RA. Other than CZP, anti-TNFs that have marketing authorisation for use in both the AS and nr-axSpA subpopulations include ADA and ETA.[26, 27] Hence there is a need for alternative treatments that show efficacy in axSpA, irrespective of the presence of absence of radiographic damage. Five anti-TNF therapies have marketing authorisation for the AS subpopulation only and therefore, to consider the alternative treatments available, the subpopulations will now be covered separately.

Ankylosing spondylitis
For adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs, the current treatment options are one of five anti-TNF therapies with marketing authorisation and/or a recommendation by NICE (CZP, ADA, ETA, GOL and IFX)[1, 24-26, 38-41] or CC, which would consist of primarily NSAIDs.

Although IFX did not gain a recommendation from NICE for use in AS in May 2008,[24] it has been included in the scope for this MTA and will therefore be considered as an alternative therapy.

Axial spondyloarthritis without radiographic evidence of AS
For adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs, there are currently three anti-TNFs with marketing authorisation, CZP, ADA or ETA,[1, 26, 27] in addition to CC, which would consist of primarily NSAIDs.

No other biologics have a marketing authorisation for the nr-axSpA patient population and therefore no further alternatives are considered. As a result, there is a lack of alternative treatment options available to nr-axSpA patients when compared to patients with AS, and consequently there is a high unmet need in these patients who have a similar burden of disease to patients with AS (described in Section 3.1).

4 Innovation

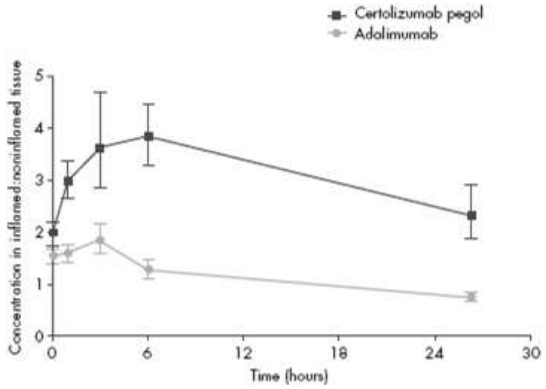
- CZP is a PEGylated, Fc-free anti-TNF with a long half-life and preferential penetration of inflamed tissues.
- CZP provides flexible dosing options, offering more convenience to patients.
- The RAPID-axSpA study is the first registration trial to include patients from across the spectrum of axSpA disease, including patients with AS and nr-axSpA, which better reflects clinical practice in Britain.
- Response to CZP is rapid, with significant differences observed for many clinical outcomes as early as Week 1.
- An innovative PAS provides treatment for axSpA free of charge for the first 12 weeks to the NHS.
- In addition to clinical benefits, CZP therapy has also been shown to be associated with large benefits in workplace and household productivity outcomes.

4.1 Innovation of CZP

4.1.1 CZP Structure

The addition of the PEG part of the CZP molecule increases the stability and half-life of CZP, allowing the Fc-free molecule to have a similar half-life to a full antibody (14.4 days).[42] PEGylation may also aid retention in inflamed tissue, and CZP has been shown to preferentially accumulate in inflamed tissue in animal models. A study in naïve mice and mice with ongoing collagen-induced arthritis used fluorescently labelled CZP and ADA to show that both anti-TNF therapies achieved greater penetration into arthritic paws compared to normal tissue. Importantly, CZP also demonstrated longer and more extensive penetration into inflamed tissue than ADA (Figure 4-1).[43]

Figure 4-1: Ratio of ADA and CZP in inflamed and non-inflamed tissue in a mouse model of collagen-induced arthritis[43]



In humans, radiolabelled CZP has similarly been found to accumulate within inflamed joints within minutes of administration. Furthermore, accumulation of radiolabelled CZP had a high concordance with ultrasound and swollen joint count in patients with RA and peripheral SpA.[44]

Although CZP has not been approved for use in pregnancy,[1] pre-clinical and clinical data suggest a lack of active placental transfer of CZP which may be the consequence of the absence of an Fc region. Pre-clinical data showed that an anti-TNFα PEGylated Fab' fragment was undetectable or only detectable at a very low level in rodent foetal samples.[45] An *ex vivo* placental transfer study found that in 6 human placentas, CZP levels in the foetal circulation were consistently below levels of the anti-D IgG control.[46] An independent investigator-driven study measuring placental transfer in 10 pregnant women treated with CZP reported that CZP levels in the cord blood and infant blood on the day of birth were consistently lower than those in maternal blood, suggesting low placental transfer. In some cases, CZP levels in cord and infant blood were below levels of detection.[47, 48] The European label for CZP states that there are no adequate data from the use of Cimzia in pregnant women.[1]

4.1.2 CZP Administration Benefits

CZP offers flexible dosing options and can be administered either as 200 mg Q2W or 400 mg Q4W as a maintenance dose depending on patient choice, after the initial loading doses have been administered at Weeks 0, 2 and 4. The 400 mg Q4W dosing option offers more convenient dosing for patients, especially for patients who are frequently travelling away from home.

CZP is supplied as an award-winning,[49, 50] ergonomically-designed pre-filled syringe that was designed in collaboration with OXO Good Grips® to ensure that it is easy to use, which allows convenient self-administration for those patients who feel able to do so.

CZP also offers predictable annual costs. Patients receive the same cumulative dose of CZP regardless of the maintenance dosing regimen and irrespective of their weight: 400 mg over the course of 4 weeks, administered either 200 mg Q2W or 400 mg Q4W.

4.1.3 Study Design

The RAPID-axSpA study is the first registration trial to include patients from across the spectrum of axSpA disease, including patients AS and nr-axSpA. The study used the most recent ASAS axSpA classification criteria. All patients were first recruited based on a physician diagnosis of axSpA. Patients subsequently had met the ASAS classification criteria and had active disease plus the presence of objective signs of inflammation despite current treatment with NSAIDs. Recruited patients were then stratified into the AS and nr-axSpA subpopulations using the mNY criteria.

4.1.4 Rapid Response to CZP

The improvement in ASAS20 response rate for patients treated with CZP in the RAPID-axSpA study was seen early on, with significant differences observed by Week 1 compared to PBO ($p<0.001$; Figure 5-4, [redacted]).[18] Significant improvements in other clinical outcomes, including ASAS40 response rate, [redacted], disease activity (BASDAI) and physical function (BASFI), were also seen at Week 1. Furthermore, these improvements in clinical outcomes were complemented by improvements in PROs such as significantly reduced total back pain by Week 1 and increased work and household productivity by Week 4, the earliest timepoint for which data are available.

It is thought that the loading dose of 400 mg at Weeks 0, 2 and 4 is important for achieving this rapid improvement when treated with CZP. A post hoc analysis of data from two clinical trials in RA in Japanese patients (J-RAPID [CZP plus methotrexate [MTX] in patients with RA, n=316] and HIKARI [CZP without MTX in patients with RA, n=230]) showed that administration of CZP loading doses is associated with a more rapid onset of efficacy, development of lower anti-drug antibody levels and a sustained response compared with initiating CZP without loading doses.[51] Patients who did not receive the loading dose showed delayed initial kinetics of American College of Rheumatology (ACR)20/50/70 responses and sustained lower response to Week 24 (ACR50/70) compared to patients who did received the loading dose. Development of anti-CZP antibodies was observed more frequently in patients who did not receive the loading dose compared with patients who did receive the loading dose (J-RAPID: n=4 [6.6%] vs n=1 [1.2%]; HIKARI: n=27 [27.3%] vs n=18 [15.5%]). These results suggest administration of the initial CZP loading dose is important for improving clinical response in active RA patients.[51] Additionally, a pharmcodynamic Markov model has revealed that patients not recieiving the loading dose had reduced response to CZP, and a higher probability of discontinuing treatment, especially due to lack of response.[52] In RAPID-axSpA, CZP was also administered with the loading dose and early ASAS responses were seen, with significant differences in ASAS20 response rates compared to PBO observed by Week 1 (Figure 5-4).[18, 23]

4.1.5 An Evidence-Based 12-Week Treatment Decision Point

The ability to predict long-term response to therapy based on response at an early time point is of clinical value, permitting the early identification of patients who are unlikely to respond in the longer term and allowing prompt access to alternative therapies; decreasing unnecessary drug exposure.

In RAPID-axSpA, the response to CZP was rapid. At Week 1, significantly more CZP treated patients achieved an ASAS20 response (40.5% in CZP 200 mg Q2W and 34.6% in 400 mg Q4W groups vs 14.0% in

PBO group), which raised to 57.7% and 63.6% of CZP 200 mg Q2W and CZP 400 mg Q4W treated patients by Week 12 (Section 5.4.1.1).

A post hoc analysis has suggested a clear relationship between Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity from as early as Week 2 and ASDAS inactive disease at Week 48 (Table 4-1). Of the 31 patients with inactive disease (ASDAS <1.3) at Week 2, 71% (22/31) achieved inactive disease at Week 48, compared with 0% (0/27) of patients with very high disease activity (ASDAS >3.5) at Week 2 achieving inactive disease at Week 48. This trend was maintained at Week 12, whereby of the 50 patients with inactive disease at Week 12, 68% (34/50) achieved inactive disease at Week 48, compared with 0% (0/21) of patients with very high disease activity at Week 12 achieving inactive disease at Week 48.[53]

Table 4-1: Likelihood of achieving ASDAS inactive disease at Week 48 based on ASDAS classification of disease activity at Baseline, Week 2, Week 8 and Week 12[53]

Visit	ASDAS ID n/N (%)	ASDAS MD n/N (%)	ASDAS HD n/N (%)	ASDAS vHD n/N (%)
Baseline	0/0	1/3 (33.3%)	32/70 (45.7%)	34/145 (23.4%)
Week 2	22/31 (71.0%)	30/59 (50.8%)	15/100 (15.0%)	0/27
Week 8	35/49 (71.4%)	22/57 (38.6%)	10/89 (11.2%)	0/20
Week 12	34/50 (68.0%)	20/54 (37.0%)	13/86 (15.1%)	0/21

HD: high disease activity; **ID**: inactive disease, **MD**: moderate disease; **vHD**: very high disease activity
Data correspond to the randomized set (LOCF imputation)
Light grey shading represents values of 10–20%, dark grey shading represents values of 0–10%

A similar analysis has also been performed using BASDAI scores at early timepoints and attainment of treatment success (defined in this analysis as BASDAI <3) at Week 48. Of the 31 patients with low BASDAI score at Week 2 (BASDAI <2), 96.8% (30/31) achieved their treatment target at Week 48, compared with 13.1% (8/61) patients with very high BASDAI (BASDAI >6) at Week 2 achieved their treatment target at Week 48. This trend was also maintained at Week 12, whereby of the 58 patients with low BASDAI at Week 12, 91.4% (53/58) achieved the treatment target at Week 48, compared with 7.9% (3/38) of patients with very high BASDAI at Week 12 achieving the treatment target at Week 48.[23]

Table 4-2: Likelihood of achieving BASDAI <3 at Week 48 based on BASDAI score at Baseline, Week 2, Week 8 and Week 12

Visit	Low (BASDAI <2) n/N (%)	Moderate (BASDAI 2≤4) n/N (%)	High (BASDAI 4≤6) n/N (%)	Very High (BASDAI >6) n/N (%)
Baseline	0/0	6/9 (66.7%)	56/79 (70.9%)	54/130 (41.5%)
Week 2	30/31 (96.8%)	49/62 (79.0%)	29/63 (46.0%)	8/61 (13.1%)
Week 8	42/45 (93.3%)	52/74 (70.3%)	19/59 (32.2%)	3/37 (8.1%)
Week 12	53/58 (91.4%)	40/61 (65.6%)	19/54 (35.2%)	3/38 (7.9%)

BASDAI: Bath ankylosing spondylitis disease activity score
Data correspond to the randomized set (LOCF imputation)
Light grey shading represents values of 10–20%, dark grey shading represents values of 0–10%

Using disease activity state or BASDAI score during the first 12 weeks of CZP treatment, it may therefore be possible to identify a subset of patients who are unlikely to achieve long-term treatment goals. This approach may help physicians to determine early on when to change therapy in patients not responding to CZP, therefore helping to avoid unnecessary exposure, increase cost-effectiveness and improve the chance of achieving long-term treatment goals.

4.1.6 Patient Access Scheme

A primary concern with anti-TNF treatment is the cost of failure in patients who do not respond to treatment. In recognition of the link between the attained degree of clinical benefit after the first 12 weeks and the long-term outcome of CZP-based therapy, UCB developed an innovative PAS for the CZP treatment of patients

with RA, in which treatment for patients is provided to the NHS free of charge for the first 12 weeks. This approved PAS has been extended to CZP treatment of patients with axSpA.

4.1.7 Health-Related Benefits Unlikely to be Included in the Quality-Adjusted Life Year Calculation

4.1.7.1 Productivity Benefits

In addition to clinical benefits, CZP therapy has also been shown to be associated with large benefits in productivity outcomes compared to PBO. Baseline data from the RAPID-axSpA study indicated a high burden of axSpA, as well as a similarly high burden in AS and nr-axSpA on workplace and household productivity, as reflected by increased work disability at work and within the home.[35] The high burden of axSpA on workplace and household productivity could lead to a large financial burden for both patients and society. Data from RAPID-axSpA indicated that CZP-treated patients reported greater and continued improvements over time, in workplace productivity as well as household productivity and increased participation in social, family and leisure activities.[35]

5 Clinical Efficacy

- Both CZP dosing regimens resulted in statistically significant increases versus PBO in the proportion of ASAS20 responders at Week 12 (primary endpoint) and at Week 24, with rapid improvements as early as Week 1. CZP also resulted in statistically significant improvements versus PBO in levels of disease activity (BASDAI), physical function (BASFI) and spinal mobility (BASMI linear) at Week 24.[18]
- CZP-treated patients in both AS and nr-axSpA subpopulations reported greater improvements in the signs and symptoms of disease, physical function, pain, fatigue, HRQoL, extra-articular and extra-spinal manifestations and workplace and household productivity than PBO-treated patients at Week 24.[18, 20-22, 54, 55] Overall, these data demonstrate that irrespective of the presence or absence of evidence of radiographic damage, treatment with CZP results in meaningful benefits to patients in the management of disease.
- Improvements in all efficacy outcomes, clinical and patient-reported, were maintained long-term to Week 96. Maintenance of benefit was seen in both CZP dosing arms and in both subpopulations.[23, 56]
- RAPID-axSpA is the first registration trial to study patients across the active axSpA disease spectrum, including patients both with and without radiographic evidence of sacroiliitis. This may therefore make the trial more representative of clinical practice where treatment decisions are driven by the levels of pain, fatigue and difficulty with daily life, not the presence or absence of structural changes in the sacroiliac joints. This study evaluated the efficacy of CZP using a large number of outcomes that are clinically meaningful and relevant to patients.
- The baseline characteristics of the active axSpA population recruited into the RAPID-axSpA study demonstrate the high and similar burden of disease, both humanistic and economic, between the AS and nr-axSpA subpopulations. At baseline, levels of disease activity, reductions in HRQoL and the detrimental impact of disease on work productivity were all substantial and similar between AS and nr-axSpA patients.[18, 35, 55]

5.1 Identification of Relevant Studies

There is only one PBO-controlled, multicentre trial to examine the efficacy of CZP across the spectrum of patients with active axSpA, as defined by the ASAS criteria. This is the first and currently only study that allows a direct comparison of the burden of disease and efficacy of treatment to be made between the active axSpA, AS and nr-axSpA populations within a single study, addressing questions about the similarities of the subpopulations. All patients were first recruited based on a physician diagnosis of axSpA. Patients subsequently had met the ASAS classification criteria and had active disease plus the presence of objective signs of inflammation despite current treatment with NSAIDs. Recruited patients were then stratified into the AS and nr-axSpA subpopulations using the mNY criteria.
The study is summarised in Table 5-1, and the inclusion and exclusion criteria for this study, known as RAPID-axSpA (or AS001), are described in Section 5.2.2.

Table 5-1: RAPID-axSpA study summary

Trial no.	NCT01087762 (RAPID-axSpA Study; AS001)
Intervention	CZP at two different dosing regimens (200 mg every 2 weeks [Q2W] or 400 mg every 4 weeks [Q4W]) after equivalent initial loading doses of 400 mg at weeks 0, 2 and 4, double-blind, PBO-controlled for 24 weeks, with dose-blind extension to 48 weeks and open-label to 204 weeks.
Comparator	PBO
Population	325 patients with axSpA by the ASAS criteria and active disease, as defined by BASDAI ≥4, spinal pain ≥4 and CRP >ULN (>7.9 mg/L) **and/or** sacroiliitis by MRI who had failed ≥1 NSAID. 178 (55%) patients met the mNY criteria and were therefore defined as having AS, 147 (45%) patients did not meet the mNY criteria and were therefore defined as having nr-axSpA.
Primary study ref.	Landewé et al. Ann Rheum Dis. 2014[18]

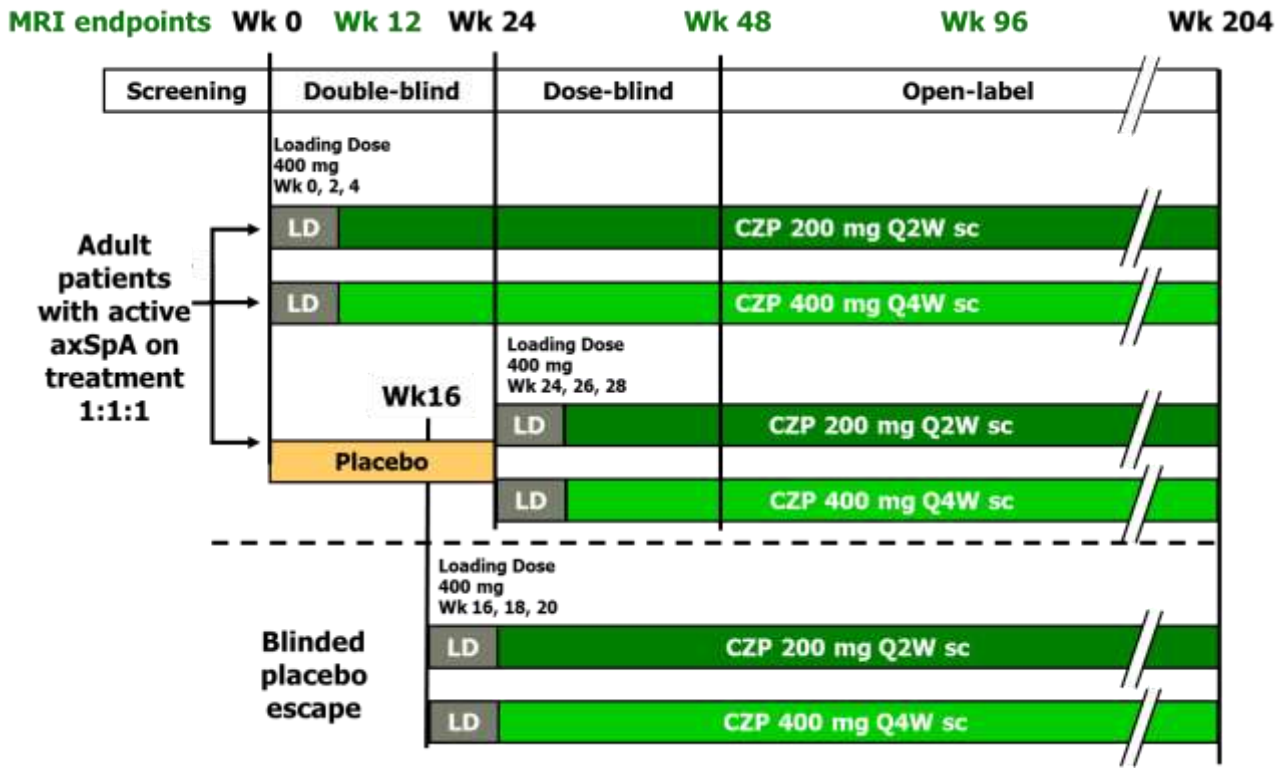
AS: Ankylosing spondylitis; **ASAS**: Assessment of SpondyloArthritis International Society; **axSpA**: Axial spondyloarthritis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **CRP**: C-reactive protein; **CZP**: Certolizumab pegol; **mNY**: Modified New York; **MRI**: Magnetic resonance imaging; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **NSAID**: Non-steroidal anti-inflammatory drug; **PBO**: Placebo; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **ULN**: Upper limit of normal

5.2 Methodology of the Study

5.2.1 Study Design

The RAPID-axSpA study is an ongoing phase 3, multinational, multicentre, randomised, parallel group study. The study was PBO-controlled and double-blind until Week 24, at which point all PBO patients were moved into the active arms. The study was then dose-blind until Week 48 after which the study became open-label. The study will continue as open-label until Week 204.
There were two active arms with different CZP dosing regimens plus a PBO arm during the double-blind 24-week phase of the study. A schematic of the study design is shown in Figure 5-1 and details of the methodologies employed are summarised in Appendix 11.2.1.1 (Table 11-1). The calculations for the powering of the study are described in Appendix 11.2.1.1.

Figure 5-1: RAPID-axSpA trial design schematic



PBO escape was mandatory at Week 16 for all subjects who had not achieved an ASAS20 response at Week 14 and Week 16 of the study. These subjects were re-randomised to both CZP arms 1:1 at Week 16. Subjects who completed to Week 24 in the PBO arm were re-randomised to the CZP arms 1:1 at Week 24.

At study baseline, patients were randomised to treatment using an interactive voice/web response system (IXRS) in a 1:1:1 ratio to receive PBO, or 400 mg CZP administered subcutaneously (sc) at weeks 0, 2 and 4 followed by either CZP 200 mg every two weeks (Q2W) or CZP 400 mg every four weeks (Q4W). Cumulative doses of CZP administered over time were the same in both dosing regimens. All patients received injections Q2W, either CZP or PBO, to maintain blinding. Treatment randomisation was performed centrally and was stratified by site, fulfilment of mNY criteria, and prior anti-TNF therapy exposure.[18]

In order to treat patients randomised to receive PBO in RAPID-axSpA ethically and offer the best outcome in the event of limited response, escape from the PBO arm to receive CZP was required by the protocol at Week 16 for patients who had not achieved an ASAS20 response at Week 14 and Week 16. PBO patients who underwent mandatory early escape remained blinded but were re-randomised to active treatment at Week 16 in a 1:1 ratio (CZP 200 mg Q2W: CZP 400 mg Q4W). Subjects originally randomised to PBO who completed Week 24 were re-randomised at Week 24 in a similar manner.[18] Randomisation of patients escaping at Week 16 and Week 24 was performed using the same IXRS system as used at baseline. Subjects in the CZP 400 mg Q4W arm received injections of CZP alternately with PBO injections to conceal allocation. [redacted]

[redacted]
Subgroup analyses by mNY criteria (yes/no) were performed, and this was pre-specified in the study protocol.

The RAPID-axSpA study was the first to include patients from across the spectrum of axSpA disease by including patients with and without radiographic damage. This may therefore make the trial more representative of clinical practice where treatment decisions are driven by the levels of pain, fatigue and difficulty with daily life, not the presence or absence of structural changes in the sacroiliac joints.[9, 10, 55, 57] The additional benefit of recruiting a spectrum of axSpA patients allows for the direct comparison of disease burden at baseline and treatment efficacy between the overall axSpA population, the AS subpopulation and the nr-axSpA subpopulation. The RAPID-axSpA study population includes both patient groups for which licensed anti-TNF therapies will be appraised by NICE in their update to TA143 and TA233 in 2015.[58]

A further advantage of the study design was that the study protocol involved the collection of data across a wide range of patient relevant outcomes, including workplace and household productivity. These provide evidence that the improvements in clinical signs and symptoms of disease also translate into meaningful patient-relevant outcomes, which benefit the patient as well as society overall. However, in being the first trial conducted in this broader patient population, its comparison to clinical studies of relevant comparators cannot be made using the overall axSpA population, but rather by using the AS or nr-axSpA subpopulations separately, in which the comparators have been previously investigated in terms of efficacy and safety.

5.2.2 Participant Eligibility

Details of the key inclusion and exclusion criteria for the study are shown below in Table 5-2. The full inclusion and exclusion criteria for the study can be found in Appendix 11.2.2.

Table 5-2: RAPID-axSpA study main eligibility criteria

	NCT01087762 RAPID-axSpA study
Inclusion criteria	• Age ≥18 years • History of adult onset axSpA • Active axSpA of ≥3 months duration and meets ASAS criteria for axSpA • BASDAI ≥4 • Spinal pain ≥4 • CRP >7.9 mg/L (>ULN) **and/or** sacroiliitis on MRI (as defined by the ASAS/Outcome Measures in Rheumatology (OMERACT) definition[12]) • Failed or intolerant to ≥1 NSAID during ≥30 days of continuous therapy (highest tolerated dose) or ≥2 weeks each for ≥2 NSAIDs
Exclusion criteria	• Previous exposure to CZP • Hypersensitivity to any component of CZP, PBO, or with a history of an adverse reaction to polyethylene glycol • History of chronic alcohol abuse or drug abuse within the last year • Exposure to >2 previous biological agents (>1 anti-TNF therapy) for axSpA. Up to 40% of subjects were permitted to have exposure to 1 previous anti-TNF >3 months prior to baseline (or >28 days for etanercept) • AxSpA-disease related exclusions: a) Diagnosis of total spinal ankylosis ("bamboo spine") or any other inflammatory arthritis b) Secondary, non-inflammatory condition symptomatic enough to interfere with evaluation of effect of CZP on axSpA • Female subjects who were breastfeeding, pregnant or planned to become pregnant during the study or within 3 months following the last dose • A history of chronic or recurrent infections, recent serious or life–threatening infection (<6 months prior to baseline, including herpes zoster), or known TB disease, high risk of acquiring TB infection or latent TB infection

ASAS: Assessment of SpondyloArthritis International Society; **axSpA**: Axial spondyloarthritis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **CRP**: C-reactive protein; **CZP**: Certolizumab pegol; **MRI**: magnetic resonance imaging; **NSAIDs**: Non-steroidal anti-inflammatory drugs; **OMERACT**: Outcomes Measures in Rheumatology; **PBO**: Placebo; **TB**: Tuberculosis; **TNF**: Tumour necrosis factor; **ULN**: Upper limit of normal

In order to recruit a broadly balanced population between AS and nr-axSpA patients, at least 50% of the study population had to fulfil the diagnosis of AS according to the mNY criteria for AS,[59] thereby fulfilling the X-ray based imaging criteria within the ASAS criteria. Of those patients who did not fulfil mNY criteria due to lack of definitive evidence of sacroiliitis on X-ray, at least 50% were recruited based on the ASAS MRI criteria (by evidence of sacroiliitis on MRI using the ASAS/Outcomes Measures in Rheumatology [OMERACT] criteria[12]). The remaining patients were recruited based on the presence of HLA-B27 plus two

other ASAS clinical criteria (including an elevated CRP level).[18] The presence of sacroiliitis on MRI or elevated CRP have been shown to be significant predictors for the development of axial radiographic lesions (MRI: odds ratio = 2.25, [p=0.001]; CRP: odds ratio = 1.44 [p=0.003]).[60] The use of active disease and objective signs of inflammation to select patients for anti-TNF therapy is consistent with clinical practice in England and Wales, whereby patients with axSpA are treated without needing to have both sacroiliitis on MRI and elevated CRP, as confirmed by a rheumatologist practising in Britain:

- "It is unnecessary to have both raised CRP and positive MRI as they are both inconsistently positive/raised and can fluctuate. They are both useful as objective evidence of disease in a disease with many subjective measures so one or the other helps confirm to the rheumatologist that they are dealing with active axial-SpA. Having both is ideal but unnecessary, especially as both MRI positivity and raised CRP are both inconsistent."[61]

Patients who were enrolled on the basis of meeting the imaging criteria must have been diagnosed on the basis of sacroiliac X-rays (read by a radiologist or rheumatologist) or MRIs (read by a radiologist) prior to the screening visit. All X-ray and MRI reports were included in source documentation.

Specific axSpA disease-related exclusions meant that patients must not have had total spinal ankylosis ("bamboo spine"), a diagnosis of any other inflammatory arthritis (eg. RA, systemic lupus erythematosus, sarcoidosis) or a known diagnosis of fibromyalgia. In addition, patients must not have had a secondary, non-inflammatory condition (eg. osteoarthritis) symptomatic enough to interfere with evaluation of the effect of CZP on the subject's primary diagnosis of axSpA. Prior medical exclusion criteria included previous exposure to two or more biological agents, or more than one anti-TNF therapy. Previous withdrawal from an anti-TNF therapy could not have been due to primary failure, but could have been due to secondary failure, or withdrawal due to economic or other reasons.[18]

5.2.3 Efficacy Analyses

5.2.3.1 Datasets

Randomisation was performed centrally and was stratified by site, fulfilment of mNY criteria and prior anti-TNF therapy exposure.

The 'Randomised Set' (RS) consisted of all subjects randomised into the study. The RS was used for the analysis of the primary endpoint (ASAS20 at Week 12) and key secondary efficacy endpoints (ASAS20 at Week 24, change from baseline in BASDAI, BASFI and BASMI linear at Week 24).

The 'Full Analysis Set' (FAS) referred to patients who received ≥1 dose of study medication and had a valid baseline and post-baseline measurement for ASAS20 and consisted of all patients in the RS minus 1 PBO patient. The FAS was used for the analysis of other secondary outcomes and exploratory outcomes.

Data are shown as observed case (OC) and with imputation. Non-responder imputation (NRI) was used for categorical measures, last observation carried forward (LOCF) for continuous measures.

The 'Safety Set' (SS) consisted of all subjects in the RS who had received at least 1 dose of study medication. The SS was used for the analyses of safety data at Weeks 24, 48 and 96 (reported in Section 7).

Efficacy data at Week 24 in the CZP-treated arms present patients who were randomised to the CZP dosing arms at baseline and does not include PBO patients who escaped at Week 16. Safety data at Week 24 present all CZP-exposed patients whether they received CZP at baseline or at Week 16.

Efficacy data up to Week 48 are presented for patients who were randomised to the CZP dosing arms at baseline only and does not include PBO patients who escaped at Week 16 and Week 24. Safety data at Week 48 present all CZP-exposed patients whether they received CZP at baseline, Week 16 or Week 24.

Efficacy data up to Week 96 are presented for patients who were randomised to the CZP dosing arms at baseline only and does not include PBO patients who escaped at Week 16 and Week 24. The OC data set was used. Safety data at Week 96 present all CZP-exposed patients whether they received CZP at baseline, Week 16 or Week 24.

5.2.3.2 Outcomes

The primary outcome of the RAPID-axSpA study was the ASAS20 response at Week 12. Key secondary outcomes included the ASAS20 response at Week 24, the change from baseline at Weeks 12 and 24 in BASFI, BASDAI and BASMI linear. These outcomes are all ASAS-endorsed for assessing the core domains of axSpA disease activity for clinical record keeping, disease-controlling- and symptom-modifying anti-rheumatic treatments or drugs.[62, 63] In addition, BASFI, BASDAI and BASMI linear are used by clinicians in clinical practice. For example, the ASAS20 response criteria were designed by clinicians working in the rheumatology field, and in particular for AS patients.[64] Furthermore, this outcome has been reported in RCTs of all anti-TNF therapies in this disease area.[62] Since the signs and symptoms of nr-axSpA disease are largely the same as AS, measures used in AS are accepted for use in nr-axSpA. For a more detailed list of outcomes in the RAPID-axSpA study, please see Appendix 11.2.1.1 (Table 11-1), and for a more detailed description of the outcomes presented in this submission, please see Appendix 11.2.3.

5.2.4 Hierarchical Test Procedure

In the RAPID-axSpA study, a hierarchical test procedure was applied for the primary endpoint and key secondary endpoints in the overall axSpA population in order to protect the overall significance level for the multiplicity of dose groups and endpoints. The pre-defined order of hypothesis testing, each at a 2-sided 5% alpha level versus PBO, was performed in the randomised set (RS) with imputation. The predefined hierarchical testing of the primary and key secondary efficacy endpoints is shown in Appendix 11.2.1.3 (Figure 11-1).

5.2.5 Missing Data

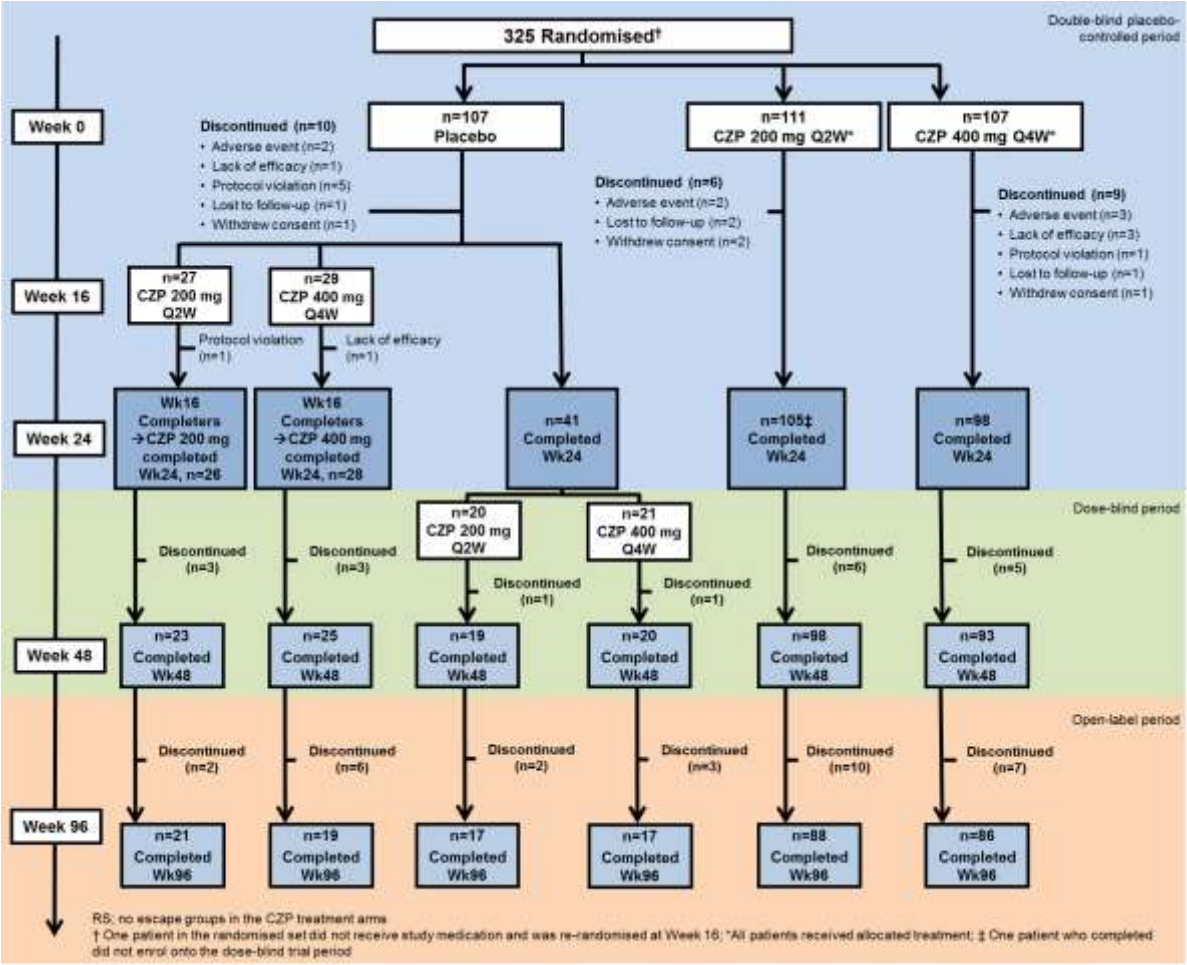
Missing data due to study withdrawal, any other reason, and all post-Week 16 data for PBO patients escaping to active treatment were imputed using NRI for categorical outcomes (eg. ASAS20) and LOCF for continuous variables (eg. BASFI and BASDAI).[18] The handling of missing data is described in detail for the key outcomes in Appendix 11.2.4 (Table 11-3).

5.3 RAPID-axSpA Study Results

5.3.1 Participant Flow

Participant flow in the RAPID-axSpA study is summarised in Figure 5-2. A total of 325 patients with active axSpA, according to the ASAS classification criteria, were studied in RAPID-axSpA. At Week 0, 218 patients were randomised to CZP treatment and 107 patients were randomised to PBO. At Week 16, 56 PBO patients escaped and were re-randomised to CZP 200 mg Q2W (27 subjects) or CZP 400 mg Q4W (29 subjects) through to the end of the study. Most (91.7%) subjects completed the double-blind PBO-controlled treatment period (up to Week 24). Overall, the most common reasons for discontinuation from the study by Week 24 were adverse events (AEs) and protocol violation.[18]

Figure 5-2: RAPID-axSpA study patient numbers through double-blind and dose-blind phases to Week 96[18, 56]



5.3.2 Baseline Characteristics and Burden of Disease

Patient characteristics at baseline are presented in Table 5-3 and by AS or nr-axSpA subpopulation in Table 5-4. The treatment groups and study populations in the RAPID-axSpA trial were generally well-balanced with respect to demographics and baseline characteristics. All patients had highly active disease, which was similar between AS and nr-axSpA subpopulations. Of the 147 nr-axSpA patients, 80 were enrolled via ASAS MRI imaging criteria and the other 67 via ASAS clinical criteria (see section 5.2.2).[18]

Some differences were noted between the AS and nr-axSpA patient subpopulations (Table 5-4). More males than females were found in the AS subpopulation whereas the gender balance was approximately equal in the nr-axSpA subpopulation, which is consistent with previous reports.[65, 66] Subjects in the nr-axSpA subpopulation were, on average, younger than subjects in the AS subpopulation, had a shorter time since symptom onset, and had lower CRP levels. Function and spinal mobility were also worse in the AS subpopulation, likely to be a consequence of the permanent structural changes seen in AS. However, except for CRP levels, similar baseline disease activity as measured by the BASDAI and ASDAS was observed for AS and nr-axSpA subpopulations.[18]

Furthermore, the humanistic and economic burden of disease was similar between the AS and nr-axSpA subpopulations at study baseline (Table 5-5). The burden was similar in terms of the health-related quality of life, assessed through the Short Form 36 (SF-36), which measures both physical and mental components of well-being, and the ASQoL, which is a validated disease-specific 18-item questionnaire for measuring HRQoL in subjects with AS.[16] The ASQoL ranges from 0 to 18 with a higher score indicating worse HRQoL and can also be used in axSpA patients.[8, 17]

In addition, at study baseline 69.2% of axSpA patients were employed outside the home, slightly more nr-axSpA patients were employed (71.4%) compared to AS (67.4%). More AS patients, compared to nr-axSpA patients, were unable to work due to spondyloarthritis (15.7% vs 8.2%, respectively). A similarly high burden of disease on workplace and household productivity was seen in AS and nr-axSpA patients, with an average

of >1 week of paid work affected by disease over previous month and approximately 2 weeks of household duties affected/month (Table 5-5).

[redacted]

Concomitant NSAIDs and DMARDs (sulfasalazine and MTX) were taken by 87.8% and 30.7% of patients at baseline, respectively.[18]

Table 5-3: RAPID-axSpA study patient demographics at baseline (randomised set)[18, 23]

	PBO n=107	CZP 200 mg Q2W n=111	CZP 400 mg Q4W n=107	Overall n=325
Demographic characteristics				
Age, mean years (SD)	39.9 (12.4)	39.1 (11.9)	39.8 (11.3)	39.6 (11.9)
Male, %	60.7	60.4	63.6	61.5
axSpA characteristics				
Symptom duration, median, years (min, max)	7.7 (0.3, 50.9)	6.9 (0.3, 34.2)	7.9 (0.3, 44.8)	7.7 (0.3, 50.9)
Symptom duration <5 years, n (%)	42 (39.3)	50 (45.0)	34 (31.8)	126 (38.8)
Positive for HLA-B27, n (%)	87 (81.3)	87 (78.4)	81 (75.7)	255 (78.5)
CRP, mg/L				
Median, (min, max)	15.0 (0.1, 156.2)	12.7 (0.1, 174.8)	12.3 (0.1, 159.9)	13.9 (0.1, 174.8)
>ULN, n (%)	77 (72.0)	75 (67.6)	71 (66.4)	223 (68.6)
≥15 mg/L, n (%)	53 (49.5)	42 (37.8)	38 (35.5)	133 (40.9)
BASDAI,[#] mean (SD)	6.4 (1.7)	6.5 (1.6)	6.4 (1.5)	6.4 (1.6)
BASFI,[#] mean (SD)	5.5 (2.1)	5.3 (2.3)	5.4 (2.3)	5.4 (2.3)
BASMI linear,[#] mean (SD)	4.0 (1.8)	3.7 (1.6)	3.8 (1.7)	3.8 (1.7)
ASDAS,[#] mean (SD)	4.0 (0.9)	3.9 (0.9)	3.8 (0.8)	3.9 (0.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior and concomitant medication				
Concomitant NSAIDs, n (%)	92 (86.0)	97 (87.4)	95 (88.8)	285 (87.8)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allowed concomitant DMARDs, n (%)	38 (35.5)	31 (27.9)	31 (29.0)	100 (30.7)
Prior anti-TNF exposure, n (%)	26 (24.3)	15 (13.5)	11 (10.3)	52 (16.0)

ASAS: Assessment of SpondyloArthritis International Society; **ASDAS**: Ankylosing Spondylitis Disease Activity Score; **axSpA**: Axial spondyloarthritis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **BASMI**: Bath Ankylosing Spondylitis Metrology Index in linear definition; **CRP**: C-reactive protein; **DMARDs**: Disease modifying anti-

rheumatic drugs; **FAS**: Full analysis set; **HLA-B27**: Human leukocyte antigen B27; **MASES**: Maastricht Ankylosing Spondylitis Enthesitis Score; **NSAIDs**: Non-steroidal anti-inflammatory drugs; **Q2W**: Every 2 weeks; Q4W**:** Every 4 weeks; **SD**: Standard deviation, **TNF**: Tumour necrosis factor; **ULN**: Upper limit of normal
in FAS dataset; † defined as at least 1 swollen joint in 44 joint assessment; ‡ defined as ≥1 point in MASES; § defined using ASAS criteria
CRP ULN=7.9 mg/L (defined by central lab)

Table 5-4: RAPID-axSpA study baseline demographics of AS and nr-axSpA subpopulations (randomised set)[18, 23]

	AS n=178	**nr-axSpA n=147**
Demographic characteristics		
Age, mean years (SD)	41.5 (11.6)	37.4 (11.8)
Male, %	72.5	48.3
axSpA characteristics		
Symptom duration, median, years (min, max)	9.1 (0.3, 50.9)	5.5 (0.3, 41.5)
Symptom duration <5 years, n (%)	57 (32.0)	69 (46.9)
Positive for HLA-B27, n (%)	145 (81.5)	110 (74.8)
CRP, mg/L		
Median, (min, max)	14.3 (0.1, 174.8)	11.9 (0.1, 156.2)
>ULN, n (%)	130 (73.0)	93 (63.3)
≥15 mg/L, n (%)	80 (44.9)	53 (36.1)
BASDAI,[#] mean (SD)	6.4 (1.6)	6.5 (1.5)
BASFI,[#] mean (SD)	5.7 (2.2)	4.9 (2.3)
BASMI linear,[#] mean (SD)	4.4 (1.7)	3.2 (1.5)
ASDAS,[#] mean (SD)	4.0 (0.9)	3.8 (0.9)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Prior and concomitant medication		
Concomitant NSAIDs, n (%)	162 (91.0)	123 (83.7)
[redacted]	[redacted]	[redacted]
Allowed concomitant DMARDs, n (%)	63 (35.4)	37 (25.2)
Prior anti-TNF exposure, n (%)	36 (20.2)	16 (10.9)

ASAS: Assessment of SpondyloArthritis International Society; **AS**: Ankylosing spondylitis; **ASDAS**: Ankylosing Spondylitis Disease Activity Score; **axSpA**: Axial spondyloarthritis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **BASMI**: Bath Ankylosing Spondylitis Metrology Index in linear definition; **CRP**: C-reactive protein; **DMARDs**: Disease modifying anti-rheumatic drugs; **FAS**: Full analysis set; **HLA-B27**: Human leukocyte antigen B27; **MASES**; Maastricht Ankylosing Spondylitis Enthesitis Score; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **NSAIDs**: Non-steroidal anti-inflammatory drugs; **SD**: Standard deviation, **TNF**: Tumour necrosis factor; **ULN**: Upper limit of normal
in FAS dataset; † defined as at least 1 swollen joint in 44 joint assessment; ‡ defined as ≥1 point in MASES; § defined using ASAS criteria
CRP ULN=7.9 mg/L (defined by central lab)

Table 5-5: RAPID-axSpA study baseline burden of disease in the AS and nr-axSpA subpopulations[35, 67]

	axSpA n=325	AS n=178	nr-axSpA n=147
Health-related quality of life*			
ASQoL, mean (SD)	11.75 (4.3)	11.8 (4.3)	11.7 (4.3)
SF-36 PCS, mean (SD) MCS, mean (SD)	 32.5 (7.5) 40.5 (12.1)	 32.0 (7.3) 40.9 (12.0)	 33.1 (7.8) 40.0 (12.3)
Workplace and household productivity#			
Mean number of working days affected by arthritis over previous month†	7.2	6.3	8.3
Mean level of arthritis interference with work productivity over previous month§	4.6	4.5	4.8
Mean number of household work days affected by disease over previous month¶	13.3	12.2	14.6
Mean level of arthritis interference with household work productivity over previous month§	4.9	4.9	4.8
Mean number of days missed of family, social and leisure activities because of arthritis over previous month	4.4	3.6	5.4

AS: Ankylosing spondylitis; **ASQoL**: Ankylosing spondylitis quality of life; **AxSpA**: Axial spondyloarthritis; **MCS**: Mental component summary; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **PCS**: Physical component summary; **SD**: Standard deviation, **SF-36**: Short Form 36
* FAS population, LOCF imputation used
# RS, observed data
† Includes both absenteeism and presenteeism at work. Absenteeism: work days missed due to arthritis over previous month. Presenteeism: days with work productivity reduced by ≥50% due to arthritis over previous month (does not include days counted in absenteeism)
§ 0-10 point scale (0=no interference, 10=complete interference)
¶ Includes both the number of full household work days missed due to arthritis and days with household productivity reduced by ≥50% due to arthritis (not counted in full days missed)

5.3.3 Compliance

[redacted]

[redacted]

5.4 Efficacy Results

All endpoints in the hierarchical testing plan were met and therefore all 10 of the endpoints in the hierarchical testing plan can be designated as statistically significant. For further details of the hierarchical testing plan for the RAPID-axSpA study please see Appendix 11.2.1.3. Outcomes presented here are as follows:

- ASAS responses (ASAS20, ASAS40, ASAS5/6 and ASAS partial response)
- Bath Ankylosing Spondylitis indices (BASDAI, BASFI and BASMI linear)
- Total and nocturnal back pain
- Daily pain, fatigue and sleep
- Health-related quality of life
- Workplace and household productivity

Further details for all of these outcomes can be found in Appendix 11.2.3.

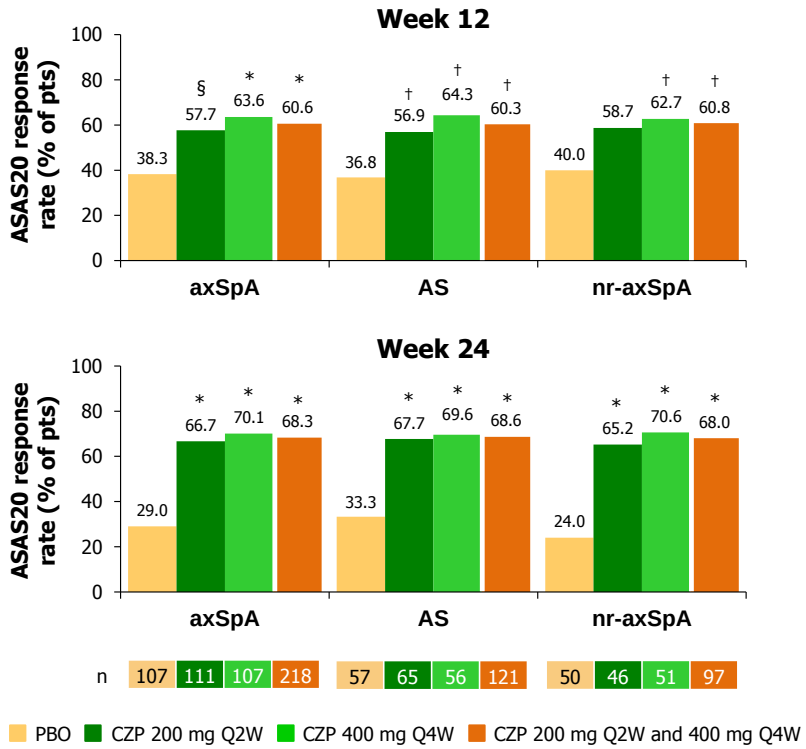
5.4.1 ASAS Responses

5.4.1.1 ASAS20 Response Criteria

The primary outcome of the RAPID-axSpA trial was ASAS20 response (≥20% improvement in ASAS) at Week 12. For the total axSpA patient population at Week 12, the ASAS20 response was statistically significantly greater in both CZP treatment groups compared with PBO (p=0.004 and p<0.001 for CZP 200 mg Q2W and CZP 400 mg Q4W, respectively) (Figure 5-3).[18] The primary endpoint of this study was therefore met.

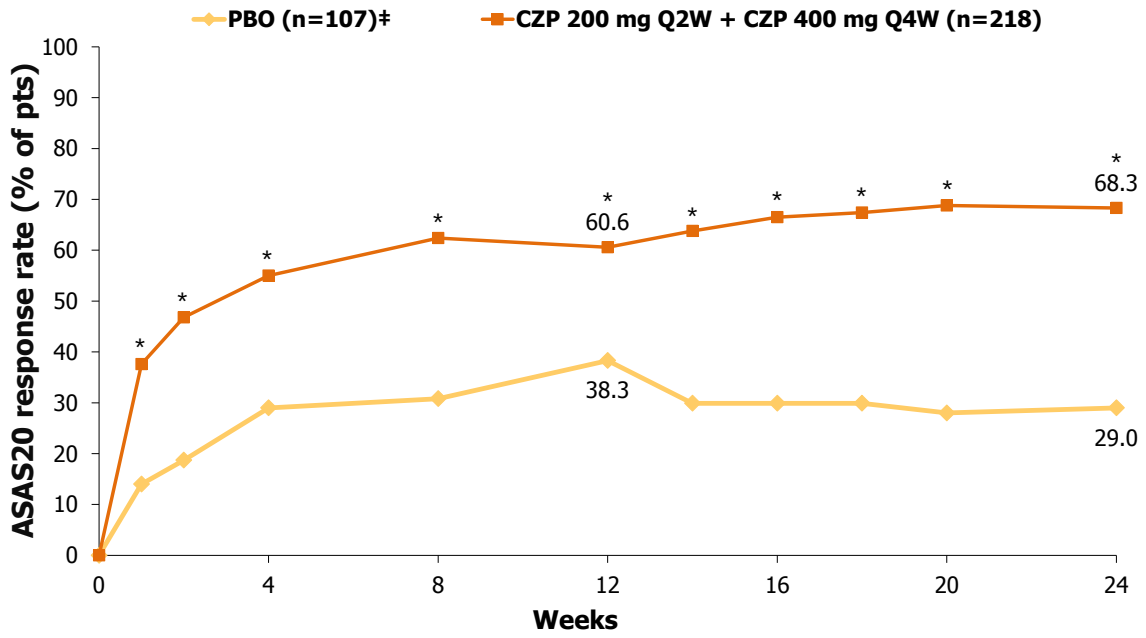
The improvement in ASAS20 response rate for patients treated with CZP was rapid, with significant differences observed by Week 1 (Figure 5-4).[18] Both subpopulations (AS and nr-axSpA) saw increased ASAS20 response rates with CZP compared to PBO (Figure 5-3).[18] The ASAS20 response was maintained through to Week 48 during the dose-blind phase of the study, and then to Week 96 during the open-label phase of the study in the CZP groups, both in the overall axSpA population and in the AS and nr-axSpA subpopulations (Table 5-6 and Appendix 11.2.5.9).[19, 23, 56]

Figure 5-3: RAPID-axSpA study ASAS20 response at Week 12 and Week 24 in the overall axSpA population and the AS and nr-axSpA subpopulations



§ p=0.004; * p<0.001; † p<0.05 CZP vs PBO (2-sided Wald asymptotic test); data correspond to the RS (NRI imputation)

Figure 5-4: RAPID-axSpA study kinetics of the ASAS20 response to Week 24 in the overall axSpA population (as per allocation at Week 0)



* p<0.001 CZP vs PBO (2-sided Wald asymptotic test); data correspond to the RS (NRI imputation); ‡ PBO patients escaping at Week 16 (n=56) were considered non-responders Weeks 16-24

Table 5-6: RAPID-axSpA study efficacy in overall axSpA population and AS and nr-axSpA subpopulations at Week 48 and Week 96 in subjects randomised to CZP at baseline[23, 56]

	Overall axSpA		AS		nr-axSpA	
	CZP 200 mg Q2W n=111	CZP 400 mg Q4W n=107	CZP 200 mg Q2W n=65	CZP 400 mg Q4W n=56	CZP 200 mg Q2W n=46	CZP 400 mg Q4W n=51
ASAS20 at Week 48, n (%) (95% CI)†	79 (71.2) (62.7–79.6)	78 (72.9) (63.5–80.5)	47 (72.3) (61.4–83.2)	42 (75.0) (63.7–86.3)	32 (69.6) (56.3–82.9)	36 (70.6) (55.9–81.4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AS: Ankylosing spondylitis; **ASAS**: Assessment of SpondyloArthritis International Society; **axSpA**: Axial spondyloarthritis; **CZP**: Certolizumab pegol; **FAS**: Full analysis set; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **NRI**: Non-responder imputation; **Q2W**: Every two weeks; **Q4W**: Every 4 weeks
† Data correspond to the FAS population; NRI was used: subjects who withdrew for any reason were considered as non-responders from the time that they dropped out. Subjects who had missing data at a visit were counted as a non-responder for the respective visit.
§ Data correspond to the RS with imputation; NRI was used: subjects who withdrew for any reason were considered as non-responders from the time that they dropped out. Subjects who had missing data at a visit were counted as a non-responder for the respective visit; 95% CIs were not generated for Week 96 and are therefore unavailable at this time.

5.4.1.2 Other ASAS Response Criteria

In addition to the ASAS20 response (Section 5.4.1.1), the following more stringent ASAS-based responses were also assessed: ASAS40 response (≥40% improvement in ASAS); ASAS5/6 response (≥20% improvement in 5 of 6 ASAS domains, including spinal mobility and CRP);[70] ASAS partial remission (a score of ≤2 units [on a 0—10 scale] in all 4 domains).

At Week 24, the proportion of patients achieving an ASAS40 response, [redacted] and ASAS partial remission was significantly greater in the CZP 200 mg Q2W and CZP 400 mg Q4W groups compared with PBO (p<0.001) (Table 5-7,Table 5-8). These responses versus PBO were similar across the AS and nr-axSpA subpopulations, and these levels of response were maintained to Week 96 during the dose-blind and open-label phases of the study (Section 5.4.12 and Appendix 11.2.5.9).[18, 19, 23]

Table 5-7: RAPID-axSpA study ASAS40, ASAS 5/6 and ASAS partial remission response rates at Week 12 and Week 24 in the overall axSpA population

	PBO n=107	CZP 200 mg Q2W n=111	CZP 400 mg Q4W n=107	CZP 200 mg Q2W and 400 mg Q4W n=218
ASAS40 response rate, n (%)				
Week 12	19 (17.9)	48 (43.2)*	52 (48.6)*	100 (45.9)*
Week 24	16 (15.1)	57 (51.4)*	56 (52.3)*	113 (51.8)*
[redacted]				
ASAS partial remission response rate, n (%)				
Week 12	4 (3.7)	26 (23.4)*	26 (24.3)*	52 (23.9)*
Week 24	9 (8.4)	34 (30.6)*	32 (29.9)*	66 (30.3)*

ASAS: Assessment of SpondyloArthritis International Society; **CZP**: Certolizumab pegol; **NRI**: Non-responder imputation; **PBO**: Placebo; **Q2W**: Every two weeks; **Q4W**: Every 4 weeks
* p<0.001 CZP vs PBO (2-sided Wald asymptotic test); data correspond to the randomised set (NRI imputation)

Table 5-8: RAPID-axSpA study ASAS40, ASAS 5/6 and ASAS partial remission response rates at Week 12 and Week 24 in the AS and nr-axSpA subpopulations

	AS				nr-axSpA			
	PBO n=57	CZP 200 mg Q2W n=65	CZP 400 mg Q4W n=56	CZP 200 mg Q2W and 400 mg Q4W n=121	PBO n=50	CZP 200 mg Q2W n=46	CZP 400 mg Q4W n=51	CZP 200 mg Q2W and 400 mg Q4W n=97
ASAS40 response rate, n (%)								
Week 12	11 (19.3)	26 (40.0)†	28 (50.0)*	54 (44.6)*	8 (16.0)	22 (47.8)*	24 (47.1)*	46 (47.4)*
Week 24	9 (15.8)	31 (47.7)*	33 (58.9)*	64 (52.9)*	7 (14.0)	26 (56.5)*	23 (45.1)*	49 (50.5)*
[redacted]								
ASAS partial remission response rate, n (%)								
Week 12	1 (1.8)	13 (20.0)*	11 (19.6)§	24 (19.8)*	3 (6.1)	13 (28.3)§	15 (29.4)§	28 (28.9)*
Week 24	4 (7.0)	20 (30.8)*	14 (25.0)†	34 (28.1)*	5 (10.0)	14 (30.4)†	18 (35.3)§	32 (33.0)*

AS: Ankylosing spondylitis; **ASAS**: Assessment of SpondyloArthritis International Society; **axSpA**: Axial spondyloarthritis; **CZP**: Certolizumab pegol; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **NRI**: Non-responder imputation; **PBO**: Placebo; **Q2W**: Every two weeks; **Q4W**: Every 4 weeks
* p<0.001; § p<0.005; † p<0.05 CZP vs PBO (2-sided Wald asymptotic test); data correspond to the RS (NRI imputation)

5.4.2 ASDAS

The Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated at each visit to further assess the efficacy of CZP treatment. The ASDAS is comprised of a number of assessments which are scored by the patient and their physician.[71] A decrease from baseline ASDAS ≥2.0 was defined as a major improvement (MI) and an ASDAS of <1.3 was defined as inactive disease (ID). Mean baseline ASDAS score was 3.8 in the overall axSpA population, reflecting very highly active disease. The percentage of axSpA patients showing either major improvement (MI) or inactive disease (ID) at Week 12 was significantly higher in both CZP treatment groups compared with placebo (Appendix 11.2.5.1). Further ASDAS improvement was observed at Week 24.

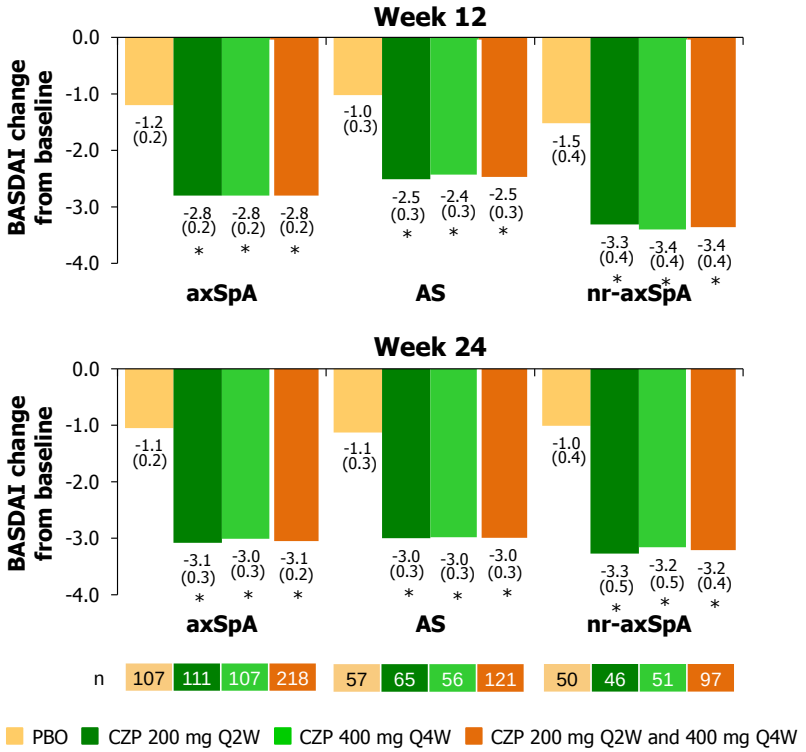
5.4.3 BASDAI (Disease Activity)

The BASDAI measures disease activity in axSpA. In the RAPID-axSpA study, the change from baseline in BASDAI to Week 24 was clinically meaningful with significant differences between CZP-treated groups and the PBO group (p<0.001) (Figure 5-5). Significant improvements versus PBO in BASDAI were noted in both CZP treatment groups and in both the AS and nr-axSpA subpopulations. The change was rapid with significant differences observed between CZP-treated groups and the PBO group at Week 1 (CZP 200 mg Q2W: p<0.001; CZP 400 mg Q4W: p<0.005). Furthermore, the effects of CZP were maintained to Week 96 during the dose-blind and open-label phases of the study (Section 5.4.12 and Appendix 11.2.5.9).[18, 19, 23]

[redacted]

[redacted]

Figure 5-5: RAPID-axSpA study mean change from baseline in BASDAI score at Week 12 and at Week 24 in the overall axSpA population and the AS and nr-axSpA subpopulations



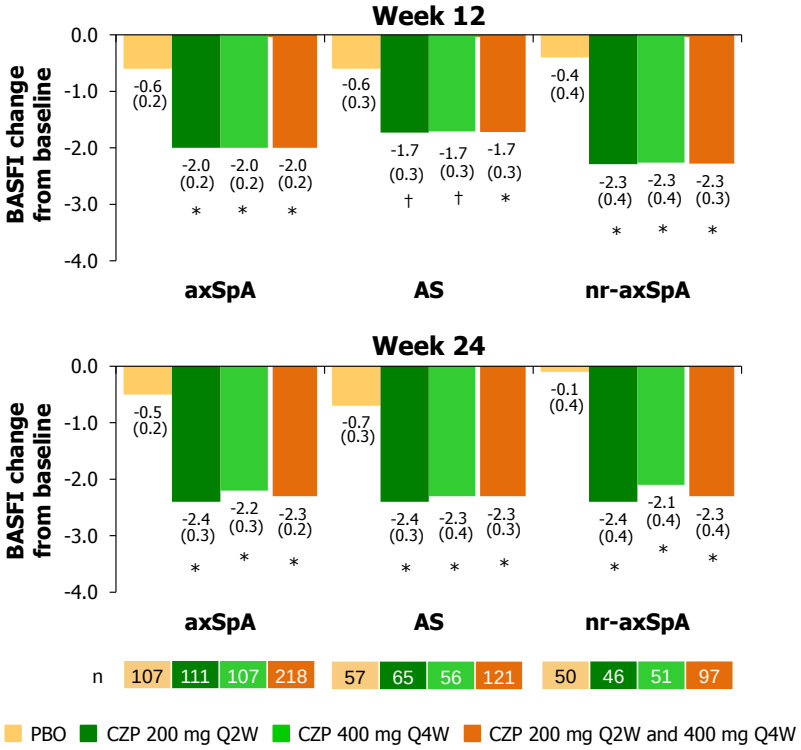
*p<0.001 for CZP vs PBO (ANCOVA model); data correspond to the RS (LOCF imputation) and presented as mean (standard error)

5.4.4 BASFI (Physical Function)

Change from baseline in BASFI was used to measure changes in physical function at Week 24. Change from baseline in BASFI at Week 24 in CZP-treated groups in the RS was clinically meaningful and significant in the overall axSpA population. At Week 24, the least squares (LS) mean change from baseline in BASFI was greater in both CZP dosing groups compared with the PBO group (Figure 5-6). BASFI MCID (defined as a ≥1 unit decrease) response rates at Week 24 for CZP 200 mg Q2W and CZP 400 mg Q4W patients were significantly higher than PBO at 64.0% (71/111) and 71.0% (76/107), respectively, versus 29.2% (31/106) (p<0.001 for both).

The mean baseline BASFI score in the nr-axSpA subpopulation (mean ±SD=4.9 ±2.3) was lower than in the AS subpopulation (mean ±SD=5.7 ±2.2) at baseline, reflecting a lesser degree of impaired function in the nr-axSpA subpopulation (Table 5-4). However, the CZP treatment effect was similar in the AS and nr-axSpA subpopulations at Week 24, with improvements being clinically meaningful and significant compared to PBO (Figure 5-6). The effects of CZP on the BASFI score were maintained to Week 96 during the dose-blind and open-label phases of the study (Section 5.4.12 and Appendix 11.2.5.9).[18, 19, 23]

Figure 5-6: RAPID-axSpA study mean change from baseline in BASFI score at Week 12 and at Week 24 in the overall axSpA population and the AS and nr-axSpA subpopulations

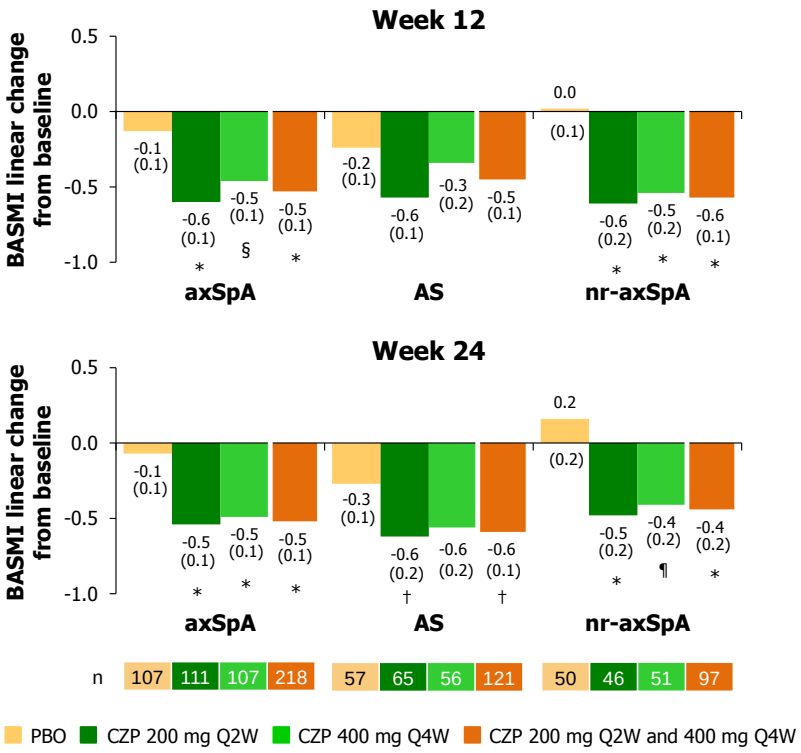


*p<0.001; † p<0.005 CZP vs PBO (ANCOVA model); data correspond to the RS (LOCF imputation) and presented as mean (standard error)

5.4.5 BASMI Linear (Spinal Mobility)

The BASMI linear measures spinal mobility in axSpA by combining five different measures of mobility. The change from baseline in BASMI linear at Week 12 and Week 24 was clinically meaningful and significant compared to PBO in the overall axSpA population (Figure 5-7). Following a similar pattern to BASFI scores, the mean baseline BASMI linear score in the nr-axSpA subpopulation (mean ±SD=3.2 ±1.5) was lower than that seen in the AS subpopulation (mean ±SD=4.4 ±1.7) at baseline (Table 5-4) reflecting less impaired spinal mobility. Despite considerably lower baseline BASMI linear scores, comparable changes from baseline and greater differences to PBO were observed in the nr-axSpA subpopulation as compared to the AS subpopulation (Figure 5-7). In addition, these reductions were maintained to Week 96 during the dose-blind and open-label phases of the study (Section 5.4.12 and Appendix 11.2.5.9).[18, 19, 23]

Figure 5-7: RAPID-axSpA study mean change from baseline in BASMI linear score at Week 12 and at Week 24 in the overall axSpA population and the AS and nr-axSpA subpopulations



* p<0.001; ¶ p=0.002; § p=0.005; † p<0.05; CZP vs PBO all ANCOVA; data correspond to the RS (LOCF imputation) and presented as mean (standard error)

5.4.6 Total and Nocturnal Back Pain

Baseline values indicated total and nocturnal back pain to be a significant burden in axSpA patients (total back pain score mean±SD=7.02±1.89, nocturnal back pain score mean±SD=6.90±2.30). No differences between treatment groups were noted at baseline for total or nocturnal back pain.

Significantly greater decreases from baseline (ie. improvement) in total back pain and in nocturnal back pain were seen in CZP-treated subjects through to Week 24 in the overall axSpA population (Table 5-9). The analysis of change from baseline in total back pain at Week 24 yielded clinically meaningful treatment-related differences in the overall axSpA population. Differences were maintained [redacted]. No differences were evident between the two CZP treatment groups. Patients who achieved the MCID (≥1 point change from baseline) at any visit were considered responders. A significantly greater percentage of subjects were total and [redacted] back pain MCID responders in both CZP treatment groups compared with PBO at Week 24 (CZP 200 mg Q2W: 80.2% [89/111]; CZP 400 mg Q4W: 77.6% [83/107]; PBO: 35.8% [38/106]; Table 5-9).

Table 5-10 shows that significantly larger improvements in total and nocturnal back pain in CZP-treated patients compared to PBO-treated patients were reported in both the AS and nr-axSpA subpopulations.

Table 5-9: RAPID-axSpA study change from baseline in total and nocturnal back pain at Week 24 in the overall axSpA population

	PBO n=106	CZP 200 mg Q2W n=111	CZP 400 mg Q4W n=107	CZP 200 mg Q2W and 400 mg Q4W n=218
Total back pain				
Wk 24 mean change from baseline (SD)	-1.33 (2.16)	-3.25 (3.00)	-3.21 (2.71)	-3.23 (2.85)
Wk 24 difference to PBO, LS mean (SE)	-	-1.91 (0.34)	-1.92 (0.34)	-1.91 (0.30)
p-value	-	<0.001	<0.001	<0.001

Wk 24 MCID responders, n (%) p-value	38 (35.8) -	89 (80.2) <0.001	83 (77.6) <0.001	172 (78.9) <0.001
Nocturnal back pain				
Wk 24 mean change from baseline (SD)	-1.27 (2.61)	-3.67 (3.33)	-3.61 (2.92)	-3.64 (3.13)
Wk 24 difference to PBO, LS mean (SE) p-value	- -	-2.31 (0.35) <0.001	-2.29 (0.35) <0.001	-2.30 (0.31) <0.001
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CZP: Certolizumab pegol; **FAS**: Full analysis set; **LOCF**: Last observation carried forward; **LS**: Least squares; **MCID**: Minimal clinically important difference; **NRI**: non-responder imputation; **PBO**: Placebo; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **SD**: Standard deviation; **SE**: Standard error; **Wk**: Week
Change from baseline and difference compared to PBO: Data correspond to the FAS population (LOCF imputation), p-values were calculated using ANCOVA
Responder rate: Data correspond to the FAS (NRI imputation), p-values were calculated using the 2-sided Wald test

Table 5-10: RAPID-axSpA study change from baseline in total and nocturnal back pain at Week 24 in AS and nr-axSpA subpopulations

	AS				nr-axSpA			
	PBO n=57	**CZP 200 mg Q2W n=65**	**CZP 400 mg Q4W n=56**	**CZP 200 mg Q2W and 400 mg Q4W n=121**	**PBO n=49**	**CZP 200 mg Q2W n=46**	**CZP 400 mg Q4W n=51**	**CZP 200 mg Q2W and 400 mg Q4W n=97**
Total back pain								
Wk 24 mean change from baseline (SD)	-1.39 (2.06)	-2.94 (3.27)	-3.50 (2.57)	-3.20 (2.97)	-1.27 (2.29)	-3.70 (2.53)	-2.90 (2.84)	-3.28 (2.71)
Wk 24 difference to PBO, LS mean (SE) p-value	- -	-1.78 (0.44) <0.001	-2.39 (0.45) <0.001	-2.08 (0.39) <0.001	- -	-2.32 (0.53) <0.001	-1.61 (0.52) 0.002	-1.96 (0.46) <0.001
Wk 24 MCID responders, n (%) p-value	23 (40.4) -	48 (73.8) <0.001	45 (80.4) <0.001	93 (76.9) <0.001	15 (30.6) -	41 (89.1) <0.001	38 (74.5) <0.001	79 (81.4) <0.001
Nocturnal back pain								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AS: Ankylosing spondylitis; **CZP**: Certolizumab pegol; **FAS**: Full analysis set; **LOCF**: Last observation carried forward; **LS**: Least squares; **MCID**: Minimal clinically important difference; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **PBO**: Placebo; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **SD**: Standard deviation; **SE**: Standard error **Wk**: Week
Change from baseline and difference compared to PBO: Data correspond to the FAS population (LOCF imputation), p-values were calculated using ANCOVA
Responder rate: Data correspond to the FAS (NRI imputation), p-values were calculated using the 2-sided Wald test

5.4.7 Daily Pain and Fatigue

[redacted]

Greater changes from baseline in fatigue, as assessed by Question 1 of the BASDAI, were seen in CZP-treated subjects compared to PBO-treated subjects by Week 1 in the overall axSpA population and were continued through to Week 24. A greater improvement from baseline in fatigue was also achieved by CZP-treated patients compared with PBO in the overall axSpA population and both the AS and nr-axSpA subpopulations (Appendix 11.2.5.4). Improvements were maintained to Week 48 in the dose-blind phase of the study (Section 5.4.12) (data not available to Week 96).[56]

5.4.8 Extra-Articular Manifestations

5.4.8.1 Uveitis

Although axSpA is characterised by inflammation in the spine and sacroiliac joints, it can also manifest as inflammation at extra-spinal sites, most commonly inflammation of the uvea (uveitis).[72]

In RAPID-axSpA uveitis events were recorded on a specific case report form (for extra-articular manifestations) or as an adverse event (preferred term "Uveitis"). New incidences and flares were analysed in patients with or without a history of uveitis. Patients with a history of uveitis were defined as patients with uveitis recorded on their standard medical history, ASAS classification criteria screening assessment or baseline extra-articular assessment.

At baseline, of 218 patients randomised to CZP, 38 (17.4%) had a history of uveitis, as did 31 of 107 (29.0%) patients randomised to PBO. The proportion of patients with a history of uveitis was similar in the AS and nr-axSpA subpopulations (20.8% [37/178] and 21.1% [31/147] respectively).[21]

During the 24 week double-blind phase, the overall incidence rate (IR) of uveitis flares (regardless of previous history of uveitis) was lower in CZP-treated patients (IR=2.0/100 PY) than PBO-treated patients (IR=10.6/100 PY). There were no *de novo* cases of uveitis flares observed up to Week 24; ie. all cases were observed in patients with history of uveitis. In these patients with a history of uveitis, IR was 11.9/100 PY for CZP and 42.1/100 PY for PBO (Table 5-11). Up to Week 48 in CZP-treated patients (regardless of prior history of uveitis) the overall IR of uveitis flares was 3.8/100 PY (17.8/100 PY in patients with history of uveitis and 0.5/100 PY in patients without) (Table 5-12).[21]

Table 5-11: RAPID-axSpA study incidence of uveitis flares in patients treated with CZP or PBO to Week 24 in the overall axSpA population[21]

	CZP 200 mg Q2W and 400 mg Q4W			PBO		
	All Patients (n=218)	History of Uveitis (n=38)	No History of Uveitis (n=180)	All Patients (n=107)	History of Uveitis (n=31)	No History of Uveitis (n=76)
IR per 100 PY*	2.0	11.9	0.0	10.6	42.1	0.0
Patients (Exposure, PY)	2 (97.6)	2 (16.8)	0 (80.7)	4 (37.7)	4 (9.5)	0 (28.2)

CZP: Certolizumab pegol; **IR**: Incidence rate; **PBO**: Placebo; **PY**: Patient years; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks
*IR are reported per 100 PY with censoring at the time of event; no analyses of statistical significance were carried out on these data

Table 5-12: RAPID-axSpA study incidence of uveitis in patients treated with CZP to Week 48 in the overall axSpA population[21]

	All Patients† (n=315)	History of Uveitis (n=63)	No History of Uveitis (n=252)
IR* per 100 PY	3.8	17.8	0.5
Patients (Exposure, PY)	9 (238.1)	8 (44.9)	1 (193.2)

IR: Incidence rate; **PY**: Patient years
*IR are reported per 100 PY with censoring at the time of event; †for Week 48 analyses all patients exposed to CZP were considered; no analyses of statistical significance were carried out on these data

5.4.9 Extra-Spinal Manifestations

5.4.9.1 Enthesitis, Swollen Joints and Tender Joints

Axial SpA is frequently associated with extra-spinal manifestations such as inflammation of the entheses (enthesitis, assessed by Maastricht Ankylosing Spondylitis Enthesitis Score [MASES]) and peripheral joints (assessed by swollen joint count [SJC] and tender joint count [TJC]).

Extra-spinal manifestations were assessed in patients with ≥1 swollen joint, ≥1 tender joint or ≥1 enthesial site affected at baseline. At baseline, 229 had enthesitis in ≥1 enthesial site, with a mean±SD MASES score of 5.1±3.4; 123 had ≥1 swollen joint, with a mean±SD SJC of 4.2±5.3 and 212 had ≥1 tender joint, with a mean± TJC of 6.6±7.1.[20]

CZP-treated patients showed improvement in enthesitis, swollen joints and tender joints at Week 12 and Week 24 compared with PBO-treated patients (Appendix 11.2.5.6 [Table 11-9]).[20]

The baseline severity of extra-spinal manifestations and improvements observed to Week 24 were similar between the AS and nr-axSpA subpopulations (Appendix 11.2.5.6 [Table 11-10]).[20]

5.4.10 Health-Related Quality of Life

The baseline data from the RAPID-axSpA study showed that there is a high burden on HRQoL and that it was similar at baseline in both the AS and nr-axSpA subpopulations (Section 5.3.2). Irrespective of the dose regimen, CZP-treated patients experienced significant improvements in all domains of the SF-36, as well as the physical and mental component summary scores, and this was observed in both the AS and nr-axSpA subpopulations. Improvements in HRQoL reported in the CZP groups were maintained to [redacted]. More detailed results are presented in Appendix 11.2.5.7.2.

Baseline ASQoL scores were similar across the treatment groups, however, greater changes from baseline were observed in the CZP-treated patients as compared to PBO-treated patients. These changes were seen as early as Week 1 of the study in both the AS and nr-axSpA subpopulations, and these improvements were maintained at [redacted]. More detailed results are presented in Appendix 11.2.5.7.1.

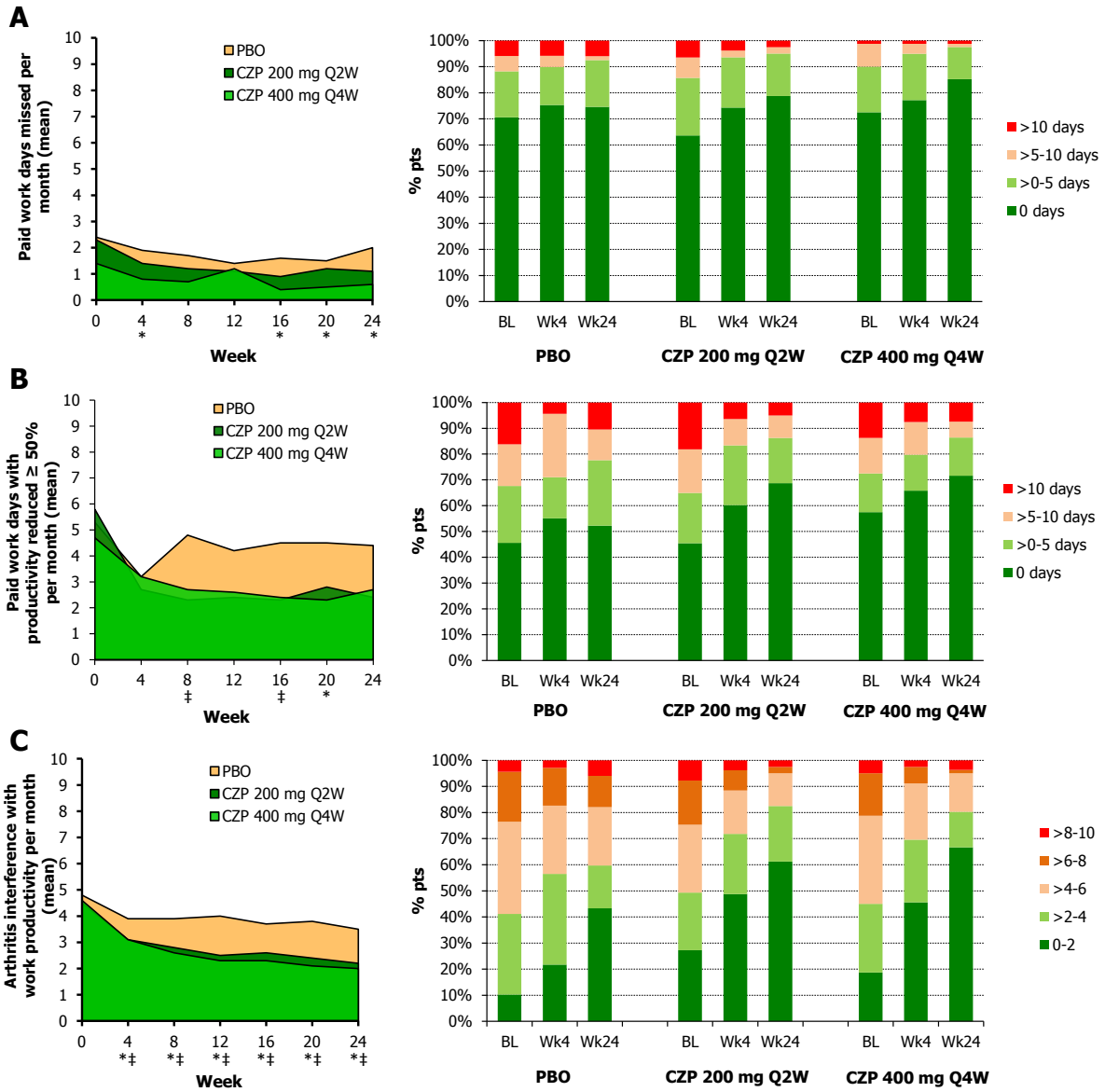
5.4.11 Workplace and Household Productivity

At study baseline, a high burden of axSpA on workplace and household productivity was reported with a slightly higher burden in nr-axSpA compared with AS (Section 5.3.2).

In the overall axSpA population at baseline, 63.2% (67/106), 69.4% (77/111), and 74.8% (80/107) of patients in the PBO, CZP 200 mg Q2W, and CZP 400 mg Q4W treatment groups were employed. At baseline, more AS than nr-axSpA patients were unable to work due to spondyloarthritis (15.7% [28/178] vs 8.2% [12/146]). A high burden of axSpA on workplace and household productivity was reported with a slightly higher burden in nr-axSpA compared with AS. On average, axSpA patients reported >1 week of paid work and 2-3 weeks of household duties or social activities affected per month.[35]

In employed patients receiving CZP, reductions in work days missed, work days with reduced productivity, and arthritis interference with productivity at work were reported as early as Week 4 and maintained through to Week 24 (Appendix 11.2.5.8). By Week 24, employed patients treated with CZP gained on average between 0.8–1.2 full days of paid work per month, compared to a mean of 0.4 days in the PBO group. Patients in the CZP-treated arms reported fewer limitations in their paid work duties, as seen by a decrease in the number of days with reduced productivity of 2.0–3.4 days per month on average compared to less than 1 day with PBO by Week 24. The interference of axSpA on paid work productivity as measured on a 0–10 scale was reduced on average by 1.4–1.5 (Week 4) and at least 2.3 (Week 24) in CZP patients compared to 0.9 (Week 4) and 1.0 (Week 24) on average in PBO-treated patients (Figure 5-8).

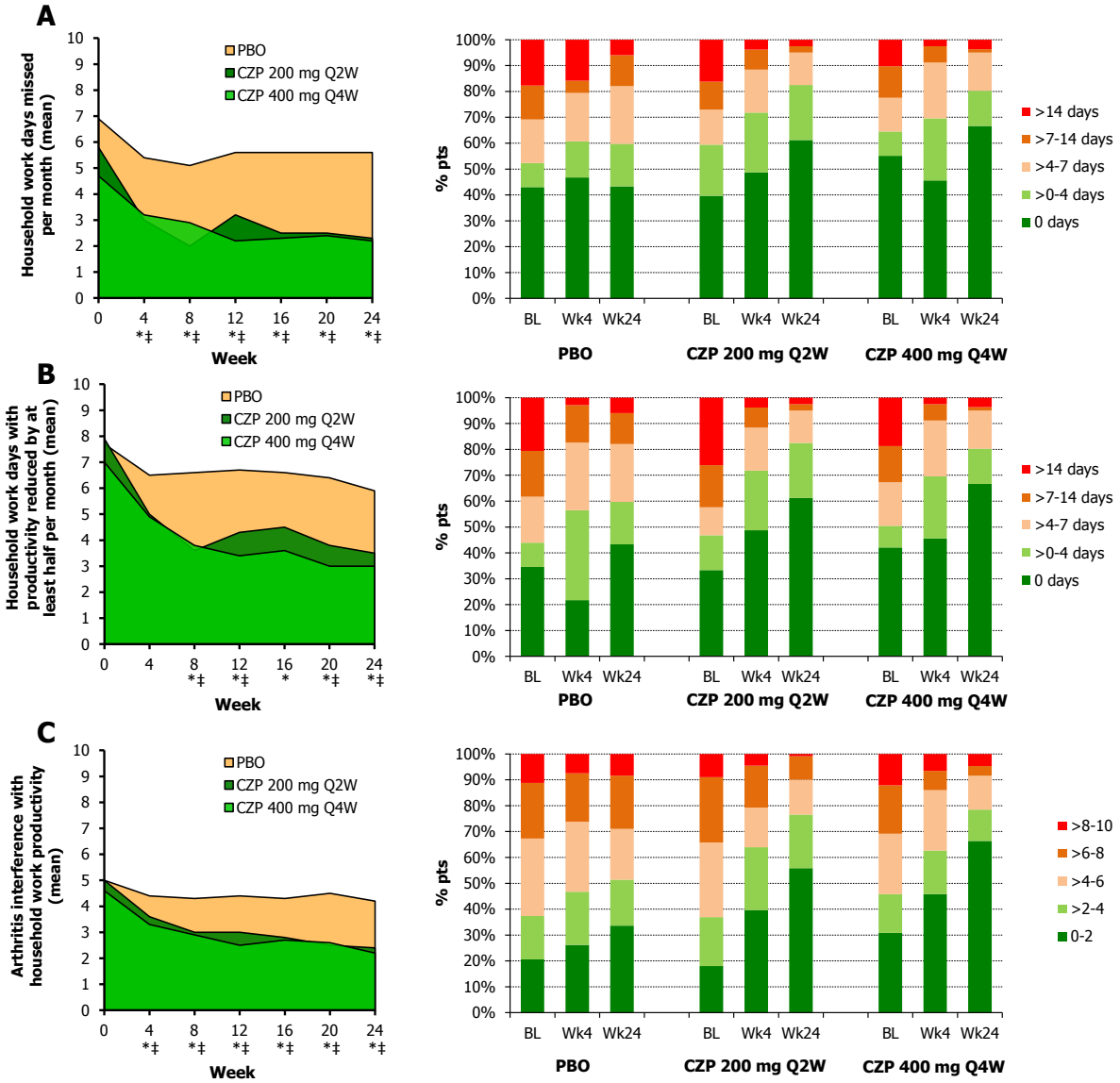
Figure 5-8: Paid work productivity (WPS) in axSpA patients at baseline, Week 4 and Week 24 in the RAPID-axSpA trial (employed patients only). (A) Work days missed per month due to arthritis; (B) Days per month with work productivity reduced by ≥50% due to arthritis; (C) Level of arthritis interference with work productivity per month†**



‡p<0.05 CZP 200 mg Q4W vs PBO; *p<0.05 CZP 400 mg Q4W vs PBO; data correspond to the full analysis set, non-parametric bootstrap t-test (LOCF imputation); †level of arthritis interference with work productivity: 0—10 point scale (0=no interference, 10=complete interference); **does not include full days missed counted in the previous question

Improvement in productivity within the home was observed as early as Week 4 and maintained through to Week 24 in both the CZP groups compared with the PBO group in the overall axSpA population (Figure 5-9).

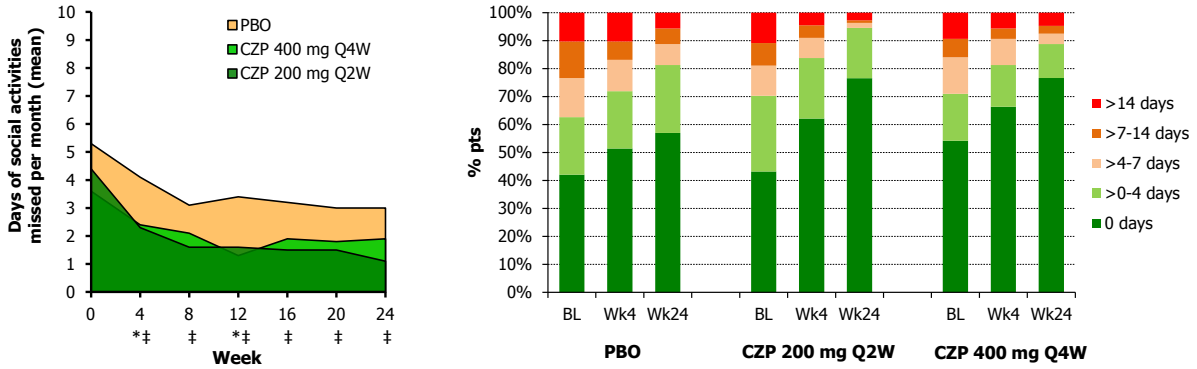
Figure 5-9: Household work productivity (WPS) in axSpA patients at baseline, Week 4 and Week 24 in the RAPID-axSpA trial. A) Household work days missed per month due to arthritis; B) Days per month with household productivity reduced by ≥50% due to arthritis; C) Level of arthritis interference with household work productivity per month†**



‡p<0.05 CZP 200 mg Q4W vs PBO; *p<0.05 CZP 400 mg Q4W vs PBO; data correspond to the full analysis set population, non-parametric bootstrap t-test (LOCF imputation); †level of arthritis interference with household work productivity: 0—10 point scale (0=no interference, 10=complete interference); **does not include full days missed counted in the previous question

Significant reductions in the number of days of family, social and leisure activities lost due to arthritis in patients receiving CZP compared to PBO patients was observed as early as Week 4 (p<0.05) and sustained through to Week 24 (Figure 5-10).

Figure 5-10: Days missed of family, social and leisure activities (WPS) in axSpA patients at baseline, Week 4 and Week 24 in the RAPID-axSpA trial



‡p<0.05 CZP 200 mg Q4W vs PBO; *p<0.05 CZP 400 mg Q4W vs PBO; data correspond to the full analysis set, non-parametric bootstrap t-test (LOCF imputation)

Similar improvements were seen in workplace and household productivity at Week 24 in AS and nr-axSpA subpopulations, as observed in the overall axSpA population (Appendix 11.2.5.8, Figure 11-5 and Figure 11-6).

The initial improvements in work and household productivity in CZP-treated patients up to Week 24, were continued up to [redacted]. These improvements were maintained in the AS and nr-axSpA subpopulations.[23]

[redacted]

5.4.12 Longer-Term Efficacy to Week 96 (Includes the Dose-Blind and the Open-Label Treatment Periods)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	CZP 200 mg Q2W and 400 mg Q4W (n=218)			
	Week 24 (NRI)	Week 48 (NRI)	Week 96 (NRI)	Week 96 (OC)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 0	Week 24 (LOCF)	Week 48 (LOCF)	Week 96 (LOCF)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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; **CZP**: Certolizumab pegol; **LOCF**: Last observation carried forward; **MCS**: Mental component summary; **NA**: Not available; **NRI**: Non-responder imputation; **OC**: Observed case; **PCS**: Physical component summary; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **SD**: Standard deviation; **SF-36**: Short-form 36

Data correspond to the RS with imputation; NRI was used for categorical measures; LOCF was used for continuous variables
Note: Fatigue data not available at Week 96

Table 5-14: RAPID-axSpA study maintenance of CZP efficacy at Week 96 in the AS and nr-axSpA subpopulations[19, 23]

	CZP 200 mg Q2W and 400 mg Q4W							
	AS (n=121)				nr-axSpA (n=97)			
	Wk 24 (NRI)	Wk 48 (NRI)	Wk 96 (NRI)	Wk 96 (OC)	Wk 24 (NRI)	Wk 48 (NRI)	Wk 96 (NRI)	Wk 96 (OC)
ASAS20 response rate, n (%)	81 (66.9)	[redacted]	78 (64.5)	78/93 (83.9)	66 (68.0)	[redacted]	59 (60.8)	59/74 (79.7)
ASAS40 response rate, n (%)	62 (51.2)	[redacted]	61 (50.4)	61/93 (65.6)	49 (50.5)	[redacted]	49 (50.5)	49/74 (66.2)
ASAS partial remission response rate, n (%)	34 (28.1)	[redacted]	30 (24.8)	30/93 (32.3)	32 (33.0)	[redacted]	32 (33.0)	32/74 (43.2)
	Wk 0	Wk 24 (LOCF)	Wk 48 (LOCF)	Wk 96 (LOCF)	Wk 0	Wk 24 (LOCF)	Wk 48 (LOCF)	Wk 96 (LOCF)
BASDAI, mean actual score (SD)	6.4 (1.5)	3.4 (2.2)	[redacted]	3.1 (2.2)	6.6 (1.5)	3.3 (2.5)	[redacted]	3.0 (2.4)
BASFI, mean actual score (SD)	5.6 (2.3)	3.3 (2.6)	[redacted]	3.0 (2.3)	5.0 (2.3)	2.6 (2.4)	[redacted]	2.4 (2.5)
BASMI linear, mean actual score (SD)	4.2 (1.7)	3.6 (1.7)	[redacted]	3.6 (1.8)	3.2 (1.5)	2.6 (1.5)	[redacted]	2.5 (1.4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AS: Ankylosing spondylitis; **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; **CZP**: Certolizumab pegol; **LOCF**: Last observation carried forward; **MCS**: Mental component summary; **NA**: Not available; **nr-axSpA**: Non-radiographic axial spondyloarthritis; **NRI**: Non-responder imputation; **OC**: Observed case; **PCS**: Physical component summary; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **SD**: Standard deviation; **SF-36**: Short-form 36 **Wk**: Week
Data correspond to the RS with imputation; NRI was used for categorical measures; LOCF was used for continuous variables
Note: Fatigue data not available at Week 96

6 Mixed Treatment Comparison

- Following a systematic literature review, a mixed treatment comparison (MTC) was performed to evaluate the relative clinical effectiveness of CZP and its relevant active comparators.
- For the AS subpopulation, the primary analysis was performed at the 24-week timepoint, since guidelines indicate that evaluation of the efficacy of treatment should be made after at least 12 weeks of continuous treatment. For the nr-axSpA subpopulation, the assessment could only be performed at the 12-week timepoint due to the availability of comparator data.
- In AS patients, CZP showed similar efficacy (with no significant difference) when compared to ADA, ETA, GOL and IFX. At 24 weeks, the analysis indicated numerically higher benefits in favour of CZP than ADA and GOL, and similar benefits compared to ETA and IFX, although none of the differences were significant.
- In nr-axSpA patients, CZP showed numerically greater improvements over ADA and ETA at 12 weeks in most outcomes assessed, in terms of ASAS responses (ASAS20, 40, partial remission, 5/6), disease activity and physical function; significant differences were noted in changes in BASFI, BASDAI and PtGADA.
- The MTC reported that treatment with anti-TNF therapies yielded greater improvements in efficacy outcomes and PROs when compared with PBO in AS and nr-axSpA.
- Clinical heterogeneity was observed across studies used in the MTC. However, sensitivity analyses were performed around prior anti-TNF therapy exposure for the AS subpopulation. These sensitivity analyses supported the conclusions of the main analysis, that anti-TNF therapies are superior to PBO and have similar efficacy to each other.

Data on the relevant clinical comparators are not available from active-controlled studies and from trials in the axSpA disease spectrum. A systematic review was therefore performed to identify studies assessing the active comparators in the axSpA subpopulations, AS and nr-axSpA. Mixed treatment comparisons (MTCs) or pairwise comparisons were then undertaken to assess the relative efficacy of CZP in the AS and nr-axSpA subpopulations. The systematic literature review and analyses were performed to include all interventions that have been approved by the European Medicines Agency EMA for axSpA (AS or nr-axSpA) and were considered in the final scope of the NICE MTA. The systematic review identified 28 studies of relevant comparators for both subpopulations, out of which 18 were included in the MTC.

6.1 Methods: Systematic Literature Review

MEDLINE-, Embase-, and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for indexed literature published from January 1991 to July 2014 for randomised controlled trials (RCTs) evaluating selected anti-TNF therapies. The search terms are detailed in Appendix 11.3.
Keyword searches of the annual proceedings for meetings of interest within the last four years (2010–2014) were also performed. Using the above criteria, abstracts from the following meetings were screened:

1. American College of Rheumatology (ACR)
2. The European League Against Rheumatism (EULAR)
3. British Society for Rheumatology (BSR)
4. International Society for Pharmacoeconomics and Outcomes Research (ISPOR, International and European meetings)

Additionally, the Cochrane Library was searched for recent (2010–2014) systematic reviews and meta-analyses of treatments of interest in axSpA. The reference lists of these studies were manually reviewed to identify potentially relevant studies that were not captured within the aforementioned searches. Similarly, the reference lists of recent pooled analyses and meta-analyses (2010–2014) captured in the systematic search were reviewed to identify any additional relevant studies.

The PICOS approach (population, intervention, comparators, outcomes, study design) was utilised to define inclusion and exclusion criteria (Table 6-1). Trials of adult patients with active axSpA (or nr-axSpA and AS subpopulations) who had failed at least one NSAID agent were included. Where specific outcomes of interest (eg. clinical efficacy, safety and tolerability, economic, and PROs) were provided in a post-hoc, subgroup, or

exploratory analyses the results were included but interpreted with caution. The outcomes of interest are listed in Appendix 11.3 (Table 11-16).

Table 6-1: PICOS inclusion and exclusion criteria for studies in the systematic literature review

	P – Patients	I– Interventions	C – Comparators	O – Outcomes	S – Study Design
Inclusion Criteria	Studies that include adult patients with clearly defined active axSpA, or nr-axSpA and AS subpopulations, who have failed at least one NSAID agent	Biological DMARDs: TNF antagonists: ADA, CZP, GOL, IFX, ETA	Biological DMARDs: TNF antagonists: ADA, CZP, GOL, IFX, ETA Conventional DMARDs: cyclosporine, SSZ, MTX, leflunomide, HCQ NSAIDs: celecoxib, etoricoxib, ibuprofen, naproxen, ketoprofen, flurbiprofen, inometacin/ indomethacin, etodolac, diclofenac, aceclofenac, sulindac, piroxicam, meloxicam, tenoxicam PBO/usual care	Selected clinical efficacy, safety and tolerability, economic outcomes, and PROs of interest (see Table 11-16)	PBO- and active-controlled RCTs with at least one arm randomised to one of the selected anti-TNFs alone or in combination with other comparator agents in adult patients with active axSpA or nr-axSpA and AS subpopulations who have failed at least one NSAID agent; randomised trials in parallel design of at least 12 weeks' duration, or those with crossover happening after 12 weeks
Exclusion Criteria	Studies of non-axSpA patients, patients that are naïve to or on their first NSAID, or studies with mixed populations in which outcomes for axSpA patients are not reported separately	Studies that do not include a treatment arm with any of the selected biological DMARDs	Studies that do not include a treatment arm with any of the selected comparators of interest	Studies lacking relevant data on any of the outcomes of interest (selected efficacy, safety, economic, and PROs of interest (see Table 11-16)	Studies that are not randomised; letters to the editor; citations with no abstract; open-label extensions of RCTs (ie. the extension phase where previous randomization has been broken); pooled analyses or meta-analyses; animal or in vitro studies; pharmacokinetic or pharmacodynamic studies; randomised trials with crossover happening before 12 weeks; dose-finding studies with no active or PBO comparator; randomised trials with fewer than 10 patients per treatment arm; studies with intended treatment duration fewer than 12 weeks

ADA: adalimumab; **AS**: ankylosing spondylitis; **axSpA**: axial spondyloarthritis; **CZP**: certolizumab pegol; **DMARD**: disease-modifying anti-rheumatic drug; **ETA**: etanercept; **GOL**: golimumab; **HCQ**: hydroxychloroquine; **IFX**: infliximab; **MTX**: methotrexate**; nr-axSpA**: non-radiographic axial spondyloarthritis; **NSAID**: non-steroidal anti-inflammatory drug; **PRO**: patient-reported outcome; **RCT**: randomised controlled trial; **SSZ**: Sulfazalazine; **TNF**: Tumour necrosis factor

6.2 Methods: Mixed Treatment Comparison

6.2.1 Bayesian Mixed Treatment Compariosn

MTCs have great potential to evaluate the comparative effectiveness of multiple treatments using an evidence base of clinical trials that individually do not compare all treatment options. Fixed-effects and random-effects Bayesian MTC meta-analyses[73, 74] were conducted that compared all treatments of interest on odds ratios (OR) or difference of mean change. An investigation of statistical heterogeneity was conducted when there were two or more studies on the same comparison. Empirical priors for random-effects variance of 1 for binary outcomes and 2*median arm-level standard deviation for continuous

outcomes were utilised for the random-effects analyses. A less informative prior (0) to assess sensitivity to prior choice was also assessed. The best model fit was selected based on a review of the deviance information criterions (DICs) and a clinical evaluation of the different model assumptions. Convergence and DIC issues were considered unlikely due to the simplicity of the evidence network.

All analyses involved a 50,000 run-in iteration phase and a 50,000 iteration phase for parameter estimation. All calculations were performed using OpenBugs 3.1.2.

6.2.2 Statistical Analyses – nr-axSpA Subpopulation

The analysis in the nr-axSpA subpopulation was performed in anti-TNF naïve patients. This analysis was completed using the R software program, which was programmed to generate relative effect estimates from both a fixed-effects MTC model and Bucher's adjusted indirect comparison simultaneously. The estimates derived from the fixed-effects MTC model are identical to those derived from the Bucher's adjusted indirect treatment comparison when there are a limited number of trials or a small network as is the case here, for the anti-TNF naïve nr-axSpA subpopulation.

Given the similarities between the two, only the estimates derived from the fixed-effect MTC model are presented in the results section (Section 6.6.2) and the methodology described in more detail.
A random-effects MTC model was considered but not conducted due to the absence of data (limited trials) with which to estimate a random-effects variance.

6.2.3 Statistical Analyses – AS Subpopulation

Where feasible, both MTC analyses (fixed- and random-effects) were performed for the AS trials. The random-effects model was considered to be optimal compared to the fixed-effects model unless limited by sparse data.

Among the trials in AS populations intended for analysis, there was some indication of population heterogeneity with respect to prior treatment with anti-TNF therapies as prior anti-TNF therapy exposure was not reported for all studies. Those studies that did not explicitly state whether patients had prior anti-TNF therapy exposure were of IFX (2), ETA (2), GOL (1), or ADA (1). As these were the first anti-TNF therapies evaluated and approved for this indication, it is reasonable to assume that it is likely that only a small proportion of patients were exposed to anti-TNF therapy prior trial enrolment.

The main analyses were therefore conducted using all AS patients. This allowed for a larger network of studies to be included, with more than one study per comparison for any given outcome. Out of the studies identified in the systematic literature review, only 6 did not provide comprehensive inclusion and exclusion criteria or information to determine prior exposure to anti-TNF therapy (2 IFX, 2 ETA, 1 GOL, 1 ADA).[75-80] Analysis of all AS patients is also more representative of the patients treated in practice where a small proportion of patients may have been previously exposed to an anti-TNF therapy. However, additional sensitivity analyses were conducted where studies with unclear prior anti-TNF therapy exposure and also patients from RAPID-axSpA with prior anti-TNF exposure were excluded. This sensitivity analysis was conducted to detect and prevent confounding factors that may exist and could impact on the overall results.

A univariate approach was used for ASAS20 and ASAS40 rather than a multivariate approach. A multivariate approach would require the assumption of equal treatment effects for the different ASAS thresholds, and given that almost all included studies reported ASAS20 and ASAS40, the additional assumption required to justify this approach may not outweigh the benefit of a slight increase in estimate efficiency. In addition, a univariate approach allows analysis of the difference between the anti-TNF therapies in the chance of achieving ASAS20 and ASAS40 responses independently; it is likely that any anti-TNF therapy could be effective at achieving the lower threshold (ASAS20), but not have the same likelihood of achieving the more stringent threshold of ASAS40.

Study heterogeneity was tested using Cochrane's Q-statistic and measured using I^2, where possible heterogeneity was explained by examining variation in the study- and treatment-level factors mentioned above. Global heterogeneity was assessed by considering the size of the sqrt(tau) from the random-effects MTCs and by examining a sequence of pairwise meta-analyses; high values of I^2 (an estimate of the per cent of variability due to heterogeneity) indicate heterogeneity for that comparison and allow for identification of trials that are outliers.

6.2.4 Feasibility Assessment for MTC

Only studies that enrolled comparable patient populations were included in the MTC. Analyses were conducted separately for the AS and nr-axSpA subpopulations. Week 12 and 24 timepoints were considered for the analyses. However, because not all AS trials presented outcomes of interest at 12 weeks and 24 weeks, the effects on multiple outcomes of interest over time were evaluated by two independent reviewers. Both reviewers determined that, among the comparators included in this study, the greatest improvements occurred between 2 and 6 weeks of treatment and that results were relatively stable between 12 and 16 weeks. Efficacy and PRO data from 12 to 16 weeks were thus pooled for the two sets of analyses; that is, if a study reported outcomes at any point between 12 and 16 weeks, it was considered in the respective analysis.

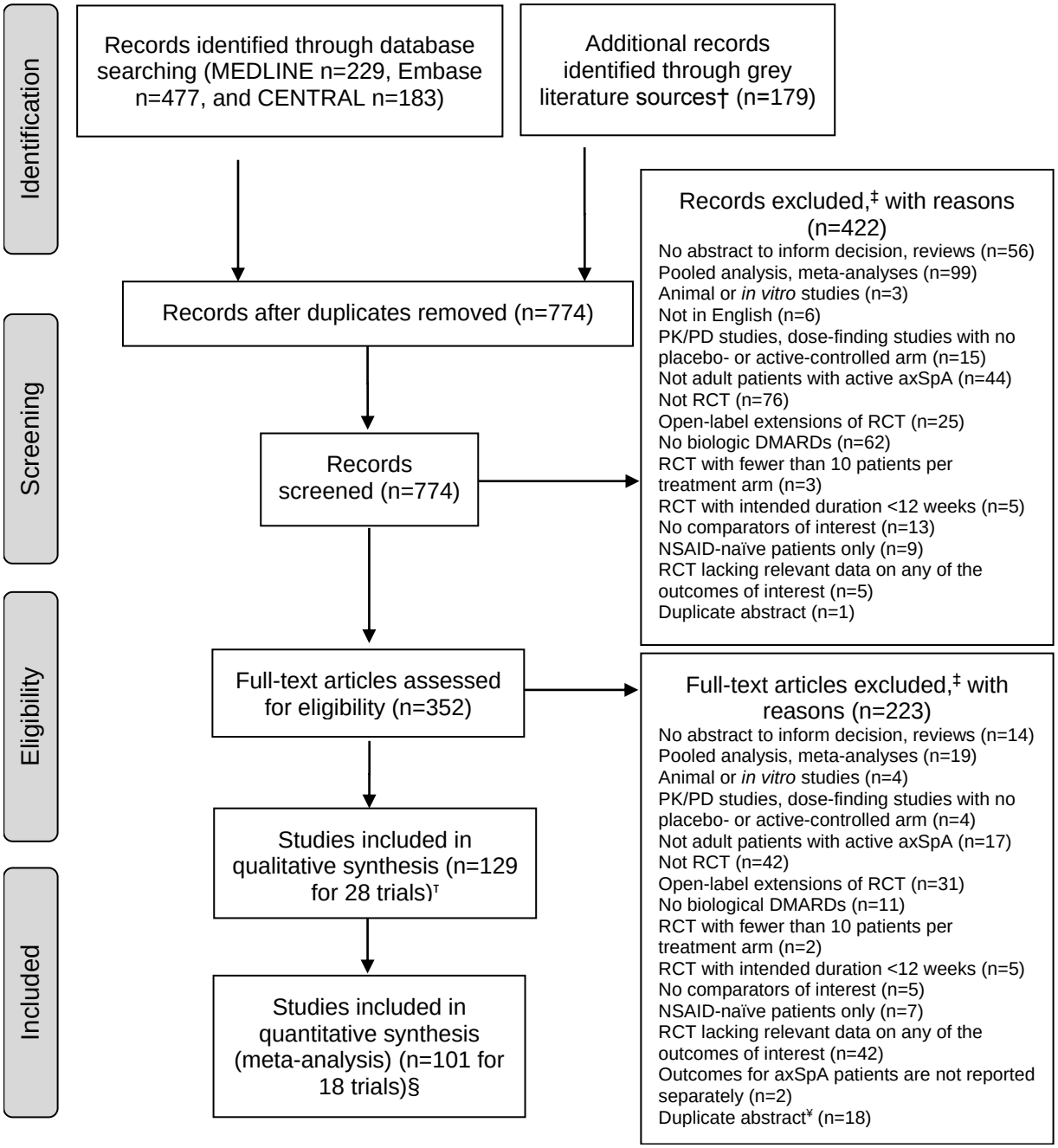
The 2010 update of the ASAS recommendations for the use of anti-TNF therapies in axSpA recommend that the time of evaluation for these agents should occur after more than 12 weeks, given that the treatment response rates plateau from 12 weeks onwards and so the evidence favours more than 12 weeks of continuous treatment before deciding on whether the treatment should be continued.[81] Following these recent recommendations, the main MTC analysis in the AS subpopulation was conducted using Week 24 with additional sensitivity analyses conducted for Week 12. Furthermore, the difference in relative effect between anti-TNF therapies at 12 weeks and 24 weeks was also observed in previous health technology assessment (HTA) submissions to NICE (TA143).[24]

6.3 Results: Systematic Literature Review

Figure 6-1 summarises the trials included in the statistical analysis, including RAPID-axSpA; the study characteristics of all trials identified are listed in Appendix 11.3 (Table 11-17) with the assessment of bias (Table 11-18). This systematic literature review identified 28 primary trials published since 1991 and included RAPID-axSpA CZP trial data from the clinical study report (CSR). Among these trials, 20 enrolled AS patients who fulfilled the mNY criteria and were comparable to the AS subpopulation enrolled in the RAPID-axSpA study. Four trials reported data in the nr-axSpA subpopulation, and patients in two trials (naïve to anti-TNF) were comparable to the nr-axSpA subpopulation enrolled in the RAPID-axSpA study. In addition, three trials included an axSpA population, and one trial included patients with severe AS with spine ankylosis; however, these four trials in the axSpA population and severe AS population did not include comparable patient populations to those included in the RAPID-axSpA study for further quantitative analysis.

The systematic literature review results included trials of the alternative anti-TNF therapies ADA, ETA, GOL, and IFX. Eighteen trials were suitable for inclusion in the MTC or indirect treatment comparison for the AS and nr-axSpA populations (Figure 6-1, Appendix 11.3.2 [Table 11-19]) and 10 trials were excluded (Appendix 11.3.2 [Table 11-20]). All 18 trials were included in the analyses and so are presented here.

Figure 6-1: PRISMA study attrition diagram for systematic literature review



axSpA: Axial spondyloarthritis; **DMARD**: Disease-modifying anti-rheumatic drug; **NSAID**: Non-steroidal anti-inflammatory drug; **PD**: Pharmacodynamic; **PK**: Pharmacokinetic; **RCT**: Randomised controlled trial

†Includes the BSR Annual Meeting (2010–2014), the EULAR Annual Congress (2011–2014), the ACR Annual Scientific Meeting (2010–2014), and the ISPOR Annual Meetings (2010–2014)

‡ When screening abstracts and full-text publications for inclusion, a hierarchy of rejection criteria were used. Once a publication met one exclusion criterion, it was not evaluated for the remaining criteria. A publication was rejected on the basis of the first criterion that it fulfilled in the following list: 1) No abstract to inform decision (for meeting abstract only), narrative reviews, guidelines, commentary, letters to the editor, conference proceedings, 2) Pooled analysis or meta-analyses, 3) Animal or *in vitro* studies, 4) Not in English, 5) Published before 1991, 6) PK/PD studies; dose-finding studies with no placebo- or active-controlled arm, 7) Not adults with active axSpA or its subpopulations, 8) Not RCT, 9) Open-label extensions of RCT where randomization was broken, 10) No biologic DMARDs, 11) Fewer than 10 patients per treatment arm, 12) RCT duration less than 12 weeks, 13) No comparators of interest, 14) NSAID-naïve patients only, 15) RCT lacking relevant data on any of the outcomes of interest, 16) Outcomes for axSpA patients are not reported separately, 17) Duplicate study.

ᵀ This number reflects studies for inclusion in the qualitative synthesis.

¥ The same abstract was presented at multiple meetings or the same abstract was identified in database and grey literature searches.

§ This number includes RAPID-axSpA (AS001), another 15 trials in the AS population and two trials in the nr-axSpA population.

6.3.1 Quality Assessment for Risk of Bias in Included Studies

The risk of bias judgement associated with each included trial identified from the literature is summarised in Table 11-21 based on the Cochrane Collaboration's tool for assessing risk of bias. Studies were evaluated in seven domains for potential biases that pertain to study methodology, analysis, and reporting.

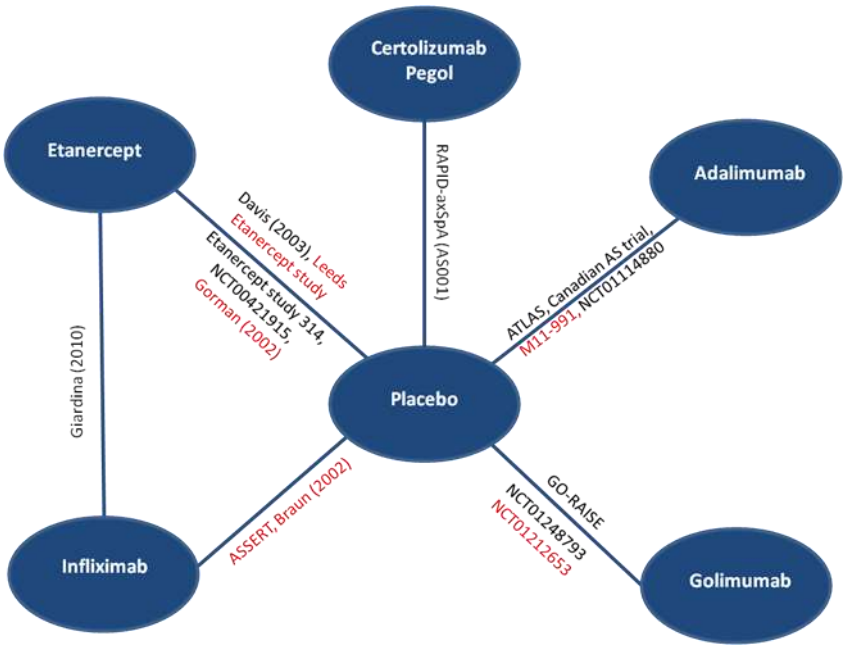
6.4 Mixed Treatment Comparison Network

Evidence network diagrams for trials included in the analysis in the AS subpopulation and the nr-axSpA subpopulation are provided in Figure 6-2 and Figure 6-3. Of note, the network for each outcome of interest may vary due to data availability; only outcomes reported in the same format, unit, and at a comparable timepoint were included in the analysis.

For the AS subpopulation, the MTC primarily evaluated data from all 16 trials of AS patients (including the RAPID-axSpA study). Further sensitivity analysis were conducted with the exclusion of studies where prior anti-TNF therapy exposure was unclear and exclusion of the subgroup of patients from RAPID-axSpA that were previously exposed to anti-TNF therapies, as explained in Section 6.2.3. This sensitivity analysis included 10 studies of AS patients.[33, 80, 82-89]

The analysis network for the AS subpopulation includes ADA, CZP, ETA, GOL and IFX; PBO was used as a common comparator in 15 trials with the exception being the University of Palermo study, which directly compared ETA with IFX (Figure 6-2). Table 11-22 (Appendix 11.3.2) lists the outcomes included in the statistical analysis in the AS population and their corresponding timepoints. Specifically, the following outcomes were included in the statistical analysis in the AS population at Week 12 and 24: ASAS20, ASAS40, ASAS5/6, BASDAI50, PtGADA, BASFI, BASDAI, SF-36 physical component summary (PCS), SF-36 mental component summary (MCS), nocturnal spine pain and fatigue. Some trials reported certain outcomes as median values or in a different scale/unit that were not comparable to other trials or contained reporting error; these values were explained in detail in the footnotes.

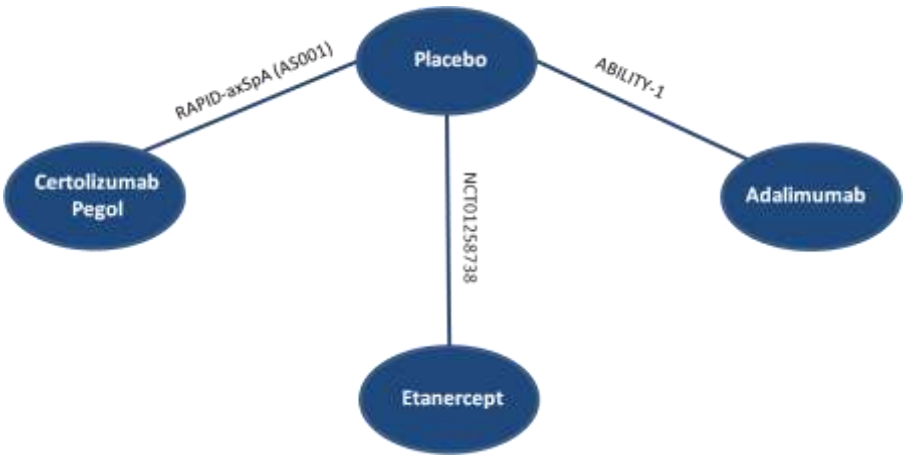
Figure 6-2 AS subpopulation evidence network diagram



This network diagram includes all AS trials regardless of anti-TNF therapy exposure.
Studies in black (besides RAPID-axSpA) enrolled only anti-TNF-naïve AS population; studies in red enrolled AS population with unclear anti-TNF exposure.

In the nr-axSpA population there were two included trials, RAPID-axSpA[23], NCT01258738[90] and ABILITY-1 (Figure 6-3).[15] The following outcomes were included in the statistical analysis in the nr-axSpA population at the Week 12 timepoint: ASAS20, ASAS40, ASAS5/6, ASAS partial remission, PtGADA, BASFI, BASDAI, SF-36 PCS and total back pain.

Figure 6-3: nr-axSpA subpopulation evidence network diagram



6.5 Relevant Differences

Of the trials identified from the systematic literature review, 16 studies were included in the statistical analyses in the AS population and three in the statistical analyses in the nr-axSpA population. The majority of these trials were double-blind RCTs; most were conducted in the US and Europe. ADA, ETA, GOL and IFX were represented in multiple trials. CZP was assessed in the RAPID-axSpA study only.

Seventeen of the 18 trials included in the statistical analyses that were able to be assessed had a low risk of bias, including the RAPID-axSpA study (Table 11-21); however, the risk was unclear in many trials, particularly with respect to randomisation methods and blinding of study outcome assessments. NCT01258738 had a high risk for selective and biased reporting because the primary endpoint was switched and the modified intention to treat population had inconsistent numbers of patients throughout the RCT period in the most recent publication, which remained as interim material pending for copy-editing and quality check.

6.5.1 Patient Populations

Among the 17 included trials identified from the literature (besides RAPID-axSpA), 15 consisted of patients who fulfilled the mNY criteria for AS, and these patients had radiographic evidence of definite sacroiliitis of either grade II bilaterally or grade III or IV unilaterally. Twelve of the 15 AS trials also excluded patients who had complete spine ankylosis (spine fusion). In the RAPID-axSpA study, approximately 50% of trial patients fulfilled the mNY criteria for AS; the data for this specific AS subgroup were used in the AS population MTC sensitivity analysis.

Other than RAPID-axSpA, two other trial in the MTC, ABILITY-1 and NCT01258738, enrolled nr-axSpA patients who did not have radiographic sacroiliitis.[15, 90] All three trials used the ASAS classification criteria for axSpA; whilst ABILITY-1 and NCT01258738 excluded patients who met the mNY criteria for AS, RAPID-axSpA required that only 50% of included patients should not have fulfilled the mNY criteria. It is data from this nr-axSpA subpopulation of RAPID-axSpA that was compared with data from ABILITY-1 and NCT01258738. The ABILITY-1 and NCT01258738 studies recruited only anti-TNF naïve patients.

6.5.2 Disease Severity

Among AS patients, RAPID-axSpA and other trials enrolled patients with similar disease activity, as defined by one or more of the following inclusion criteria: BASDAI score, morning stiffness, BASFI score, PtGADA score, and pain score. AS patients in the RAPID-axSpA study had similar disease severity to the AS patients from other trials, as indicated by baseline CRP levels and disease duration. The proportion of patients with elevated CRP at baseline was only reported in three other AS trials, ASSERT, GO-RAISE and NCT01114880 (41-53%).[79, 86, 87] RAPID-axSpA had a similar proportion of patients with elevated CRP (39-55%), although the threshold defining 'elevated CRP' was not always clearly reported and not consistent across studies (>15 mg/L, or > 3X ULN). Baseline CRP values varied across AS trials and most reported mean/median values were between 10-25 mg/L, however, consistent or commonly applied criteria are not available to distinguish patients' disease severity based on the available data. The mean disease duration of

AS patients in RAPID-axSpA falls within the range reported in other trials, and most trials did not specify if the duration was since symptom onset or since diagnosis.

Among nr-axSpA patients, RAPID-axSpA, ABILITY-1 and NCT01258738 enrolled patients with similar disease activity, as defined by the inclusion BASDAI score and pain score.[15] These three trials had a similar proportion of patients with elevated CRP (30–45%), although the threshold of elevated CRP was not consistent between studies (> 15 mg/L, or > 1X ULN, or by high-sensitivity CRP [hsCRP] standard). The mean baseline CRP values of nr-axSpA patients in RAPID-axSpA (13.4–19.3 mg/L) were higher than those of patients in ABILITY-1 (6.8–7.6 mg/L); however a standard is not available to distinguish patients' disease severity based on the available data. NCT01258738 used hsCRP, which cannot be compared to CRP directly. The mean disease duration since symptom onset was slightly shorter in the RAPID-axSpA study (8.1–9.1 years) than the ABILITY-1 trial (10.1 years), and NCT01258738 enrolled patients with dramatically shorter disease duration since symptom onset (2.5 years).

6.5.3 Additional Treatments

Of the 17 trials from the systematic literature review that were included in the MTC, 11 trials only included patients who were naïve to anti-TNF therapy; 6 trials did not specify patients' prior exposure to anti-TNF therapy; and RAPID-axSpA included patients both with and without prior exposure, although the majority of patients did not have prior anti-TNF therapy exposure (86.0%). Multiple studies reported data after PBO-treated patients crossed over to anti-TNF treatment in long-term, open-label phases.

Concomitant therapy use was reported in all but one trial, the GOL trial in Chinese patients.[82] Where reported, concomitant therapy use was allowed. The most commonly used concomitant treatments were DMARDs and NSAIDs; however, the specific information related to DMARDs, such as dose and schedule were often underreported.

6.5.4 Trial Design (Methodology, Length of Study, Outcomes)

The duration of the randomised portion for all trials was between 12 and 24 weeks. Most trial populations consisted of more than 50 patients with axSpA, AS or nr-axSpA. The majority of trials were comparable for disease duration and gender, and RAPID-axSpA had a similar gender and age distribution to the other trials. RAPID-axSpA allowed subjects in the PBO arm of the study who did not achieve at least a minimal response (ASAS20) at both 14 and 16 weeks to receive escape treatment. Three other trials also allowed early PBO escape, including ATLAS[33] (between 12 and 20 weeks), GO-RAISE[87] (at 16 weeks) and NCT01212653[80] (at 24 weeks). In addition, 10 studies, and RAPID-axSpA, reported cross-over of PBO- or DMARD-treated patients to anti-TNF therapy at 12 to 24 weeks.[15, 33, 77-79, 82, 84, 86-88, 91]

In terms of assessment timepoints for some of the outcomes of interest, three trials assessed outcomes at Week 14 or 16 instead of Week 12. More precisely, the GO-RAISE trial (GOL) and NCT01248793 trial (GOL) reported outcomes at Week 14 and the University of California trial (ETA), reported outcomes at Week 16. This 2 to 4 week difference in the assessment timepoints may bias the results of the Week 12 analysis, since it allows a longer exposure to certain anti-TNF therapies, thus an increased benefit, compared to the other treatments.

As shown in Appendix 11.3.2 (Table 11-22), not all trials assessed all of the outcomes of interest, which resulted in sparse networks for particular outcomes. However, the key clinical outcomes of ASAS20 response, BASDAI and BASFI were reported by the majority of trials.

6.6 Results: Mixed Treatment Comparison

Overall, the included trials found that AS and nr-axSpA patients assigned to treatment with anti-TNFs yielded better efficacy outcomes than those assigned to PBO. Whilst the sizes of point estimates differed among anti-TNF therapies, there were no significant differences between the anti-TNF therapies in the AS subpopulation. The evidence was consistent across the spectrum of disease, in patients with both AS and nr-axSpA.

Data are presented from analyses undertaken using CZP pooled data from the two dosing arms.

6.6.1 AS Subpopulation

In the AS subpopulation, the MTC showed that anti-TNF therapies were superior to PBO on key clinical outcomes and the majority of PROs considered. There were also no significant differences between CZP and the other anti-TNF therapies on most of the clinical outcomes and the PROs evaluated (ASAS20, ASAS40, ASAS5/6 and BASDAI50 responses, BASDAI and BASFI changes). At 24 weeks, the analysis indicated numerically higher benefits in favour of CZP than ADA and GOL, and similar benefits compared to ETA and IFX, although none of the differences were significant.

The results using CZP pooled were generally similar to those using the individual dosing (Appendix 11.3.3.3.1) and in the sensitivity analysis on trials in patients with who were definitively anti-TNF therapy-naïve (Appendix 11.3.3.4).

Results from the meta-analyses in the AS population between CZP, PBO and other anti-TNF therapies are summarised in Table 6-2–Table 6-7 for the following outcomes:

- ASAS response criteria (ASAS20, ASAS40 and ASAS5/6 response rates)
- Bath Ankylosing Spondylitis indices (change in BASDAI, BASDAI50 response rate and change in BASFI)

Additional results for PROs (changes in PtGADA, SF-36 PCS and MCS, nocturnal back pain and fatigue) can be found in Appendix 11.3.3.1 (Table 11-23–Table 11-27). These results were in line with the previous findings.

Table 6-2: ASAS20 response (AS population)

Comparison OR [95% CrI]	ASAS20 Response	
	12–16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable: OR: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Random-effects model

Table 6-3: ASAS40 response (AS population)

Comparison OR [95% CrI]	ASAS40 Response	
	12—16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Random-effects model

Table 6-4: ASAS5/6 response (AS population)

Comparison OR [95% CrI]	ASAS5/6 Response	
	12—16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Random-effects model

Table 6-5: BASDAI difference between mean change (AS population)

Comparison Difference of mean change [95% CrI]	BASDAI Change	
	12–16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable
Note: Advantage (↑) was defined using the MCID of 1 point for BASDAI difference of mean change. ↓ indicates disadvantage, whilst ↔ indicates similar BASDAI change.
Random-effects model

Table 6-6: BASDAI50 response (AS population)

Comparison OR [95% CrI]	BASDAI50 Reponses	
	12–16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Random-effects model

Table 6-7: BASFI difference between mean change (AS population)

Comparison Difference of mean change [95% CrI]	BASFI Change	
	12–16 weeks	Primary analysis 24 weeks
Anti-TNF therapies vs placebo		
CZP pooled vs placebo	[redacted]	[redacted]
ADA vs placebo	[redacted]	[redacted]
ETA vs placebo	[redacted]	[redacted]
GOL vs placebo	[redacted]	[redacted]
IFX vs placebo	[redacted]	[redacted]
CZP vs anti-TNF therapies		
CZP pooled vs ADA	[redacted]	[redacted]
CZP pooled vs ETA	[redacted]	[redacted]
CZP pooled vs GOL	[redacted]	[redacted]
CZP pooled vs IFX	[redacted]	[redacted]

ADA: Adalimumab; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **GOL**: Golimumab; **IFX**: Infliximab; **NA**: Not applicable
Note: Advantage (↑) was defined using the MCID of 1 point for BASFI difference of mean change. ↓ indicates disadvantage, whilst ↔ indicates similar BASFI change.
Random-effects model (Week 12–16) and fixed-effects model (Week 24)

6.6.2 nr-axSpA Subpopulation

In the nr-axSpA population, the MTC showed that ADA, ETA and CZP demonstrated significantly greater improvement compared to PBO on all outcomes considered, except for ADA in BASFI change and ETA in BASFI, BASDAI, PtGADA and SF-36 PCS changes, where the improvements were numerically greater than PBO, but not significantly different.

The MTC analysis also indicated that CZP showed numerically greater improvements over ADA and ETA at 12 weeks in most outcomes assessed, in terms of ASAS responses (ASAS20, ASAS40, ASAS partial remission, ASAS5/6), disease activity and physical function; significant differences were noted in changes in BASFI, BASDAI and PtGADA. The results obtained were similar for the individual CZP doses (Appendix 11.3.3.3.2).

Results from the meta-analyses in the nr-axSpA population between CZP, ADA, ETA and PBO are summarised in Table 6-8–Table 6-14 for the following outcomes:

- ASAS response criteria (ASAS20, ASAS40, ASAS5/6 and ASAS partial remission response rates)
- Bath Ankylosing Spondylitis indices (change in BASDAI, change in BASFI)
- PROs (changes in PtGADA)

Findings for additional PROs (SF-36 PCS, total back pain) can be found in Appendix 11.3.3.2 (Table 11-28 and Table 11-29).These results were in line with the previous findings.

Table 6-8: ASAS20 response (nr-axSpA population)

Comparison OR [95% CrI]	ASAS20 Response 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Fixed-effects model

Table 6-9: ASAS40 response (nr-axSpA population)

Comparison OR [95% CrI]	ASAS40 Response 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Fixed-effects model

Table 6-10: ASAS5/6 response (nr-axSpA population)

Comparison OR [95% CrI]	ASAS5/6 Response 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.

Fixed-effects model

Table 6-11: ASAS partial remission response (nr-axSpA population)

Comparison OR [95% CrI]	ASAS Partial Response 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable; **OR**: Odds ratio
Note: Similar odds (↔) were defined as OR of 1 ±0.10 inclusive. ↑Indicates increased odds, whilst ↓ indicates decreased odds.
Fixed-effects model

Table 6-12: BASDAI difference between mean change (nr-axSpA population)

Comparison Difference of mean change [95% CrI]	BASDAI Change 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable
Note: Advantage (↑) was defined using the MCID of 1 point for BASDAI difference of mean change. ↓ indicates disadvantage, whilst ↔ indicates similar BASDAI change.
Fixed-effects model

Table 6-13: BASFI difference between mean change (nr-axSpA population)

Comparison Difference of mean change [95% CrI]	BASFI Change 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]

Comparison Difference of mean change [95% CrI]	BASFI Change 12 weeks
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable
Note: Advantage (↑) was defined using the MCID of 1 point for BASFI difference of mean change. ↓ indicates disadvantage, whilst ↔ indicates similar BASFI change.
Fixed-effects model

Table 6-14: PtGADA difference between mean change (nr-axSpA population)

Comparison Difference of mean change [95% CrI]	PtGADA Change 12 weeks
Anti-TNF therapies vs placebo	
CZP pooled vs placebo	[redacted]
ADA vs placebo	[redacted]
ETA vs placebo	[redacted]
CZP vs anti-TNF therapies	
CZP pooled vs ADA	[redacted]
CZP pooled vs ETA	[redacted]

ADA: Adalimumab; **CrI**: Credible interval; **CZP**: Certolizumab pegol; **ETA**: Etanercept; **NA**: Not applicable; **PtGADA**: Patient global assessment of disease activity
Note: Advantage (↑) was defined using the MCID of 1 point for PtGADA difference of mean change. ↓ indicates disadvantage, whilst ↔ indicates similar PtGADA change.
Fixed-effects model

6.7 Clinical Heterogeneity

Clinical heterogeneity was observed across studies identified in the systematic literature review. Major sources of heterogeneity in the trials were from patient populations, which included patient inclusion criteria, disease severity and prior therapy (especially with anti-TNF therapy).

To address the heterogeneity in patient population, the statistical analyses were performed on AS and nr-axSpA patient subpopulations separately. RAPID-axSpA is the only included trial that included patients with axSpA from both the AS and nr-axSpA subpopulations. Therefore, the statistical analyses were performed with corresponding subsets of patient data from the RAPID-axSpA study instead of the entire spectrum of axSpA patients evaluated in the trial. This approach leads to a lower sample size of each subpopulation in RAPID-axSpA, reducing the statistical power in the analysis, which could be the cause of some inconclusive MTC results, ie. reducing the chance of achieving statistical significance.

With regards to the nr-axSpA subpopulation, data are only available from three trials, RAPID-axSpA, ABILITY-1 and NCT01258738. There were certain differences in the baseline characteristics of the nr-axSpA patients enrolled in these trials, which need to be taken into consideration when interpreting the results from the pairwise analyses. For instance, all trials had a similar proportion of patients with elevated CRP (30–45%), although the threshold of elevated CRP was not consistent between studies (> 15 mg/L or > 1X ULN or by hsCRP standard). The mean time since symptom onset was slightly shorter in the RAPID-axSpA study (8.1–9.1 years) than the ABILITY-1 trial (10.1 years), whilst the NCT01258738 enrolled patients with dramatically shorter duration of symptoms (2.5 years). Conversely, the ABILITY-1 trial had a shorter average time since disease diagnosis (mean 2–3 years) compared to RAPID-axSpA (mean 4–6 years).

To address the heterogeneity related to prior anti-TNF therapy in the AS subpopulation, statistical analyses on anti-TNF therapy-naïve and anti-TNF therapy-exposed patient subpopulations would have been the ideal approach. However, data on anti-TNF therapy-exposed AS patients were not available to facilitate such analyses for all trials, likely due to anti-TNF therapy not being widely used or approved in AS at the time of

the trials conducted. A limited number of trials specified the prior anti-TNF therapy status of patients and all these studies were explicit to ensure that the AS patients were anti-TNF therapy-naïve.

Other trials were unclear on the inclusion or exclusion criteria regarding prior anti-TNF therapy use or, in those instances where prior anti-TNF therapy exposure was mentioned, the trial did not report the number of patients previously exposed to anti-TNF therapies. Most of these studies were conducted at a time when there were unlikely to have been many anti-TNF therapy failure patients and it is therefore likely that they were conducted mostly in anti-TNF naïve AS patients. To remove this uncertainty, a sensitivity analysis was conducted on AS patients who were anti-TNF therapy-naïve by excluding those studies with unclear or limited prior anti-TNF therapy. This allowed a reduction in the potential clinical heterogeneities into the statistical analyses.

Although minimal statistical heterogeneity was observed during the analyses, this was largely due to the sparse data included in the network; the limited evidence available resulted in a low statistical power to detect heterogeneity.

6.8 Mixed Treatment Comparison Summary

In summary, the results of the MTC indicate that treatment with anti-TNF therapies are superior to PBO in the AS and nr-axSpA subpopulations.

In AS patients, CZP generally showed similar efficacy to ADA, ETA, GOL and IFX at 12 to 16 weeks and 24 weeks; the difference between CZP and other anti-TNF therapies did not reach significance. Similar findings were obtained in the analysis of the individual CZP doses and in the sensitivity analysis of the anti-TNF therapy-naïve population.

In nr-axSpA patients, CZP showed numerically greater improvements over ADA and ETA at 12 weeks in most outcomes assessed, in terms of ASAS responses (ASAS20, 40, partial remission, 5/6), disease activity and physical function; significant differences were noted in changes in BASFI, BASDAI and PtGADA. Similar conclusions were obtained from the analyses of the individual CZP doses.

Clinical heterogeneity was observed across studies used in the MTC. However, sensitivity analyses were performed around prior anti-TNF therapy exposure for the AS subpopulation. These sensitivity analyses supported the conclusions of the main analysis, that anti-TNF therapies are superior to PBO and have similar efficacy to each other.

7 Clinical Safety

- No new safety signals were observed in the RAPID-axSpA study up to Week 96. The safety profile of CZP in patients with axSpA over a period of 96 weeks was comparable with that reported over shorter time periods and in other indications, with no new previously unreported safety signals compared with the use of CZP in other indications occurring over the 96-week trial period.
- Treatment-emergent AE (TEAE) rates were similar between All CZP and PBO groups up to Week 24, with >80% of the TEAEs being mild to moderate severity in CZP or PBO groups, and generally considered by the investigator as unrelated to study medication.
- As expected for an anti-TNF, the most common infectious TEAE up to Week 24 was nasopharyngitis (8.8% All CZP vs 6.5% PBO). The most common non-infectious TEAE up to Week 24 was headache (6.2% All CZP vs 6.5% PBO).
- Few serious TEAEs were reported up to Week 24 (4.7% All CZP vs 4.7% PBO).
- No deaths or malignancies were reported in the combined double-blind PBO-controlled, dose-blind and open-label treatment periods over the 96 weeks of study.

7.1 Adverse Events in the RAPID-axSpA Study

Safety data collected during the RAPID-axSpA study have been analysed up to Week 24, the end of the double-blind PBO-controlled treatment period, up to Week 48, the end of the dose-blind treatment period and up to Week 96 of the open-label period.

All randomised patients who received at least one dose of study medication were included in the safety analysis:

- Week 24: Patients who were randomised to CZP either at baseline or after escaping the PBO arm at Week 16;
- Week 96: Patients who were randomised to CZP either at baseline or after escaping from the PBO arm at Week 16 or Week 24.

For ethical reasons and as required by EMA regulatory guidance and by the RAPID-axSpA protocol, patients in the PBO arm who had not achieved a clinical response (ASAS20) at Week 14 and Week 16 escaped from the PBO arm to receive CZP. Therefore, at Week 16, 56 PBO patients escaped and were re-randomised to CZP 200 mg Q2W (27 patients) or CZP 400 mg Q4W (29 patients) through to the end of the double-blind treatment period (Week 24).[18] Therefore the original PBO group was depleted by 56 patients from Week 18 onwards and the original CZP groups were enriched by these patients.

Therefore, the number of patients within each group is different in the safety analysis to those in the efficacy analysis set. Additionally, since PBO escape patients were re-randomised to the CZP treatment arms, there is a clear imbalance between the total number of patients within the PBO and CZP-treated groups.

For this reason, the safety data are also presented over the first 16 weeks, when the number of patients between treatment groups and the exposure are similar but with the caveat that such a short treatment duration will not allow the occurrence or the diagnosis of some type of TEAE's, such as malignancies or possibly TB, due to the pathophysiological development of these events.

The 'All CZP' group consists of CZP 200 mg Q2W, CZP 400 mg Q4W, and the escaped PBO patients at Week 16. For the safety data presented for the PBO group, PBO exposure ends with the date of first CZP injection for patients escaping from PBO to CZP. Therefore the most relevant safety comparison could be considered to be at Week 16, where the number of patients and the duration of exposure is similar between the three study groups.[23]

Adverse events were coded to a System Organ Class (SOC), Higher Level Term (HLT) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1). The definitions of AEs, TEAEs and serious AEs (SAEs) used in the RAPID-axSpA study can be found in Appendix 11.4. TEAEs are reported as the number of patients experiencing each event and percentages report the proportion of patients experiencing each event. Safety data from Week 24 and 96 cut-offs are presented in this section.

7.2 Double-Blind PBO-Controlled Treatment Period (to Week 24)

7.2.1 Patient Exposure

A total of 274 patients were exposed to at least one dose of CZP during the double-blind treatment period up to Week 24. [redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.2.2 Treatment-emergent Adverse Events to Week 24

[redacted]

During the double-blind PBO-controlled treatment period (Week 0 to Week 24), the incidence of overall TEAEs was higher in the All CZP treatment group compared with PBO (70.4% All CZP vs 62.6% PBO) as was the incidence of drug-related TEAEs (33.2% All CZP vs 20.6% PBO) (Table 7-2). TEAEs were similar between All CZP and PBO groups, mostly mild (56.2% All CZP vs 48.6% PBO) to moderate (n=99 patients [36.1%] All CZP vs n=36 patients [33.6%] PBO) in severity, and generally considered by the investigator as unrelated to study medication. The incidences in the All CZP treatment group were similar compared to PBO for serious TEAEs (4.7% each) and TEAEs leading to permanent study medication discontinuation (2.2% All CZP vs 1.9% PBO), and lower compared with PBO for severe TEAEs (3.6% All CZP vs 6.5% PBO).[18]

Table 7-2: RAPID-axSpA study overall summary of TEAEs during the 24-week double-blind PBO-controlled treatment period (number of patients experiencing each event)[18]

	PBO n=107	CZP 200 mg Q2W n=111	CZP 400 mg Q4W n=107	All CZP* n=274
Total exposure in patient-years	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAEs, n (%) IR / 100 PY	67 (62.6) [redacted]	85 (76.6) [redacted]	80 (74.8) [redacted]	193 (70.4) [redacted]
Mild, n (%) IR / 100 PY	52 (48.6) [redacted]	65 (58.6) [redacted]	64 (59.8) [redacted]	154 (56.2) [redacted]
Moderate, n (%) IR / 100 PY	36 (33.6) [redacted]	46 (41.4) [redacted]	43 (40.2) [redacted]	99 (36.1) [redacted]
Severe, n (%) IR / 100 PY	7 (6.5) [redacted]	4 (3.6) [redacted]	3 (2.8) [redacted]	10 (3.6) [redacted]
Drug-related TEAEs, n (%) IR / 100 PY	22 (20.6) [redacted]	41 (36.9) [redacted]	36 (33.6) [redacted]	91 (33.2) [redacted]
Serious TEAEs, n (%) IR / 100 PY	5 (4.7) [redacted]	4 (3.6) [redacted]	7 (6.5) [redacted]	13 (4.7) [redacted]
Discontinuation due to TEAEs, n (%) IR / 100 PY	2 (1.9) [redacted]	2 (1.8) [redacted]	4 (3.7) [redacted]	6 (2.2) [redacted]
Adverse events leading to death, n	0	0	0	0

CZP: Certolizumab pegol; **IR**: Incidence rate; **PBO**: Placebo; **PY**: Patient year; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks; **SD**: Standard deviation; **TEAE**: Treatment-emergent adverse event
*Includes CZP 200 mg, CZP 400 mg, and the escaped PBO patients with their CZP data
n refers to the number patients experiencing each event

During the RAPID-axSpA 24-week double-blind PBO-controlled treatment period [redacted]. TEAEs in the All CZP group were most commonly reported in the SOC of infections and infestations (34.7% [redacted] vs. 23.4% [redacted] PBO), followed by the SOCs of skin and subcutaneous tissue disorders (14.6% [redacted] vs. 13.1% [redacted] PBO), gastrointestinal disorders (13.9% [redacted] vs. 14.0% [redacted] PBO), investigations (13.5% [redacted] vs. 6.5% [redacted] PBO), and general disorders and administration site conditions (12.4% [redacted] vs. 7.5% [redacted] PBO) (Appendix 11.4.2, Table 11-64). Of note, the PBO group reported a higher incidence of TEAEs in the SOC of musculoskeletal and connective tissue disorders compared with the All CZP group (8.0% [redacted] All CZP vs.19.6% [redacted] PBO). The SOC of investigations includes laboratory investigations such as cholesterol, liver function and renal function analyses.[92]

The most commonly reported TEAEs (by PT) in the All CZP group were nasopharyngitis (8.8% [redacted] All CZP vs 6.5% [redacted] PBO), headache (6.2% [redacted] All CZP vs 6.5% [redacted] PBO), and increased blood creatine phosphokinase (5.1% [redacted] All CZP vs. 1.9% [redacted] PBO). Increases in creatine phosphokinase were transient, resolved spontaneously despite continued CZP therapy and considered to be due to increased physical activity. No elevations were associated with an ischaemic cardiac event or resulted in study discontinuation.[18]

The most common SAEs in the double-blind PBO-controlled treatment period were infections (n=3 patients [1.1%; [redacted] All CZP vs n=0 patients for PBO) (Appendix 11.4.2, Table 11-65). For all other SOCs, the incidence was ≤0.7% ([redacted]) in the All CZP group. Other than one serious and one non-serious AE of oesophageal candidiasis, no other rare or opportunistic infections or cases of tuberculosis (TB) were reported during the double-blind PBO-controlled treatment period.[92] TB events are discussed separately below in Section 7.4.[18]

[redacted]

[redacted]

[redacted]

[redacted]. These Week 96 safety data have been presented at the recent EULAR annual meeting,[19] [redacted]

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.3 Adverse Events of Special Interest to Week 96

Data to Week 96 are presented in this section, where available. Data to Week 24 are also presented to allow comparison with PBO during the double-blind PBO-controlled phase.

7.3.1 Infections

The infection rate in the RAPID-axSpA patient population is consistent with other anti-TNF therapies. During the double-blind PBO-controlled treatment period, the overall incidence of infection TEAEs was higher in CZP-treated versus PBO-treated subjects (All CZP: 34.7% [redacted]; PBO: 23.4% [redacted]), as was the incidence of serious infection TEAEs (All CZP: 1.1% [redacted]; PBO: 0).[18] Other than one serious and one non-serious AE of oesophageal candidiasis, no other rare or opportunistic infections or cases of TB were reported during the double-blind PBO-controlled treatment period.[92]

When taking the dose-blind and open-label periods of treatment into account, the incidence of infection TEAEs in the combined double-blind PBO-controlled, dose-blind and open-label treatment periods was [redacted], and for serious infection TEAEs it was [redacted]. One case of active TB infection was identified up to Week 96.[19]

7.3.2 Malignancies

No malignancies were reported during the 96 weeks of CZP treatment.[19]

7.3.3 Autoimmune Disorders

[redacted]

7.3.4 Cardiovascular

During the double-blind treatment period, the incidence of TEAEs in the Cardiac disorders SOC was low in the All CZP (1.8% [redacted]) and PBO (0.9% [redacted]) groups. Hypertension was the most commonly reported vascular event in all groups, with no difference in incidence between the All CZP and PBO groups (2.9% [redacted] and 3.7%, respectively [redacted]). All other vascular events (by PT) were reported in 2 or fewer subjects. The profile of cardiovascular events associated with CZP treatment was generally similar between the RAPID-axSpA population and the RA studies and is consistent with other anti-TNFα therapies.[92]

7.3.5 Neurological Events

[redacted]

7.3.6 Haematology

[redacted]

7.3.7 Serious Bleeding Events

There were no SAEs of bleeding events reported during the 24-week double-blind treatment period,[92] [redacted]

7.3.8 Hepatic Disorders

During the double-blind treatment period, the incidence of TEAEs related to liver function parameters was similar in the All CZP group compared with the PBO group. The most commonly reported hepatic TEAEs were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and gamma glutamyltransferase (GGT) increased.[92]

7.3.9 Serious Skin Disorders

There were no SAEs of skin reactions reported during the 24-week double-blind treatment period,[92] [redacted]

7.3.10 Deaths

No deaths were reported during the combined double-blind PBO-controlled, dose-blind and open-label treatment periods of the RAPID-axSpA trial.[18, 19, 56]

7.3.11 Injection Site Reactions

During the double-blind PBO-controlled treatment period (Week 0 to Week 24), injection site reactions (HLT) were reported in 6.6% of the All CZP group ([redacted]) and 0.9% of subjects in the PBO group ([redacted]). Due to the PBO non-responders being re-randomised to CZP, the total number of patients in the CZP groups increased and the number of injections was far higher in the CZP groups compared to the PBO group, especially for the All CZP group. The rate of injection site reaction for the PBO and All CZP groups were comparable.

[redacted]

[redacted]

[redacted]

[redacted] Increases in creatine phosphokinase were transient, resolved spontaneously despite continued CZP therapy, and were often considered by investigators as possibly related to increased physical activity. No elevations were associated with an ischaemic cardiac event or resulted in study discontinuation.[18] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.4 Conclusions

The safety profile of CZP in axSpA up to Week 96 was in line with that previously reported from the RAPID-axSpA trial over 24 weeks, with no new safety signals observed with increased, long-term exposure up to Week 96.[19] Furthermore, the magnitude of the safety signal (such as increased rate of infection) was lower in the axSpA population, probably due to the different demographic (younger and more males) of the population, as compared to RA. There were no deaths or malignancies reported during the long-term exposure.[18, 93, 94] Incidence of discontinuation from the RAPID-axSpA study due to TEAEs was low at Week 24 and incidence of TEAEs with CZP was consistent with the known safety profile for patients with inflammatory joint diseases receiving anti-TNF therapy (eg. hypersensitivity and infections).[18]

8 Cost-Effectiveness

- A Markov model was used to evaluate the cost-utility (CU) of CZP in the AS and nr-axSpA subpopulations due to constraints associated with availability of data for the overall axSpA population and differences in comparators for the two subpopulations. A lifetime time horizon was used to reflect the chronic nature of the disease. Costs and utility were linked to levels of disease activity and physical function.
- The base case analyses indicated that CZP with the PAS is cost-effective against conventional care (CC; NSAIDs) at a willingness-to-pay threshold of £20,000 per quality-adjusted life year (QALY), in both the AS and nr-axSpA subpopulations.
- In the AS subpopulation, the base case analysis indicated that CZP with the PAS dominates ADA, ETA and GOL, being more effective and less costly. Compared to IFX, CZP is cost effective (ICER for IFX vs CZP: £114,097).
- The base case analysis in the nr-axSpA subpopulation showed that CZP with the PAS dominates both ADA and ETA, being more effective and less costly.
- One-way sensitivity analyses in both the AS and nr-axSpA subpopulation showed that ICERs were most sensitive to the probability of achieving an ASAS20 response, discount factors for health outcomes and costs, and CZP drug acquisition cost. In the AS subpopulation, probabilistic sensitivity analyses (PSA) showed that CZP was similar to ADA, ETA and GOL in terms of costs and QALYs and that all anti-TNF therapies except IFX were similarly more effective and more costly than CC. Results also show that IFX is generally more costly and marginally more effective than CZP, ADA, ETA and GOL. In the nr-axSpA subpopulation, PSA showed that CZP is more cost-effective than ADA, ETA and CC; CZP had high probability of being the most cost-effective amongst all treatment options (74.2% at £20,000/QALY threshold) for the nr-axSpA subpopulation.

8.1 Design of Economic Evaluation

8.1.1 Objective and Decision Question

A pharmaco-economic model was developed to estimate from the perspective of the NHS and social work in England and Wales, the incremental costs, health benefits and cost-effectiveness of CZP for the treatment of adult patients with severe active axSpA. CZP was compared to CC treatment, defined as non-biologic therapy consisting of NSAIDs, and compared to other biologics with the same mechanism of action (anti-TNF therapies). The pharmaco-economic model addresses the cost-effectiveness separately and independently in the two axSpA subpopulations: patients with AS and patients with nr-axSpA.

8.1.2 Alternatives

Axial spondyloarthritis (axSpA)

There are limited treatment options that cover the spectrum of axSpA disease compared to other diseases with a similar burden of disease such as RA. Other anti-TNFs that have marketing authorisation for use in both the AS and nr-axSpA subpopulations are ADA and ETA.[26, 27] Hence there is a need for alternative treatments that show efficacy in axSpA, irrespective of the presence of absence of radiographic damage. Five anti-TNF therapies have marketing authorisation for the AS subpopulation only and therefore, to consider the alternative treatments available, the subpopulations will now be covered separately.

Ankylosing spondylitis (AS)

For adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs, the current treatment options are one of five anti-TNF therapies with marketing authorisation and/or a recommendation by NICE, as indicated in the NICE MTA Final Scope (CZP, ADA, ETA, GOL and IFX).[1, 24, 25, 39] The other alternative includes CC, which is described below.

Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA)

For adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to

NSAIDs, there are currently three anti-TNFs with marketing authorisation, CZP, ADA or ETA.[26 27] The other alternative treatment for these patients would be to continue on CC, which is described below.

Conventional care

For both AS and nr-axSpA, CC without biologics was defined as a mixture of the following NSAIDs: etoricoxib 90 mg daily, naproxen 500–1,000 mg daily (assumed 1,000 mg) and diclofenac 75–150 mg daily (assumed 150 mg), ibuprofen 2,000 mg daily, sulfasalazine 2,000 mg daily. These NSAIDs and DMARDs that define CC were deemed relevant and appropriate by a practising rheumatologist in England, Wales and Scotland.[61, 95, 96]

8.1.3 Patient Groups

The target population included in the economic evaluation was adult patients with severe active axSpA, considered as two separate subpopulations:

- AS: Adults with severe active AS who have had an inadequate response to, or are intolerant to NSAIDs.
- nr-axSpA: Adults with severe active axSpA without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

The economic evaluation was conducted separately and independently in patients who had AS and patients who had nr-axSpA. It was necessary to perform separate sets of analyses for the two subpopulations given that the comparators considered appropriate for each subpopulation differed. Specifically, GOL and IFX are relevant alternatives for the AS subpopulation, but do not have market authorisation for use in nr-axSpA patients. Additionally, unlike the RAPID-axSpA trial for CZP, efficacy data for most anti-TNF therapies were available for either AS or nr-axSpA only; necessitating the separation of these different populations in MTC analyses. Analyses performed for the AS subpopulation consisted of all patients with AS from the RAPID-axSpA study, including those who were anti-TNF therapy-experienced or -naïve. The nr-axSpA subpopulation consisted of anti-TNF therapy-naïve patients only, as there were no anti-TNF therapy-experienced patients in this subpopulation. The rationale for using these patient groups in the AS and nr-axSpA subpopulation analyses is detailed in Section 6.2.3.

The baseline characteristics of the target subpopulations that were used in the pharmaco-economic model were derived from the CZP RAPID-axSpA phase 3 clinical trial and are shown in Table 8-1.

Table 8-1: Base case characteristics of all patient populations used in the pharmaco-economic analyses (derived from RAPID-axSpA trial, Baseline data)

	Age in years (SD)	Proportion Male %	Average Weight in kg (SD)	Baseline BASDAI (SD)	Baseline BASFI (SD)
AS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AS: Ankylosing spondylitis; **BASDAI**: Bath ankylosing spondylitis disease activity index; **BASFI**: Bath ankylosing spondylitis functional index; **nr-axSpA**: non-radiographic axial spondyloarthritis; **SD**: standard deviation

8.1.4 Viewpoint

The analysis undertaken adopts the perspective of the NHS in England and Wales and personal social services in England and Wales and therefore includes direct healthcare costs specific to England and Wales wherever possible that are associated with the management of patients with axSpA. UK-specific costs were used if costs specific to England and Wales were unavailable. In the present economic evaluation, these costs include medication acquisition costs, healthcare professional contact costs, laboratory and monitoring costs, and costs of management of AEs. Given that this is the preferred perspective of NICE, the analyses did not include indirect costs, such as out-of-pocket patient expenses (eg. transportation costs, private nursing) or the costs of patient 'time' (eg. productivity losses for the patient).

8.1.5 Time Horizon and Discounting

The analyses used a lifetime time horizon in the base case. This time horizon was chosen due to the lifelong nature of axSpA and, consequently, the lifelong nature of its treatment and associated costs. An alternative time horizon of 20 years was tested in a scenario analysis.

An annual discount rate of 3.5% was applied to both costs and benefits in the base case. Alternative values of 0.0% and 6.0% were tested in the one-way deterministic sensitivity analysis (OSA).

8.1.6 Evaluation Outcome Measures

CU analyses were conducted to capture the benefits, consequences, and costs for the treatment of axSpA; comparing CZP to CC and to other anti-TNF therapies. The main health outcome included in the model was QALYs. A Markov model was used to combine health outcomes with costs to estimate ICERs per QALY gained over the lifetime time horizon, from start of treatment through treatment discontinuation until death.

8.1.7 Definition of Base Case for Analyses

The pharmaco-economic analysis was conducted separately and independently per subpopulation. For the AS subpopulation, assessment was at 24 weeks based upon clinical practice as indicated by British key opinion leaders[61, 95, 96] (KOL) and, as described in Section 6.2.4 the evaluation of efficacy at greater than 12 weeks of continuous treatment was recommended by ASAS in their updated guidelines.[81] Furthermore, differences between anti-TNF therapies at 12 weeks and 24 weeks have been seen in previous HTA submissions.[24]
For the nr-axSpA subpopulation, assessment was at 12 weeks given that comparator data were available at that time point only.

For the AS subpopulation, the following assumptions were adopted in the base case:

- The CZP efficacy data used in the MTC were based upon all AS patients from the RAPID-axSpA study
- The clinical response was assessed at 24 weeks
- Alternatives were ADA, ETA, GOL, IFX and CC

For the nr-axSpA subpopulation, the following assumptions were adopted in the base case:

- The CZP efficacy data used in the MTC were based upon anti-TNF therapy-naive nr-axSpA patients in the RAPID-axSpA study (as this was also the population available in the ADA and ETA studies)
- The clinical response was assessed at 12 weeks
- Comparators were ADA, ETA and CC

Additional assumptions were made in base case scenarios for both subpopulations, which included the following:

- Patients assigned to the CC arm were assumed not to receive a benefit in terms of improvement in BASFI and BASDAI
- Disease management costs were derived from a published equation linking costs to BASFI
- The efficacy data were based upon the MTC analysis of the CZP pooled data (combining 200 mg Q2W and 400 mg Q4W arms) of the RAPID-axSpA study
- The time horizon was set at lifetime
- The costs and health benefits were discounted at 3.5%
- All costs represent 2013 values. As no inflation was assumed between 2013 and the year in progress, results may represent 2014 values.
- The perspective was payer (England and Wales NHS and social work)
- The PAS defined in Section 1e is in effect.

8.1.8 Evidence Linking Disease-Specific Outcomes to Final Health Outcomes

Disease-specific outcomes used in the pharmaco-economic analysis were ASAS20, BASFI and BASDAI. QALYs were derived from BASFI and BASDAI through a statistical relationship constructed from RAPID-axSpA trial data and described in Section 8.2.2.3. The ASAS20 response determined initial changes from baseline for BASFI and BASDAI, described in Sections 8.2.2.1.

8.2 Data Collection

8.2.1 Sources of Effectiveness

The effectiveness of CZP compared to CC was derived from the MTC presented in Section 6.6, which included the RAPID-axSpA phase 3 clinical trial. In the absence of head-to-head trials comparing anti-TNF therapies, separate MTCs were conducted for the AS and nr-axSpA subpopulations and for the time of assessment (12 and 24 weeks [for AS only]). The MTC provided the data for the model inputs for ASAS20 response, change from baseline in BASDAI, and change from baseline in BASFI.

The primary efficacy endpoint for the RAPID-axSpA study was the ASAS20 response at Week 12 and as a secondary endpoint at Week 24, and this was incorporated into the model to define response to anti-TNF therapy. Long-term evolution of the disease, captured through change in BASFI and BASDAI over time, was based upon best available literature, review of NICE TA143 and on recommendations for conducting pharmaco-economic evaluations for AS.[97, 98] Further details on how ASAS20 responses, BASFI and BASDAI were used to model utilities are provided below in Section 8.2.2.

8.2.2 Methods to Value Health States

Health states in the pharmaco-economic model were assigned cost and utility values according to evolving BASDAI and BASFI scores, which depend on: whether a patient is assigned to CC or anti-TNF therapy, whether a patient has responded and is continuing to respond to anti-TNF therapy or whether they have discontinued and been placed on CC. In the base cases for the AS subpopulation, all patients who start anti-TNF therapy have their response to treatment assessed at 24 weeks following onset of treatment. The model continuously links the patients' utility to BASDAI and BASFI according to the explanations provided in Section 8.2.2.3. Similarly, the model attributes costs of managing patients according to a cost equation that is linked to BASFI, described in Section 8.2.3.1. Patients could die at any point in the model based upon the mortality parameter described in Section 8.2.2.6.

8.2.2.1 ASAS20 Treatment Response

The MTC provided estimates of the ASAS20 response at 12 and 24 weeks for the AS subpopulation and at 12 weeks for the nr-axSpA subpopulation (Table 8-2 and Table 8-3).

Previous pharmaco-economic models and treatment guidelines reveal that recommended response criteria and time of measurement of response are evolving. It should be noted that the NICE committee chose AS treatment to be evaluated at 12 weeks using the BSR criteria, namely a reduction in BASDAI score by 50% of the pre-treatment value (BASDAI50) or a fall of ≥2 units in the BASDAI and a reduction of the spinal pain VAS (pain assessed over past week) by ≥2 cm.[24, 99] However, according to the BSR guidelines, there is comparable performance of the ASAS combined score and the BASDAI50 by ≥2 units in assessing response to treatment.[100] Given current recommendations by the ASAS working group, the need to assess treatment response using a composite score that considers both pain and well-being, and that the primary endpoint in the RAPID-axSpA study was ASAS20 response, the model adopted the ASAS20 response as the primary assessment criterion at either 12 or 24 weeks post initiation of therapy.

Table 8-2 below presents the ASAS20 response rates for CZP and the relative risk (RR) of response of other anti-TNF therapies relative to CZP for the AS subpopulation base cases.

Table 8-2: Base case model inputs: ASAS20 response at Week 24 (AS subpopulation, CZP pooled dosing[§])

Treatment	ASAS20 Response (%)	SE	RR[†]	CI	Source
CZP	[redacted]	[redacted]	-	-	MTC

Adalimumab†	-	-	[redacted]	[redacted]	MTC
Etanercept†	-	-	[redacted]	[redacted]	MTC
Golimumab†	-	-	[redacted]	[redacted]	MTC
Infliximab†	-	-	[redacted]	[redacted]	MTC

ASAS: Assessment in SpondyloArthritis international Society (criteria); **CC**: Conventional care; **CI**: Confidence interval; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **RR**: Relative risk; **SE**: Standard error
* proportion responding
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
†CZP versus comparator

For the nr-axSpA subpopulation, the ASAS20 response rates listed below in Table 8-3 were used in the pharmaco-economic model.

Table 8-3: Base case model inputs: ASAS20 response at Week 12 (nr-axSpA subpopulation, CZP pooled dosing§)

Treatment†	ASAS20 Response (%)	SE	RR†	CI	Source
CZP	[redacted]	[redacted]	-	-	MTC
Adalimumab†	-	-	[redacted]	[redacted]	MTC
Etanercept†	-	-	[redacted]	[redacted]	MTC

ASAS: Assessment in SpondyloArthritis international Society (criteria); **CC**: Conventional care; **CI**: Confidence interval; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **RR**: Relative risk; **SE**: Standard error
* proportion responding
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
†CZP versus comparator

8.2.2.2 Evolution of BASDAI and BASFI

The development of economic models requires a choice of the disease-related measures that represent clinically and economically important events in the disease process. For this purpose, BASDAI and BASFI have been most frequently used in previous economic models of AS.[99, 101-105] BASFI has been extensively validated and is the most common measure of functional activity in AS.[106]

Patients who enter the model start at a mean BASDAI and BASFI score informed by the baseline data from the RAPID-axSpA study (see Table 5-4 for baseline values and Table 8-1 for values taken forward into the model). Upon initiation of treatment with anti-TNF therapy, patients experience an initial improvement in BASDAI and BASFI up to the end of the 12- or 24-week assessment period, as observed in RAPID-axSpA and other trials of anti-TNF therapies. It is assumed that patients who continue to respond and remain on anti-TNF therapy will thereafter maintain this improved BASDAI and BASFI score at a constant, unchanging level. This assumption has been generally accepted for biologic treatment in RA, based upon the evidence that functional deterioration might be prevented in those patients in whom the inflammatory process is controlled, as indicated by a sustained reduction in disease activity (although such evidence of disease modification in axSpA is lacking).[98, 107] Other cost-effectiveness evaluations have made similar assumptions with regard to the evolution of BASDAI and BASFI for patients on sustained anti-TNF therapy. [102, 104, 108] When patients withdraw from anti-TNF therapy, it is assumed that the BASFI (and BASDAI) score rebounds or worsens gradually (during the tunnel states of the model) to the average BASFI score of patients on CC. In this way, patients who have exhausted their anti-TNF therapy option are equivalent to patients on CC in terms of their BASFI and BASDAI score. This way of modelling the evolution of BASFI and BASDAI is consistent with that recommended by Wailoo et al. in 2008.[98]

For patients on CC, there is an assumed, gradual annual increase of 0.07 points in BASFI, indicating worsening of disease, as per assumptions deemed reasonable by a NICE committee.[24, 63, 99] This figure was obtained by combining data from a population survey first carried out between 1992 and 1994 at the University of Bath and later from a cohort of 700 patients regularly followed for up to nine years in which questionnaires elicited patients' current disease state (BASDAI, BASFI) allowing estimation of disease progression.[109] However, we assume no worsening in BASDAI for patients on CC, based upon a follow-up of 279 patients that showed no significant progression in BASDAI scores over five years.[110] This was also deemed reasonable by the NICE committee.[24, 99]

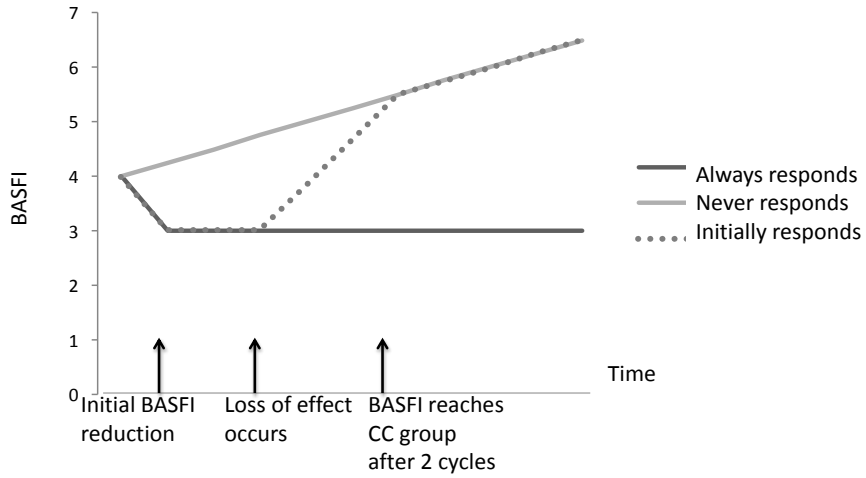
Patients assigned to the CC arm are assumed not to receive an initial benefit in terms of BASFI and BASDAI. It is reasonable to assume that patients receiving CC do not achieve a change from baseline

(worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[15, 18, 33, 91] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process".[111] This assumption is consistent with previous manufacturers' submissions to NICE in AS.[24] However, this assumption is tested in sensitivity analyses.

Figure 8-1 and Figure 8-2 below illustrate the evolution of BASFI and BASDAI respectively in the base case for three cases: patients who always respond to anti-TNF therapy; patients who begin and continue indefinitely with CC; and patients who initially respond to anti-TNF therapy but then discontinue and switch to CC.

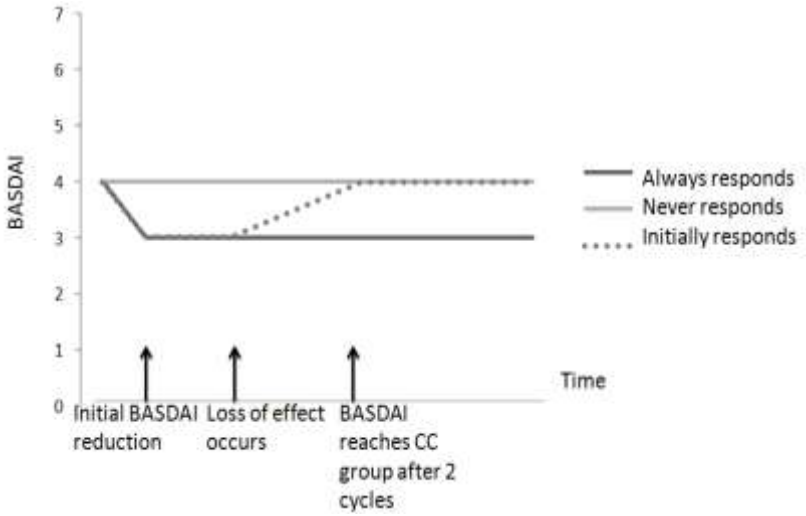
The base case inputs that informed the initial improvement in BASDAI and BASFI for each anti-TNF therapy were provided by the MTC analyses presented in Section 6.6 (AS subpopulation inputs: Table 8-4 and Table 8-5; nr-axSpA subpopulation inputs: Table 8-6 and Table 8-7).

Figure 8-1. Diagrammatic representation of BASFI trajectories for the 3 patient cases



BASFI: Bath Ankylosing Spondylitis Functional Index; **CC**: Conventional care

Figure 8-2. Diagrammatic representation of BASDAI trajectories for the 3 patient cases



BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **CC**: Conventional care

Model base case inputs for change from baseline in BASFI and BASDAI at Week 24 for the AS subpopulation are given in Table 8-4 and Table 8-5. It should be noted that the mean change from baseline noted below is that observed per trial arm, which includes both the ASAS20 responders and non-responders in each arm. In order to determine the change in BASFI and BASDAI for responders alone, the equation below is used:

Mean change in BASFI = (change in BASFI amongst ASAS20 responders * proportion ASAS20 responders) + (change in BASFI amongst ASAS20 non-responders * proportion ASAS20 non-responders)

It is assumed that the change in BASFI amongst ASAS20 non-responders is equal to that of the CC arm. Thus, the equation is solved algebraically for change in BASFI amongst ASAS20 responders. As an example for the AS subpopulation base case, the change in BASFI amongst ASAS20 responders for CZP is: [-1.93 – (0*0.443)] / (0.5569) = -3.46. Thus, in this example, the actual change from baseline in AS responders to CZP is -3.46. The same approach was used for change from baseline for BASDAI. This approach, where the change from baseline for BASDAI and BASFI is calculated amongst responders only, is consistent with previous evaluations pharmaco-economic evaluations conducted for AS.[24]

Table 8-4: Base case model inputs: Change from baseline in BASFI score at Week 24 (AS subpopulation, CZP pooled dosing[§])

Treatment	Change from Baseline in BASFI Score at Week 24: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Golimumab*	[redacted]	[redacted]	MTC*
Infliximab	[redacted]	[redacted]	MTC
Conventional care**	[redacted]	[redacted]	Assumed zero in base case**

BASFI: Bath Ankylosing Spondylitis Functional Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* GOL assumed same values as ADA, given that specific input values for BASFI at 24 weeks were not available from MTC.
** Conventional care assumed to produce no change in BASFI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[15, 18, 33, 91] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process".[111] This assumption is consistent with previous manufacturers' submissions to NICE in AS.[24] However, a mean change in BASFI of [redacted] estimated from the MTC was used in the sensitivity analysis.

Table 8-5: Base case model inputs: Change from baseline in BASDAI score at Week 24 (AS subpopulation, CZP pooled dosing[§])

Treatment	Change from Baseline in BASDAI Score at Week 24: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Golimumab	[redacted]	[redacted]	MTC
Infliximab	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* Conventional care assumed to produce no change in BASDAI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[15, 18, 33, 91] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process".[111] This assumption is consistent with previous manufacturers' submissions to NICE in AS.[24] However, a mean change in BASDAI of [redacted] estimated from the MTC was used in the sensitivity analysis.

Model base case inputs for change from baseline in BASFI and BASDAI at Week 12 for the nr-axSpA subpopulation are given in Table 8-6 and Table 8-7.

Table 8-6: Base case model inputs: Change from baseline in BASFI score at Week 12 (nr-axSpA subpopulation, CZP pooled dosing[§])

Treatment	Change from Baseline in BASFI Score at Week 12:Initial Response Assessment Period	Source

	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASFI: Bath Ankylosing Spondylitis Functional Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* Conventional care assumed to produce no change in BASFI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[15, 18, 33, 91] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process".[111] This assumption is consistent with previous manufacturers' submissions to NICE in AS.[24] However, a mean change in BASFI of [redacted] estimated from the MTC was used in the sensitivity analysis.

Table 8-7: Base case model inputs: Change from baseline in BASDAI score at Week 12 (nr-axSpA subpopulation, CZP pooled dosing[§])

Treatment	Change from Baseline in BASDAI Score at Week 12: Initial Response Assessment Period		Source
	Mean	SD	
CZP	[redacted]	[redacted]	MTC
Adalimumab	[redacted]	[redacted]	MTC
Etanercept	[redacted]	[redacted]	MTC
Conventional care*	[redacted]	[redacted]	Assumed zero in base case*

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **CZP**: Certolizumab pegol; **MTC**: Mixed treatment comparison; **SD**: Standard deviation
§ Based upon pooled CZP 200 mg Q2W and 400 mg Q4W arms from RAPID-axSpA
* Conventional care assumed to produce no change in BASDAI score initially in the base case. As noted in main text, it is reasonable to assume patients receiving CC do not achieve a change from baseline (worsening or improvement) in BASDAI or BASFI as evidence from RAPID-axSpA, ATLAS and ABILITY-1 demonstrate that in the PBO arms of these studies where patients were essentially maintained on CC, patients did not achieve MCID for BASDAI or BASFI.[15, 18, 33, 91] Furthermore, Dougados and colleagues describe CC regimens as "palliative at best, providing no alteration of the disease process".[111] This assumption is consistent with previous manufacturers' submissions to NICE in AS.[24] However, a mean change in BASDAI of [redacted] estimated from the MTC was used in the sensitivity analysis.

8.2.2.3 Utility

A UK value-set was applied to obtain utilities from patient responses to the EuroQoL Health Status Questionnaire (5 dimensions) (EQ-5D) collected in the RAPID-axSpA study. Data from subjects having EQ-5D, BASDAI and BASFI scores available at baseline, Week 12 and Week 24 were used to estimate a relationship between utility and BASDAI and BASFI. Since utilities may have floor or ceiling effects as they are bounded at 0 and 1, the utilities were converted using a logistic transformation. A repeated-measures logistic regression was used to model the relationship between utility, BASDAI, and BASFI scores according to the equation (where "rhs" refers to the right-hand side of the equation):

$$\text{LN (Utility/(1-Utility))} = \text{Intercept + Coefficient_BASFI*BASFI + Coefficient_BASDAI*BASDAI} = \text{rhs}$$

The normal distribution was selected to specify the distribution of the error term in the statistical model. The result of the fitted model was used to obtain the utilities according to the equation: Utility = EXP(rhs) / 1 + EXP(rhs). This equation was applied to both subpopulations and was used to continually update utility as patients' BASFI and BASDAI scores evolved through time.

The final model fit is given below in Table 8-8 and Table 8-9. Additional detail on utility estimates is given in Appendix 11.5.1.1.

Table 8-8: Utility regression equation fit – parameter estimates*

Parameter	Estimate	SE**	95% Confidence Limits		Z	Pr > |Z|
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASFI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BASDAI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **SE**: Standard error
* Analysis of generalised estimating equations parameter estimates
** Based on SAS PROC GENMOD using empirical standard error estimates

Table 8-9: Utility regression equation fit – covariance matrix (model-based)*

Parameter	Intercept	BASFI	BASDAI
Intercept	[redacted]	[redacted]	[redacted]
BASFI	[redacted]	[redacted]	[redacted]
BASDAI	[redacted]	[redacted]	[redacted]

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index
* Analysis of generalised estimating equations parameter estimates

8.2.2.4 Discontinuation, Adverse Events, and Loss of Effect

Discontinuation in the model may occur due to two possible causes: loss of treatment effect or AEs; and can occur only after the Week 12 or Week 24 timepoint. A rate of loss of treatment effect or of discontinuation due to AEs can be specified according to the specific anti-TNF therapy; however, due to lack of long-term evidence on either of these rates, the model assumes the same overall rate of discontinuation for all anti-TNF therapies.

The NICE committee assumed a discontinuation rate of 7% per year (all causes combined) in AS patients.[24, 99] It was noted that all RCT evidence for discontinuation is short term, and estimates of discontinuation beyond the first year could be based on patient registries or open-label follow-up studies. They also noted that there is currently little evidence to suggest that AEs differ between different anti-TNF therapies. Given the lack of more granular data on rates and causes of discontinuation, the NICE assumptions of an overall base case value of 7% discontinuation rate per year were adopted for the AS subpopulation.

Previous models by Botteman et al. and Jansen et al. did include AEs;[102, 103] however, these were not detailed or were limited to AEs such as gastrointestinal events (eg. ulcers and bleeding associated with NSAIDs [eg. etoricoxib, celecoxib]) and were limited to the first year of the model only. According to the SmPCs of all anti-TNF therapies, common AEs included injection-site reactions for drugs given sc, infections and non-serious allergic reactions. Given that these AEs are similar for all anti-TNF therapies, AEs are not likely to be an important driver of costs or QALYs in an economic evaluation. The literature on the safety of biological DMARDs is reported by means of different outcomes, which makes reliable direct comparison between agents difficult. As the broad safety profile of CZP compared to PBO appears to be similar to that reported for other anti-TNF therapies compared to PBO, the costs and outcomes associated with AEs were not explicitly included in the model.

In the model, it is assumed that CC patients do not discontinue from their treatment. Table 8-10 below shows the discontinuation rates assumed for the AS base case population. For the nr-axSpA subpopulation, identical assumptions for the discontinuation rates were used.

Table 8-10: Assumed base case treatment discontinuation rates (AS and nr-axSpA subpopulations)

Treatment		Source
Discontinuation, rate per 100 person-years (SE)		
CZP	7% (1.75%)	TA143.
Risk of discontinuation relative to CZP (CI)		
Golimumab	1.00 (0.75, 1.25)	Discontinuation rates are assumed to be equal to CZP
Adalimumab	1.00 (0.75, 1.25)	Discontinuation rates are assumed to be equal to CZP
Etanercept	1.00 (0.75, 1.25)	Discontinuation rates are assumed to be equal to CZP
Infliximab	1.00 (0.75, 1.25)	Discontinuation rates are assumed to be equal to CZP

CI: Confidence interval; **CZP**: Certolizumab pegol; **SE**: Standard error

8.2.2.5 Disease Progression for nr-axSpA Patients

In the base case analysis of the nr-axSpA subpopulation, it is assumed that some nr-axSpA patients may progress to AS during their course of treatment. The model adopts an estimate for disease progression for the nr-axSpA subpopulation based on a German cohort of axSpA patients, the German Spondyloarthritis

Inception Cohort (GESPIC).[112] In this cohort, the rates and predictors of radiographic spinal progression over two years were estimated based on the modified Stoke Ankylosing Spondylitis Spine Score scoring system (mSASSS). Data indicated that 7.4% of the 95 nr-axSpA patients showed spinal radiographic progression, which was defined as a worsening of mSASSS by ≥2 units over two years. As this 7.4% progression represents a proportion it was converted to a rate for use in the economic model, assuming an exponential distribution through the following formula:

1-0.074 = exp(-rate*2 years); rate = 0.0384 or 3.84 per 100 pt-year

8.2.2.6 Mortality

Patients with AS are thought to have a higher mortality rate when compared to the general population, largely due to their increased risk of cardiovascular events.[113-115] Previous studies have shown that AS patients have a standardised mortality ratio (SMR) of 1.5 or higher.[113, 115] This was subsequently confirmed in a more recent case-control study of AS patients in Norway, which found that circulatory disease was the most frequent cause of death in AS patients followed by malignancies and infections.[113] The SMR ratio was also in line with previous estimates found in an AS population (average 1.50), though it was slightly higher for males (1.63) than females (1.38). This approach to mortality using SMR is consistent with previously published economic models and HTAs in AS.[99]

Given the lack of mortality data in the nr-axSpA subpopulation, the same SMR for an AS or nr-axSpA patient was assumed to be 1.5. It is acknowledged by KOLs that there is a higher mortality risk for patients with axSpA compared to the general population, but it is unclear whether this is due to the disease process itself or to prolonged use of NSAIDS. This SMR was then applied to the mortality rates from the general population found in the interim life tables relating to England and Wales, generated by the Office for National Statistics, UK.[116]

8.2.3 Resource Use and Costs

8.2.3.1 Disease Management Costs

There are currently no guidelines on the appropriate management of nr-axSpA and AS subpopulations in relation to resource utilisation. Guidelines normally advocate that patients with suspected AS should be referred to a rheumatologist, have access to anti-TNF therapy and non-pharmacological care such as physiotherapy, and have regular follow-up visits. These recommendations provide some insight into the types of medical resources an AS or nr-axSpA patient would consume but do not give a clear utilisation algorithm that could be used for modelling purposes.

Previous published economic evaluations employed observational cohort studies to estimate disease management costs and modelled these according to BASDAI and/or BASFI.[24, 99] The NICE committee judged that the Outcomes in Ankylosing Spondylitis International Study (OASIS) data were the most reliable source, being a two-year prospective study of 208 AS patients from four centres in France, Belgium and The Netherlands, and collecting clinical assessments and economic data including BASDAI and BASFI every 2 or 6 months. The NICE committee also judged that only BASFI should be employed as the major predictor of costs as it reflects long-term disease progression, whilst BASDAI appears to fluctuate but not increase over time. An exponential cost model was constructed to the weighted aggregate OASIS data, derived using the equation below:

Annual mean AS-related NHS cost = £1585.30 x exp(0.1832xBASFI)

Due to the lack of alternative sources for estimation of disease management costs, we adopted this equation for our pharmaco-economic model. However, given the year of publication of this source, it was assumed that this equation represents 2007 costs, and that these costs are not recent and that resource use might have changed over time. However, this equation is the best available source for modelling disease management costs. The costs in the equation above were adjusted for inflation to 2013 costs with an inflation factor of 1.204.[117] The costs included in the equation represent drug costs (excluding anti-TNF therapies), administration, monitoring, hospitalisation, healthcare visits, aids and appliances, and AEs. Interestingly, the OASIS data were also used by Botteman et al. for estimating disease management costs, however, they chose a linear equation that related costs to BASDAI alone.[102]

Additional details about disease management cost modelling are described in Appendix 11.5.1.1.

8.2.3.2 Drug Acquisition Costs

The assumed dose administration and unit costs of the anti-TNF therapies and NSAIDs used for CC are displayed in Table 8-11.[2] The drugs used by patients in the CC arm, dose, and the percent of patients utilising the drug were determined by practising KOLs in the UK.

Table 8-11: Base case drug costs for CZP and alternatives (both subpopulations)

	Unit Size	Cost Per Unit[a]	Formulation	No. Units in Loading	Frequency of Dosing in Maintenance
Anti-TNF therapies					
CZP	200 mg	£357.50	Prefilled syringe	6 units (400 mg as 2 injections of 200 mg each on one day at weeks 0, 2 and 4)[b]	200 mg Q2W or 400 mg Q4W
Adalimumab	40 mg	£352.14	Prefilled syringe	NA	Q2W[c]
Etanercept	50 mg	£178.80	Prefilled syringe	NA	Once weekly[d]
Golimumab	50 mg	£762.97	Prefilled syringe	NA	Same date each month[e]
Infliximab	100 mg	£419.62	Infusion	5 mg/kg (at Weeks 0, 2 and 6)	Every 6–8 weeks[f]; every 7 weeks assumed
Conventional care[g]					
Naproxen	500 mg	£1.82 / 500 mg x 28-tab pack = £0.07 per tablet	Tablet	NA	1000 mg daily; ,50% of patients on CC utilise
Diclofenac	25 mg	£3.23 / 25 mg x 28-tab pack = £0.35 per tablet	Tablet	NA	150 mg daily; 10% of patients on CC utilise
Etoricoxib	90 mg	£22.96 / 90 mg x 28tab pack = £0.82 per tablet	Tablet	NA	90 mg daily; 40% of patients on CC utilise
Ibuprofen	600 mg	£6.93 / 600 mg x 84-tab pack = £0.08 per tablet	Tablet	NA	1,600–2,400 mg daily (assumed 2,000 mg daily); 10% of patients utilise
Sulfasalazine	500 mg	£8.07 / 500 mg x 112-tab pack = £0.07 per tablet	Tablet	NA	2,000 mg daily; 5% of patients utilise

CZP: Certolizumab pegol; **mg**: Milligram; **NA**: Not applicable; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks
For all treatments, unit doses do not vary by subgroup (nr-axSpA and AS) or by BASDAI and BASFI.
Source:
a Cost per unit taken from the British National Formulary (BNF)[2]
b The estimated number of units used for CZP is based on the recommended dose for treating axSpA is 400 mg (as two injections of 200 mg each on one day) at Weeks 0, 2 and 4, followed by a maintenance dose of 200 mg Q2W or 400 mg Q4W.
c The estimated number of units used for adalimumab is based on the recommended dose for treating AS of 40 mg on alternate weeks; discontinue treatment if no response within 12 weeks.
d The estimated number of units used for etanercept is based on the recommended dose for treating AS of 25 mg twice weekly or 50 mg once weekly.
e The estimated number of units used for golimumab is based on the recommended dose for treating AS of 50 mg once a month on the same date each month, review treatment if no response after 3–4 doses.
f The estimated number of units used for infliximab is based on the recommended dose for treating AS of 5 mg/kg infusions every 6–8 weeks; discontinue treatment if no response within 6 weeks.
g For additional detail on use of CC drugs see Table 9-7

8.2.3.3 Administration Costs

In addition to medication acquisition costs, a one-time administration cost was included in the model and was derived from Personal Social Services Research Unit (PSSRU) costings. These costs are presented below in Table 8-12. It was assumed that for the anti-TNF therapies, which are sc injections, an hour of a specialist nurse's time in a community setting was required. It was assumed that 10% of patients receiving intravenous (IV) infusions (ie. IFX) would receive their infusions in an outpatient setting with the remaining proportion receiving infusions through day clinics.

Table 8-12: Base case administration costs for oral and subcutaneous drugs (both subpopulations)

Administration Type	Unit Cost
Cost for nurse training (for subcutaneously administered anti-TNF therapies)	£48.00[a]
IV administration cost	£389.10[b]
Oral medication (for CC)	£0.00

CC: Conventional care; **IV**: Intravenous
a PSSRU, 2012 Schema 10.4: Nurse specialist (community). The cost per hour of client contact includes wages/salary, salary costs, qualifications, overheads, and capital overheads.[118] The figure shown is for 2012, which was inflated to 2013 values (£49.21) by the model.
b Based upon 10% of IV patients receiving outpatient administration (£246.00) and 90% of IV patients receiving day-case administration (£405.00). The figure shown is for 2012, which was inflates to 2013 (£398.91) by the model.

8.2.3.4 Conventional Care Costs

In the model, it was assumed that CC was a mixture of treatment consisting of the treatments listed in

Table 8-13. The CC was a weighted average of the percentage of patients taking the drugs listed below. Combining the unit costs from Table 8-11 with the percentage of patients taking each NSAID, the average medication acquisition cost of CC is £0.47 daily, equivalent to £171.55 annually.

Table 8-13: Base case conventional care drug usage (both subpopulations)

Treatment	Percent of Patients	Source
Naproxen	50%	KOL
Diclofenac	10%	KOL
Etoricoxib	40%	KOL
Ibuprofen	10%	KOL
Sulfasalazine	5%	KOL

KOL: Key opinion leader

8.2.4 Model Approach

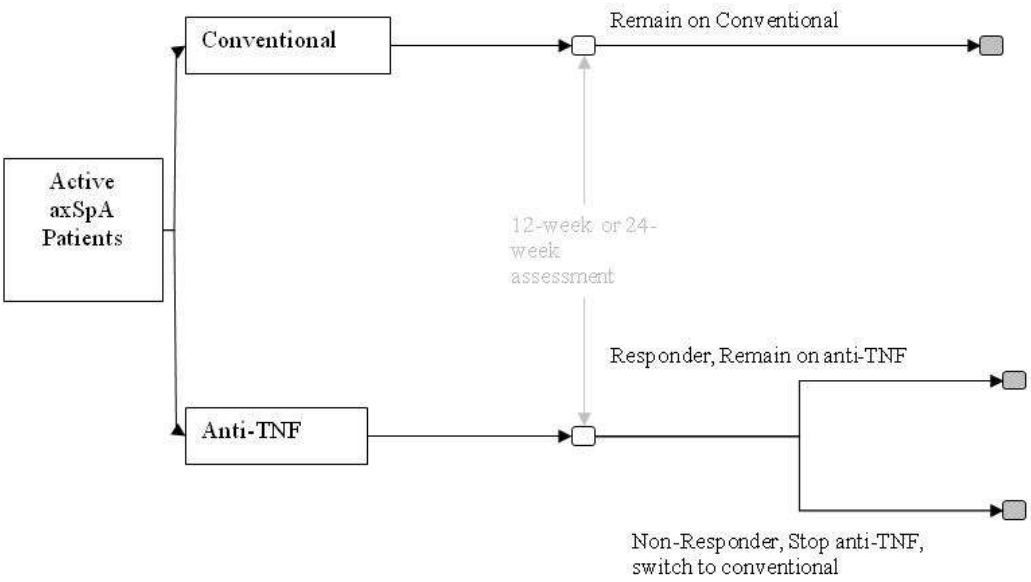
A Markov cohort model was developed in Microsoft® Excel to follow patients with AS or nr-axSpA from the start of treatment through lifetime. Markov model structures have been used in previous economic evaluations[101, 103, 109] and previous assessments by NICE for AS.[24, 99] These models are able to forecast and estimate the long-term consequences of managing axSpA, including morbidity, mortality, and costs. There are no previously published models on the nr-axSpA population. Long-term disease progression is modelled using BASFI and BASDAI, which evolve over time according to time on or off anti-TNF therapy. The model consists of a short-term trial period and a long-term follow-up period.

Figure 8-3 describes the short-term model in the form of a decision tree. Patients enter the model with an active diagnosis of axSpA (either AS or nr-axSpA) and failure to respond to treatment of at least one NSAID or intolerance of NSAIDs. They are allocated to begin treatment on either CC or anti-TNF therapy. A patient's response to treatment is evaluated at the end of a 12-week (for nr-axSpA or AS subpopulations) or 24-week (for AS subpopulation) assessment period according to the ASAS20 response definition. A probability of responding to treatment is associated with each anti-TNF therapy. If a patient responds to anti-TNF therapy, they continue on that treatment. If they fail to respond, the patient is switched to CC. Patients who initiate treatment on CC remain on CC throughout their lifetime. The duration of the short-term model is either 12 or 24 weeks, selected for determining the time of ASAS20 assessment for response to the anti-TNF therapy (refer to Section 8.2.2.1). After this period, patients transition to the long-term model.

Figure 8-4 depicts the flow of patients through the long-term model. Patients continue on their assigned first line anti-TNF therapy or they discontinue and switch to CC. The two axSpA subpopulations in the model are treated slightly differently. For the nr-axSpA subpopulation, the model assumes that patients may progress from nr-axSpA to AS.[119] Patients who progress from nr-axSpA to AS will continue to receive the treatment

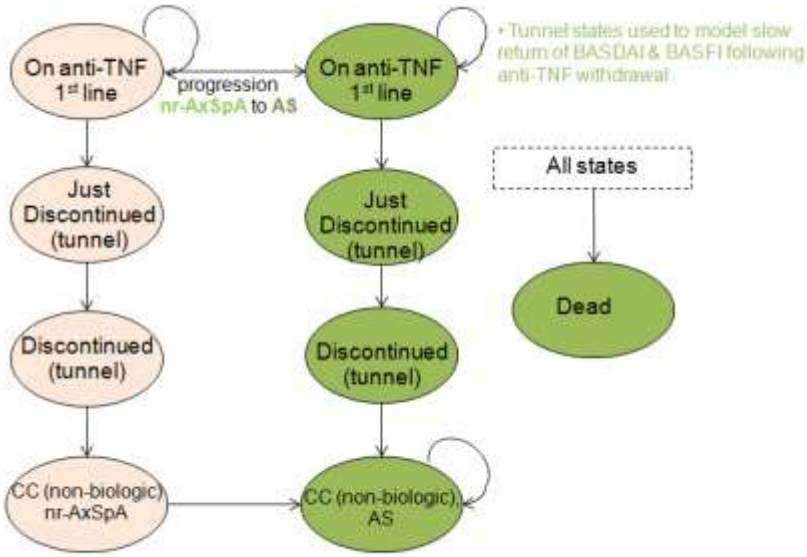
they had been receiving prior to progression. Therefore, there is no change in the current treatment that the patient receives when progressing to AS. Patients may then discontinue treatment due to a lack of effect or an AE. Patients who discontinue treatment with an anti-TNF therapy pass through two consecutive, identical tunnel states corresponding to two model cycles (24 weeks) to allow for a gradual worsening of BASFI before starting on CC where they remain until death. Death may occur from any state in any model cycle.

Figure 8-3: Short-term model: decision tree for active axSpA patients (AS and nr-axSpA subpopulations)



axSpA: Axial spondyloarthritis; **TNF**: Tumour necrosis factor

Figure 8-4: Long-term model diagram



AS: Ankylosing spondylitis; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **CC**: Conventional care; **nr-axSpA**: Non-radiographic axSpA; **TNF**: Tumour necrosis factor
* Discontinuation due to adverse events or lack of efficacy.

8.3 Analysis Plan

The model was run for the base case scenarios defined in Section 8.1.7 in both subpopulations over a lifetime time horizon for a population size of 1,000.

One-way and probabilistic sensitivity analyses as well as scenario analyses were also performed to explore the potential impact of the choice of inputs to the model. These are described in Section 8.3. All three types of sensitivity analysis were run on the base case scenarios for the AS and nr-axSpA subpopulations to test the robustness of the model.

For the nr-axSpA subpopulation, an alternative CU scenario was conducted, where ASAS20 was assumed the same for ADA, ETA and CZP, and was set equal to the efficacy of CZP as determined by the MTC. Changes in BASDAI and BASFI remained specific to each comparator as determined by the MTC for each intervention.

8.3.1 Structural Uncertainty

Structural uncertainty arises due to uncertainty about the functional form of the model or whether the model adequately reflects clinical practice. It may also arise due to gaps in knowledge in terms of natural history or long-term evolution of the disease. To minimise structural uncertainty, the most recent available guidelines on how to conduct economic models in this disease area were reviewed. In addition to previous assessments by NICE for AS,[24, 99] two papers that offered recommendations on performing economic evaluation of anti-TNF-therapies in AS were reviewed prior to developing the present model.[97, 98] Note that no specific guidance on how to perform economic evaluations for nr-axSpA are available. Our model and analysis plan was consistent with recommendations for AS:

- The evaluations reviewed presented analyses based on a lifetime horizon.
- The models included initial response criteria that are pertinent to both economic and clinical consequences and that determine discontinuation in non-responders (as well as including discontinuation in a long-term model corresponding to treatment withdrawal and mortality).
- The economic models included a CC comparator.
- Outcome measures for both disease functioning and disease activity were modelled (i.e. BASDAI and BASFI)
- Valuation of quality of life was included by linking clinical outcome measures (i.e. BASDAI and BASFI) to health utilities.
- Population subgroups (nr-axSpA and AS) were analysed.
- The long-term evolution of BASDAI and BASFI in the model amongst responders to anti-TNF therapies and those receiving CC as described in Section 8.2.2.2 was consistent with NICE recommendations and Wailoo et al. [97, 98]

Additionally, our analyses permitted investigation of structural uncertainty through scenario analyses for:

- The statistical relationship constructed between utility and BASDAI and BASFI by using an alternative utility equation published by NICE.[99] The alternative utility equation is described in Appendix 11.5.1.1.
- The time of assessment of response to anti-TNF therapies (24 weeks for the AS subpopulation in the base-case). The difference in relative effect between anti-TNF therapies at 12 weeks and 24 weeks was also observed in previous HTA submissions to NICE (TA143).[24] Therefore, using 24-week data were favoured where data availability allowed MTC analyses to be performed. An alternative assessment period (applicable to the AS subpopulation only) of treatment response at 12 weeks (instead of 24 weeks) was evaluated in the scenario analysis. However, for the nr-axSpA base case, the limited trial data meant that only a 12-week cycle length could be used.
- The uncertainty around the benefit of maintenance of CC. In the base case it was assumed that patients would experience no additional benefit in terms of BASFI and BASDAI, which determine the utilities associated with the disease state. This assumption was justified as patients maintaining on ≥2 NSAIDs would only be eligible for treatment with anti-TNF therapy if they did not experience improvement in their symptoms. However, in the MTC, patients in the PBO arm did experience

benefit. Therefore, this assumption was also explored in scenario sensitivity analyses; patients on CC were assumed to receive a benefit in the form of BASFI and BASDAI improvement.

8.3.2 Approach to Alternative Sensitivity Scenarios

To reduce the potential for selection bias in this analysis, input values for the efficacy of the anti-TNF therapies were derived from an MTC, which was based on a systematic literature review.

Where inputs were based on assumptions, alternative sensitivity scenarios were performed in both subpopulations and are defined as outlined below. The alternative inputs used in these scenarios can be found in Appendix 11.5.1.3.

- *Efficacy of CC Scenario*: Patients on CC are assumed to receive a benefit in the form of BASFI and BASDAI improvement.
- *Assessment Period Scenario*: Response to anti-TNF therapy is assessed at 12 week rather than 24 weeks (performed for AS subpopulation only)
- *Discontinuation Rate Scenario*: An alternative discontinuation rate of 15% was evaluated.
- *Time Horizon Scenario*: Instead of the lifetime time horizon, an alternative time horizon of 20 years was evaluated.
- *Utility Function Scenario*: Utilities based on the McLeod 2007 equation were evaluated.
- *Equal ASAS20 Response in nr-axSpA:* ADA, ETA and CZP were assumed to have equivalent ASAS20 response (that of the CZP pooled dose estimated from the MTC), but their BASFI and BASDAI inputs remained as the values generated for each in the MTC.

8.3.3 Parameter Uncertainty

There is a degree of uncertainty regarding the inputs of the model. Therefore, all major efficacy and economic inputs in the model were varied in the sensitivity analysis in order to examine how they affected the results of the model. The OSA is described in Section 8.3.4 and the PSA is described in Section 8.3.5. The sensitivity analyses were run on each of the base case scenarios for the AS and nr-axSpA subpopulations to test the robustness of the model.

8.3.4 Approach to One-Way Deterministic Sensitivity Analysis

A series of OSAs were conducted around key model variables to test the impact on the model results comparing CZP to CC. Parameters were varied between a minimum and maximum range that was determined either directly from data or if data were not available to inform this range, then the minimum and maximum values were assumed to be ±25% of the base case value. The types of parameters tested in the OSA included:

- Age, proportion of males to females, weight
- Discount factors for health and cost inputs
- Probability and RR of ASAS20 response for both subpopulations on either CZP or other anti-TNF therapies
- Baseline, annual change, and rebound in BASFI and BASDAI scores for both subpopulations
- Discontinuation
- Mortality
- Utility
- Drug and administration costs

A complete list of parameters and the associated mean, lower bound, and upper bound values with which they were tested are provided in Appendix 11.5.1.4.

Estimates of incremental outcomes (costs, QALYs) and ICERs (cost/QALY) are provided in the OSA. A tornado diagram was created to illustrate the results of the OSA by showing the outcomes when using both the lower and upper bounds of selected input parameters. The difference between these results from the

base case shows the effect of the uncertainty of the parameters. By putting the differences in ascending order, the diagram depicts the variables and changes to which the results are most sensitive.

8.3.5 Approach to Probabilistic Sensitivity Analysis

To account for multivariate and stochastic uncertainty in the model, a PSA was performed. The uncertainty in parameters was characterised using statistical distributions (see Table 8-14) and analysed using 10,000 iterations. The selection of distributions was dependent on the nature of the underlying parameter or how it was estimated. Where parameters were estimated from statistical relationships (eg. parameters for the statistical relationship between utility and BASDAI, BASFI), these were sampled from a multivariate normal distribution generated through Cholesky decomposition to allow for correlation between parameters. For probabilities, the Beta distribution was used. For positively valued parameters such as rates, the chosen distribution was Gamma. RRs assumed a lognormal distribution. The parameters varied in the PSA as well as the distributions they were assigned are presented below in Table 8-14.

Table 8-14: Model parameters varied in PSA

Parameter	Distribution
Probability of ASAS20 response	Beta
Probability of ASAS20 response, RR anti-TNF therapies	Lognormal
Rate of discontinuation due to AEs CZP	Gamma
Rate of discontinuation due to AEs RR anti-TNF therapies	Lognormal
Rate of discontinuation due to LOE CZP	Gamma
Rate of discontinuation due to LOE RR anti-TNF therapies	Lognormal
Baseline BASFI scores	Normal
Baseline BASDAI scores	Normal
Annual BASFI change	Beta
Standardised mortality ratio versus the general population	Gamma
Utility equation coefficient intercept	Multivariate normal
Utility equation coefficient BASDAI	Multivariate normal
Utility equation coefficient BASFI	Multivariate normal

AE: Adverse event; **AS**: Ankylosing spondylitis; **ASAS**: Assessment in SpondyloArthritis international Society (criteria); **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **BASFI**: Bath Ankylosing Spondylitis Functional Index; **CZP**: Certolizumab pegol; **LOE**: Loss of effect; **RR**: Relative risk; **TNF**: Tumour necrosis factor

Based on the PSA, the incremental costs are plotted against incremental gains in terms of QALYs comparing CZP versus CC on the cost-effectiveness plane and anti-TNF therapies versus CC. The cost-effectiveness acceptability curve (CEAC) shows the probability of being cost-effective for each anti-TNF willingness-to-pay value for a QALY.

8.4 Results

8.4.1 Summary of Results

The base case analyses indicated that with the PAS, CZP is cost-effective against CC (primarily NSAIDs) at a willingness-to-pay threshold of £20,000 per QALY, in both the AS (ICER £16,647) and nr-axSpA (ICER £15,615) subpopulations.

The base case analyses also showed that, in the AS subpopulation, CZP with the PAS dominates ADA, GOL, and ETA, being more effective and less costly. Compared to IFX, CZP was cost-effective, being significantly less costly and slightly less effective (difference in cost of £67,184 and QALY difference of 0.589 QALYs over a lifetime).

OSAs in the AS subpopulation showed that ICERs were most sensitive to the probability of achieving an ASAS20 response, discount factors for health outcomes and costs, and CZP drug acquisition cost. At a

willingness-to-pay threshold of £20,000 per QALY, the PSA indicated that CZP had the highest likelihood of being the most cost-effective compared to all alternatives, anti-TNF therapies and CC, in the AS subpopulation (CZP 30.6% followed by ETA 20.8%).

In the nr-axSpA subpopulation, the base case analysis indicated that CZP with the PAS dominates ADA and ETA, being more effective and less costly than both alternatives.

OSAs in the nr-axSpA subpopulation showed that ICERs were most sensitive to the probability of achieving an ASAS20 response, discount factors for health outcomes and costs, and CZP drug acquisition cost. At a willingness-to-pay threshold of £20,000 per QALY, the PSA indicated that CZP had the highest probability of being most cost-effective compared to ADA, ETA and CC at this threshold (CZP 74.2% followed by CC 25.8%).

8.4.2 AS Subpopulation Results

8.4.2.1 AS Subpopulation Base Case

The results of the base case in the AS subpopulation indicate that, over a lifetime time horizon, CZP with the PAS is cost-effective versus CC and other anti-TNF therapies at a willingness-to-pay threshold of £20,000 per QALY.

The analysis shows that treatment with all of the anti-TNF therapies is significantly more effective and more costly than CC and that CZP is similar to other anti-TNF therapies in terms of total costs. Comparing all anti-TNF therapies to CC shows that all treatments have comparable ICERs that fall close to the £20,000 per QALY threshold, except for IFX which has a higher ICER over £40,000 per QALY (Table 8-15).

When compared to anti-TNF therapies, CZP dominates ADA, ETA, and GOL, being more effective and less costly, and is cost effective against IFX, being substantially less costly and slightly less effective (incremental cost of -£67,184 and QALY difference of -0.589 QALYs over a lifetime). IFX is associated with substantially higher drug costs as well as substantially higher administration costs due to its mode of administration.

For disaggregated total lifetime costs by medication acquisition and disease management costs, please refer to Appendix 11.5.2.1.1.

Table 8-15: Base case results for anti-TNF therapies versus CC (AS subpopulation, CZP with the PAS, CZP pooled dosing)

	Total costs, discounted, £	Incremental costs (anti-TNF vs CC), £	Total QALYs, discounted	Incremental QALYs (anti-TNF vs CC)	Incremental ICER (anti-TNF vs CC)
Conventional care	[redacted]	-	[redacted]	-	-
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	**£16,647**
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	**£19,049**
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	**£19,932**
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	**£19,272**
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	**£42,671**

CC: Conventional care; **CZP**: Certolizumab pegol; **ICER**: Incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **TNF**: Tumour necrosis factor

Table 8-16: Base case results for CZP versus other anti-TNF therapies (AS subpopulation, CZP with the PAS, CZP pooled dosing)

	Total costs, discounted, £	Incremental costs (CZP vs anti-TNF), £	Total QALYs, discounted	Incremental QALYs (CZP vs anti-TNF)	Incremental ICER (CZP vs anti-TNF)
Certolizumab pegol	[redacted]	-	[redacted]	-	**-**
Golimumab	[redacted]	[redacted]	[redacted]	[redacted]	**CZP Dominates**

Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	**CZP Dominates**
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	**CZP Dominates**
Infliximab	[redacted]	[redacted]	[redacted]	[redacted]	**£114,097 (IFX vs CZP)***

CZP: Certolizumab pegol; **ICER**: Incremental cost-effectiveness ratio; **IFX**: Infliximab; **QALY**: Quality-adjusted life year; **TNF**: Tumour necrosis factor
* This values represents the ICER for IFX vs CZP (as opposed to CZP vs anti-TNF as for the other comparators) since CZP is less costly and less effective than IFX.

8.4.2.2 Results of the Alternative Scenario Analyses: AS Subpopulation

The results of the alternative sensitivity scenario analyses on the base case of the AS subpopulation indicate that CZP remains cost-effective under all alternative assumptions. The greatest change in the ICER comparing CZP to CC occurred when the efficacy of CC was increased, with a resulting ICER of £21,926. Other scenarios that had relatively large impacts on the ICERs were the alternative discontinuation scenario (in which the cost of CZP decreased greatly, but so too did the associated incremental QALYs) and the alternative utility calculation scenario (in which costs remained the same but QALYs decreased marginally).

A full table of incremental costs, incremental QALYs, and ICERs comparing CZP to CC in all alternative sensitivity scenarios is presented in Appendix 11.5.2.1.2. Probabilistic and one-way sensitivity analyses are also presented for the alternative scenario for AS where the assessment period for response to anti-TNF therapy is 12 weeks (alternative scenario analyses: Appendix 11.5.2.1.5; OSA: Appendix 11.5.2.1.6; PSA: Appendix 11.5.2.1.7).

8.4.2.3 Results of the One-way, Deterministic Sensitivity Analysis: AS Subpopulation

The results of the OSA of the base case in the AS subpopulation indicated that, compared to CC, the incremental costs, incremental QALYs, and ICERs of CZP were most sensitive to the probability of achieving an ASAS20 response at 24 weeks and discount factors for health and cost outcomes. The unit cost of CZP and coefficients of the utility equation (described in Section 8.2.2.3) were also drivers of variation in results. Tornado diagrams presenting the complete results of the OSA in terms of incremental costs, incremental QALYs, and ICERs of CZP compared to CC is given in Appendix 11.5.2.1.3).

8.4.2.4 Results of the Probabilistic Sensitivity Analysis: AS Subpopulation

Results of the PSA of the base case in the AS subpopulation indicate that CZP is similar to ADA, ETA and GOL in terms of incremental costs and QALYs compared to CC; CZP is cost-saving and slightly less effective compared to IFX. Results also show that IFX is generally more costly and marginally more effective than CZP, ADA, ETA and GOL.

As shown in Table 8-17, CZP had a marginally higher probability of being most cost-effective than ADA, ETA, and GOL and a significantly higher probability compared to IFX at thresholds of £20,000 per QALY and £30,000 per QALY.

Graphical presentation of the PSA results and CEACs are given in Appendix 11.5.2.1.4.

Table 8-17: PSA results: Probability of being most cost-effective at different cost-effectiveness thresholds in the base case (AS subpopulation, with the PAS, CZP pooled dosing)

WTP Threshold	Certolizumab pegol	Adalimumab	Etanercept	Golimumab	Infliximab	Conventional Care
£20,000/QALY	30.60%	17.20%	20.80%	15.20%	0.80%	15.40%
£30,000/QALY	36.60%	18.00%	24.60%	18.00%	1.40%	1.40%

QALY: Quality-adjusted life year; **WTP**: Willingness to pay

8.4.3 nr-axSpA Subpopulation Results

8.4.3.1 nr-axSpA Subpopulation Base Case

The base case analysis in the nr-axSpA subpopulation indicated that over a lifetime, CZP with the PAS is more cost-effective than CC at a WTP of £20,000 per QALY. ADA and ETA had ICERs of £30,370 and £50,692 per QALY, respectively, compared to CC.

When compared to ADA and ETA, CZP with the PAS was the dominant therapy, being more effective and less costly (Table 8-18).

For disaggregated total lifetime costs by medication acquisition and disease management costs, please refer to Appendix 11.5.2.2.1.

Table 8-18: Base case results for anti-TNF therapies versus CC (nr-axSpA subpopulation, CZP with the PAS, CZP pooled dosing)

	Total costs, discounted, £	Incremental costs (anti-TNF vs CC), £	Total QALYs, discounted	Incremental QALYs (anti-TNF vs CC)	Incremental ICER (anti-TNF vs CC)
Conventional care	[redacted]	-	[redacted]	-	-
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	**£15,615**
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	**£50,692**
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	**£30,370**

CC: Conventional care; **CZP**: Certolizumab pegol; **ICER**: Incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **TNF**: Tumour necrosis factor

Table 8-19: Base case results for CZP versus ADA and ETA (nr-axSpA subpopulation, CZP with the PAS, CZP pooled dosing)

	Total costs, discounted, £	Incremental costs (CZP vs anti-TNF), £	Total QALYs, discounted	Incremental QALYs (CZP vs anti-TNF)	Incremental ICER (CZP vs anti-TNF)
Certolizumab pegol	[redacted]	-	[redacted]	-	**-**
Etanercept	[redacted]	[redacted]	[redacted]	[redacted]	**CZP Dominates**
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	**CZP Dominates**

CZP: Certolizumab pegol; **ICER**: Incremental cost-effectiveness ratio; **QALY**: Quality-adjusted life year; **TNF**: Tumour necrosis factor

8.4.3.2 Results of the Alternative Scenario Analysis: nr-axSpA Subpopulation

The results of the alternative scenario analyses in the nr-axSpA subpopulation indicated similar trends in ICERs to those observed for the AS subpopulation. CZP remained cost-effective across all scenarios, with the highest ICER (£23,768) vs CC again resulting from the alternative efficacy scenario for CC. A full table of incremental costs, incremental QALYs, and ICERs comparing CZP to CC in all alternative sensitivity scenarios is given in Appendix 11.5.2.2.2.

The detailed results of the alternative scenarios analysis (modified CU analysis), where only ASAS20 was assumed to be the same for ADA, ETA and CZP, and being equal to the MTC estimate for CZP, whilst the changes in BASDAI and BASFI were left unchanged and equal to the estimates from the MTC for each intervention, are presented below in Appendix 11.5.2.2.2 (Table 11-78). They indicate that, over a lifetime time horizon, CZP with the PAS dominates ADA and ETA, being more effective [redacted] and less costly [redacted].

Results of the OSA and PSA of this modified CU analysis are presented in the Appendix 11.5.2.2.3 and 11.5.2.2.4. The OSA shows that incremental costs and the ICER are most influenced by the ASAS20 response of ADA and ETA relative to CZP and the drug acquisition costs of CZP, ADA and ETA and that

incremental QALYs are also influenced by the discount rate for health effects. The PSA showed CZP to be more cost-effective than ADA and ETA at any willingness-to-pay threshold.

8.4.3.3 Results of the One-way, Deterministic Sensitivity Analysis: nr-axSpA Subpopulation

Results of the OSA in the base case in the nr-axSpA subpopulation indicate that, compared to CC, the incremental costs, QALYs, and ICERs of CZP were most sensitive to changes in the probability of ASAS20 response at 12 weeks, CZP unit cost, and discount rates for cost and health outcomes. Discontinuation rate and coefficients of the utility equations were also influential in the OSA. Tornado diagrams presenting the complete results of the OSA in terms of incremental costs, incremental QALYs and ICERs of CZP compared to CC are given in Appendix 11.5.2.2.3.

8.4.3.4 Results of the Probabilistic Sensitivity Analysis: nr-axSpA Subpopulation

Results of the PSA of the base case in the nr-axSpA subpopulation indicated that CZP is more likely to be more cost-effective than ADA, ETA and CC.

Table 8-20 shows that at a willingness-to-pay threshold of £20,000/QALY, CZP has a 74.2% chance of being cost-effective whilst ADA and ETA both have a 0.0% chance, and CC has a 25.8% chance. At a willingness-to-pay threshold of £30,000/QALY, CZP has almost a 100% chance of being cost-effective. Graphical presentation of the PSA results and CEACs are given in Appendix 11.5.2.2.4.

Table 8-20: PSA results: Probability of being most cost-effective at different cost-effectiveness thresholds in the base case (nr-axSpA subpopulation, with the PAS, CZP pooled dosing)

WTP Threshold	Certolizumab pegol	Adalimumab	Etanercept	Conventional care
£20,000/QALY	74.2%	0.0%	0.0%	25.8%
£30,000/QALY	99.9%	0.0%	0.0%	0.1%

QALY: Quality-adjusted life year; **WTP**: Willingness to pay

9 Budget Impact

- The base case analysis indicated that the introduction of CZP with the PAS as an alternative treatment for axSpA would lead to an estimated net budgetary saving for the NHS in England and Wales of £9,251,887 over a 5-year time horizon. Of this amount, £5,566,617 savings would arise in the treatment of patients with AS and £3,685,270 in the treatment of patients with nr-axSpA. [redacted]
- Scenario sensitivity analyses tested assumptions about the prevalence of axSpA in England and Wales, the percentage of market share of CZP that is taken from CC for the nr-axSpA subpopulation, discontinuation rates of anti-TNF therapy, and the potential introduction of IFX and ETA alongside CZP in the AS and nr-axSpA subpopulations respectively. In these sensitivity analyses, the 5 year budget impact in the axSpA population (AS and nr-axSpA combined) ranged between savings of £36,035,518 (assuming higher disease prevalence) and expense of £4,205,185 (assuming greater displacement of patients from CC).

9.1 Background

A budget impact model (BIM) was developed to estimate the net total budget impact over 5 years of adding CZP to the NHS England and Wales formulary. As the displaced medicines, market share and uptake of CZP is likely to be different for the two subpopulations, independent BIMs were created. The approved PAS, as described in Section 1, was applied to CZP in England and Wales.

Different sensitivity analyses were conducted to address uncertainty in market share displacement assumptions, prevalence and treatment discontinuation in the AS and nr-axSpA subpopulations.

Displaced medicines included in the BIMs reflect the treatment options currently available in England and Wales for the AS and nr-axSpA subpopulations. For the AS subpopulation, the displaced medicines included in the analysis are ADA, ETA, and GOL in the base-case. For the nr-axSpA subpopulation, ADA and CC are the displaced medicines in the base-case. Sensitivity analyses considered inclusion of IFX and ETA alongside CZP for the AS and nr-axSpA subpopulations. The models take as inputs the total cost of medications, which is comprised of medication acquisition and administration costs for CZP and displaced medicines. Cost savings that arise from reduced disease management costs associated with reduced severity of axSpA are appropriate to include when patients previously on CC transition to anti-TNF therapies; these were included in the models for the nr-axSpA subpopulation but not for the AS subpopulation as the model assumes no displacement of CC in the AS subpopulation. The model assumes under the base-case that 7% of patients will discontinue from anti-TNF therapies annually.

9.2 Epidemiology and Patient Numbers

9.2.1 Population

Data from England and other countries were used to estimate the prevalence of AS and nr-axSpA. Using the NICE population benchmark,[120] epidemiological data for patients with AS in England and data from the Office for National Statistics, the prevalence of AS was quantified at 0.13% (refer to Appendix 11.6.1.1 for calculation details). This value lies within a wide range of independent estimates of AS prevalence (0.08%-0.86%; Table 9-1) provided by the NICE HTA and Saraux et al.[28, 99, 121] Furthermore, this estimate is comparable to an estimate drawn from a Finnish study[122] (0.15%) published in 1997, which was deemed the best available value by the British Society for Rheumatology based on the study timeframe, location (Europe) and standard error.

Table 9-1: Prevalence and incidence estimates of AS

Estimate	Study Location	Reference
Panel A: Prevalence		
0.08% (0.03%-0.15%)	France	121
0.129%	US-based study in Rochester, Minnesota from 1935-1973	123
0.15% (0.08%-0.27%)	Finnish study, population age ≥30	122
0.23%	Study conducted in Hungary, age ≥15	124

0.53% (0.16%-0.90%)	Study in Brittany, France	[125]
0.86%	Berlin population	[126]
0.13%	71,000 patients with AS in England	[100]
0.52–0.55%	United-States using NHANES data; prevalence of AxSpA estimate 1.0-1.4% and AS 0.52-0.55%.	[28]
Panel B: Incidence		
6.6 per 100,000	Study from Rochester, Minnesota, USA	[127]
6.9 per 100,000 (6.0-7.8)	Finnish study in diagnosed patients with AS age ≥16	[122]
7 per 100,000	Hospital-based study from Northern, Norway	[128]
7.3 per 100,000 (6.1-8.4)	USA	[129]

AS: Ankylosing spondylitis; **USA**: United States of America

In the nr-axSpA subpopulation, a prevalence of 0.126% was derived from the French HTA advice for ADA (calculation details are provided in Appendix 11.6.1.1).[130]

Due to the lack of data specific to nr-axSpA, the incidence of nr-axSpA is assumed to be the same as in the AS subpopulation (0.0069%).[122]

A mortality rate was estimated for the AS and nr-axSpA subpopulations weighted by gender and age using the following information drawn from multiple sources:

- SMR of 1.5 for patients with AS extracted from the literature[24, 114, 115, 131, 132]
- Rate of death per annum for the general population stratified by age and gender from the UK Life Table[116]
- Proportion of male AS / nr-axSpA patients (72.5% / 48.3%, respectively) as noted in RAPID-axSpA[18]
- Age distribution for the AS and nr-axSpA subpopulations from RAPID-axSpA[18]

[redacted]

Applying the prevalence (0.13% for AS and nr-axSpA), incidence (0.0069% for AS and nr-axSpA) and mortality rates to the population size of England and Wales, separately for the AS and nr-axSpA subpopulations, gives the net number of patients with the condition in each year of the initial five years following introduction of CZP as shown in Table 9-2. Appendix 11.6.1 provides further information on the calculation of the net number of patients. The population size of England and Wales in 2014 was obtained from the Office of National Statistics (assumed to be the same as the 2013 mid-year population estimates. The 2012-based national population projections were used as a proxy to estimate the change in the population size from 2014 through 2018. The change in the UK (England and Wales) population is assumed to increase linearly from 56,948,200 in 2014 to 58,956,023 by 2018. Another key assumption made on the epidemiological inputs for the analysis was that prevalence and incidence of AS and nr-axSpA both remain constant over the 5-year time horizon of the BIMs.

Table 9-2: Estimation of the net number of patients with AS and nr-axSpA

Parameter	2014	2015	2016	2017	2018
Population size	56,948,200	57,450,156	57,952,112	58,454,067	58,956,023
Net number of patients					
AS	77,627	78,311	78,995	79,680	80,364
nr-axSpA	75,439	76,104	76,769	77,433	78,098

AS: Ankylosing spondylitis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

9.2.2 Eligibility

An estimate of the number of people in England and Wales with axSpA currently receiving treatment with biologics was made using the net number of patients with axSpA and the percentage of patients who are treatment eligible *and* receiving treatment with biologics.

Treatment eligibility for the AS subpopulation was taken from the NICE population benchmark for AS where an estimated 9.7% of patients with AS were eligible for treatment and receiving treatment with an anti-TNF therapy.[120] The NICE population benchmark assumed that 20,000 patients out of 70,000 patients would be eligible for treatment (28.6%), and that 6,800 patients who were eligible would use biologic treatment (9.7%). A key assumption that has been made by using this figure is that it represents a cross-sectional proportion of patients who remain on anti-TNF therapy, and includes a mix of patients who initiate anti-TNF therapy in the current year and in previous years.

The same NICE benchmark figure and assumptions were applied to the BIM for nr-axSpA (ie. 9.7% of patients with nr-axSpA were assumed to be eligible for treatment and receiving treatment with anti-TNF therapy) in year 1. Inputs in years 2-5 assumed that the uptake of biologic treatment would increase linearly over time (2% across the 5 years) given that nr-axSpA is a fairly new condition with new treatment options on the market.

Estimation of the number of patients with AS and nr-axSpA who are treatment eligible and receiving treatment with biologics from year 1-5 is summarised in Table 9-3.

Table 9-3: Estimated number of eligible treated patients with AS and nr-axSpA

	2014	2015	2016	2017	2018
AS subpopulation					
Net number of patients with AS	77,627	78,311	78,995	79,680	80,364
Percent of cohort with AS who are treatment eligible *and* receiving treatment with biologics[120]	9.7%	9.7%	9.7%	9.7%	9.7%
Potential number of eligible patients treated each year	7,530	7,596	7,663	7,729	7,795
nr-axSpA subpopulation					
Net number of patients with nr-axSpA	75,439	76,104	76,769	77,433	78,098
Percent of cohort with nr-axSpA who are treatment eligible *and* receiving treatment with biologics	9.7%	10.2%	10.7%	11.2%	11.7%
Potential number of eligible patients treated each year	7,318	7,763	8,214	8,673	9,138
Total axSpA population					
Potential number of eligible patients treated each year	14,847	15,359	15,877	16,401	16,933

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: non-radiographic axial spondyloarthritis

9.2.3 Treatment Discontinuation and First Year Costs

As noted in Section 9.2.2, the net number of patients with axSpA currently being treated with anti-TNFs is a mix of patients initiating therapy in the current and previous years. However, first year and subsequent year consumption of anti-TNF therapy with CZP differ since three additional vials are used in the first year, therefore incurring additional first year costs (in absence of PAS). In order to determine the number of patients initiating therapy with CZP in the current year, the annual absolute increase in patient numbers were assumed to initiate CZP (eg. 1,164 nr-axSpA patients in year 2015 and 732 in 2014 = 433 new patients in 2015). In addition, 1.75% of prevalent patients are assumed to discontinue quarterly (corresponding to approximately 7% annually) whilst an equal number initiate treatment in each quarter (eg. 1.75% of 732 = 13 patients each quarter or 50 patients annually discontinue in 2014, so 50 plus 433 patients will have first year costs in 2015), in order to apply additional first year costs (in absence of PAS) for those patients initiating CZP each year. This is described under medication acquisition costs (Section 9.5.2). A sensitivity analysis was performed to consider 15% annual discontinuation.

9.3 Displaced Medicines

Displaced medicines in the BIM versions reflect treatment options currently available in England and Wales and with positive NICE guidance for the AS and nr-axSpA subpopulations. Therapies for AS per NICE guidance include ADA, ETA and GOL.[24, 25] IFX was not included in the base case since it is currently not

available for treatment in patients with AS.[24] For patients with nr-axSpA, CZP was compared to ADA, the only biologic agent with marketing authorisation for the treatment of these patients, and CC, defined by the following mix of NSAIDs: etoricoxib 90 mg daily, naproxen 500–1,000 mg daily (assumed 500 mg) and diclofenac 75–150 mg daily (assumed 75 mg). In a sensitivity analysis, ETA was considered for patients with nr-axSpA, whilst IFX was considered for patients with AS.

9.4 Market Share

Market share forecasts for CZP and displaced medicines (refer to Section 1c) in patients with AS (ADA, ETA, GOL) and nr-axSpA (ADA, CC) were based on manufacturer's projections. Table 9-4 shows the anticipated market share of CZP over 5 years by axSpA subpopulation (AS, nr-axSpA) in the base case. The market share of CZP is assumed to increase over time, taking market share from the displaced medicines for AS and nr-axSpA (Table 9-4). [redacted]

Table 9-4: Market share of certolizumab pegol and displaced medicines in the AS and nr-axSpA subpopulations

	Current market share without Certolizumab pegol (%)					New market share with Certolizumab pegol (%)				
	2014	2015	2016	2017	2018	2014	2015	2016	2017	2018
AS subpopulation										
Certolizumab pegol	[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]
nr-axSpA subpopulation										
Certolizumab pegol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conventional Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AS: Ankylosing spondylitis; **nr-axSpA**: non-radiographic axial spondyloarthritis
Source: UCB market share projections

9.5 Cost Estimates

9.5.1 Patient Access Scheme

A PAS is in operation for CZP in England and Wales (see Section 1), which was accounted for in the BIMs for CZP.

9.5.2 Medication Acquisition and Administration Costs

The following information about each treatment was employed to calculate the total annual drug acquisition cost per patient: unit costs, loading and maintenance dosage for CZP, and dosing frequency (during loading and maintenance). Unit costs for the anti-TNF therapies and CC are given in Table 9-5 along with the unit definition, unit strength, administration route and dosing regimens obtained from the British National Formulary,[2] PSSRU (2012),[118] NHS tariffs and hospital trusts.[133] The number of units (vials) consumed per patient in first and subsequent years of treatment is given in Table 9-6.

The medication acquisition cost of CC for the nr-axSpA subpopulation was calculated from a mix of individual NSAIDs (etoricoxib, naproxen and diclofenac) and DMARDs (sulfasalazine) used under CC in England, Wales and Scotland (based on KOL opinion).[61, 95, 96] The price and dosing regimen[2] along with the distribution of the NSAID mix are summarised in Table 9-7.

The weighted average medication acquisition unit cost of CC used in the model was £0.395 per day.

Using the dosing regimen for biologic therapies and CC, the annual number of units utilised per patient per annum was calculated as follows: CZP: 29 in year 1 of treatment and 26 in subsequent years; ETA: 104; ADA: 26; GOL: 12; CC: 365).

Table 9-5: Medication acquisition unit cost and dosing regimens of biologics

Treatment	Acquisition Cost per Unit	Unit Strength	Loading Dosing	Maintenance Dosing
Certolizumab pegol	£357.50	200 mg	400 mg at 0, 2 and 4 weeks	200 mg Q2W or 400 mg Q4W
Displaced or New Medicines				
Etanercept[a]	£89.38	25 mg	NA	50 mg weekly
Adalimumab[b]	£352.14	40 mg	NA	40 mg Q2W
Golimumab[a]	£762.97	50 mg	NA	50 mg monthly on the same day each month
Infliximab[c]	£419.62	100 mg	5 mg/kg infusion at 0, 2 and 6 weeks	5 mg/kg infusion every 6–8 weeks (model assumes 7 weeks)

NA: Not applicable; **Q2W**: Every 2 weeks; **Q4W**: Every 4 weeks
*Computed as the weighted average cost of the individual NSAIDs under CC
[a] Displaced medicine for the AS subpopulation only; new medicine in sensitivity analysis in nr-axSpA subpopulation [b] Displaced medicine for both the AS and nr-axSpA subpopulations, [c] New medicine in sensitivity analysis only for AS subpopulation
References: British National Formulary,[2]

Table 9-6: Annual medication units (vials) of anti-TNF therapies consumed per patient

Treatment	Number of Units	
	First Year of Treatment	Subsequent Years
Certolizumab pegol (units given)	29	26
Certolizumab pegol (units costed with PAS)	19	26
Displaced or New Medicines		
Etanercept	104	104
Adalimumab	26	26
Golimumab	12	12
Infliximab[a]	36[b]	27[b]

PAS: Patient access scheme
[a] Sensitivity analysis only
[b] Number of IFX units assume no wastage and is calculated based on an average patient weight of 81.7kg

Table 9-7: Dosing regimen, pricing and distribution of NSAIDs under CC

NSAID	Unit Strength	Package Size	Package Price (£)	Dosing Regimen	Estimated Price/Day (£)	Treatment Distribution
Etoricoxib	90 mg	28-tab pack	22.96	90 mg/day	0.82	40%
Naproxen	500 mg	28-tab pack	1.82	500 mg/day	0.065	50%
Diclofenac	25 mg	28-tab pack	3.23	75 mg/day	0.346	10%

NSAID: Non-steroidal anti-inflammatory drug

The mode of administration, which determines how often an administration cost is applied, is a typical component of direct costs. All treatments in the base case analysis, except CC, are administered sc, which is associated with a nurse visit in the rheumatology specialty at treatment initiation for a specialist nurse to train the patient to self-administer (associated with a one-time cost of £48 [national estimate]).[134] It is assumed that after the first nurse visit, patients will self-inject at home which has no additional cost. For patients

receiving IFX, cost is incurred at every IV administration. Cost of the IV administration was based on a half-day hospital in-patient visit of £309.20.[118]

For CZP, a loading dose of 400 mg is given during the first 4 weeks at treatment initiation (at Weeks 0, 2, and 4) and then a maintenance dose of 200 mg Q2W or 400 mg Q4W thereafter. The re-administration interval does not affect the cost calculations as an equal number of units per year is used under either schedule. To account for the loading dose of CZP (ie. additional medication units received in the first year of treatment) for new patients starting treatment each year over the time horizon, a correction is applied to account for additional first year treatment costs.

To estimate drug costs for CZP or other anti-TNFs, the total units (vials) required in first and subsequent years of therapy is applied to the number of patients in each year of treatment. As noted in section 9.2.3, the cost calculation accounts for the number of patients newly initiating treatment in their first year versus subsequent year in each of the five years of the analysis. Patients initiating treatment with CZP will incur the cost of 29 vials per year (19 vials in the case of the PAS), whilst patients in subsequent years incur the cost of 26 vials per year.

9.5.3 Disease Management Costs

Savings may be expected associated with disease management resulting from reduced use of healthcare resources by patients who respond to anti-TNF therapy compared to patients on CC cost whose disease severity progressively worsens. An example is reduced use of physiotherapy. For the budget impact analysis, this savings applies to patients with nr-axSpA only.

For patients with AS, disease management costs are expected to be the same across all anti-TNF therapies, assuming that treatment with one anti-TNF would not result in greater or lesser disease management cost than if a different anti-TNF were being given. Conversely, in the nr-axSpA subpopulation additional cost savings may be expected for CZP compared to CC.

The disease management costs were estimated using the pharmaco-economic model (described in Section 8) that employs an exponential cost model (see below) constructed by NICE with BASFI as the key predictor of cost to capture long-term disease progression (NICE).[99] Details on the equation and assumptions are provided in Section 8.2.3.1.

Disease management cost by BASFI = £1,585.30 x exp(0.1832 x BASFI)

The costs included in the equation represent drug costs (excluding anti-TNF therapies), monitoring, hospitalisation, healthcare visits, aids and appliances, and AEs. The pharmaco-economic model was run for a 5-year time horizon and the difference in the total disease management costs between CZP and CC was computed and divided by the time horizon (5 years). This yields an average annual estimate of savings of £1,254.70 per patient switching from CC to anti-TNF therapy. This saving was applied to the number of patients displaced from CC to CZP of each year to estimate the additional annual savings of introducing CZP in the nr-axSpA subpopulation.

9.6 Sensitivity Analysis

Sensitivity analysis model versions were developed to test assumptions about the prevalence of axSpA in England and Wales, the percentage of market share of CZP that is taken from CC for the nr-axSpA subpopulation, discontinuation rates of anti-TNF therapy, and the potential introduction of IFX and ETA alongside CZP in the AS and nr-axSpA subpopulations respectively. Definitions of five sensitivity scenarios are as follows:

- Prevalence of 0.52% for both AS and nr-axSpA, as per the recent study by Reveille and Weisman 2013[28]
- Comparator IFX is introduced alongside CZP in the AS subpopulation
- Comparator ETA is introduced alongside CZP in the nr-axSpA subpopulation
- Annual discontinuation is 15% for both AS and nr-axSpA
- A greater pool of patients on CC (up to 10% by year 5) start treatment with CZP in the nr-axSpA subpopulation

9.7 Budget Impact Results

9.7.1 Base Case Analysis

The budget impact results for the base case model by subpopulation (AS, nr-axSpA) and overall axSpA are presented in this section. Overall, a total of 1,334 patients with axSpA are expected to be treated with CZP in 2014 increasing to 4,768 in 2018 (Table 9-8). For the AS subpopulation, 602 patients are expected to be treated with CZP in 2014, rising to 2,027 patients in 2018. For the nr-axSpA subpopulation 732 patients are expected to be treated with CZP in 2014, rising to 2,741 in 2018.

The net total budget impact for the overall axSpA population (combining patients with AS and nr-axSpA) is given in Table 9-9. The net total budget impacts for the AS and nr-axSpA subpopulations are presented in Table 9-10 and Table 9-11, respectively. Tables include the yearly budget impact for medication acquisition, disaggregated for patients on CZP, other biologic therapies and CC; administration costs; and disease management cost for the nr-axSpA subpopulation.

The introduction of CZP as an alternative treatment for axSpA is projected to have an overall total budgetary impact (Table 9-9) of -£9,251,887 over the 5-year time horizon (AS subpopulation -£5,566,617; nr-axSpA subpopulation: is -£3,685,270).

For the AS subpopulation, the net total budget impact of including CZP is -£1,534,259 (ie. savings) in the first year and -£222,928 in 2018. For the nr-axSpA subpopulation, the net total budget impact of including CZP is -£1,825,378 (savings) in the first year rising to £975,023 (expense) in 2018. The net budget impact is larger for nr-axSpA since it was projected that some new patients from 2015–2018 would otherwise have received only CC, which is considerably less expensive than ADA and CZP.

Table 9-8: Epidemiological summary

	2014	2015	2016	2017	2018
AS subpopulation					
Number of patients eligible for biologic therapies	7,530	7,596	7,663	7,729	7,795
Uptake of certolizumab pegol	8.0%	15.0%	20.0%	26.0%	26.0%
Number of patients on certolizumab pegol	**602**	**1,139**	**1,533**	**2,010**	**2,027**
nr-axSpA subpopulation					
Number of patients eligible for biologic therapies	7,318	7,763	8,214	8,673	9,138
Uptake of certolizumab pegol	10.0%	15.0%	22.0%	30.0%	30.0%
Number of patients on certolizumab pegol	**732**	**1,164**	**1,807**	**2,602**	**2,741**
Total axSpA population					
Number of patients eligible for biologic therapies	14,847	15,359	15,877	16,401	16,933
Number of patients on certolizumab pegol	**1,334**	**2,304**	**3,340**	**4,611**	**4,768**

AS: Ankylosing spondylitis; **axSpA**: axial spondyloarthritis; **nr-axSpA**: non-radiographic axial spondyloarthritis

Table 9-9: Budget Impact: Overall axSpA

	2014	2015	2016	2017	2018	Total
Medication acquisition cost	**-£3,359,636**	**-£2,170,968**	**-£2,003,229**	**-£2,219,954**	**£977,165**	**-£8,776,622**
Biologic therapies	-£3,359,636	-£2,164,420	-£1,989,371	-£2,198,007	£1,007,997	-£8,703,437
Certolizumab pegol	£8,886,859	£18,626,213	£27,910,128	£38,927,483	£43,098,177	£137,448,860
Other biologic therapies*	-£12,246,496	-£20,790,633	-£29,899,499	-£41,125,490	-£42,090,180	-£146,152,298
Conventional care (NSAIDs)	£0	-£6,548	-£13,858	-£21,947	-£30,831	-£73,185
Medication administration cost	**£0**	**£19,748**	**£16,207**	**£28,834**	**£4,226**	**£69,015**
Biologic therapies	£0	£19,748	£16,207	£28,834	£4,226	£69,015
Certolizumab pegol	£67,401	£53,471	£60,071	£75,465	£23,413	£279,819
Other biologic therapies*	-£67,401	-£33,722	-£43,864	-£46,631	-£19,186	-£210,804
Conventional care (NSAIDs)	£0	£0	£0	£0	£0	£0
Disease management cost	**£0**	**-£48,698**	**-£103,064**	**-£163,222**	**-£229,297**	**-£544,281**
Total Cost	**-£3,359,636**	**-£2,199,918**	**-£2,090,085**	**-£2,354,342**	**£752,095**	**-£9,251,887**

NSAID: Non-steroidal anti-inflammatory drug
* Adalimumab, etanercept, golimumab

Table 9-10: Budget Impact: AS subpopulation

	2014	2015	2016	2017	2018	Total
Medication acquisition cost	**-£1,534,259**	**-£1,414,364**	**-£1,096,390**	**-£1,342,096**	**-£224,057**	**-£5,611,166**
Biologic therapies	-£1,534,259	-£1,414,364	-£1,096,390	-£1,342,096	-£224,057	-£5,611,166
Certolizumab pegol	£4,012,554	£9,070,939	£13,009,736	£17,153,623	£18,441,392	£61,688,244
Other biologic therapies*	-£5,546,812	-£10,485,303	-£14,106,127	-£18,495,719	-£18,665,449	-£67,299,409
Conventional care (NSAIDs)	£0	£0	£0	£0	£0	£0
Medication administration cost	**£0**	**£17,787**	**£10,259**	**£15,374**	**£1,129**	**£44,549**
Biologic therapies	£0	£17,787	£10,259	£15,374	£1,129	£44,549
Certolizumab pegol	£30,432	£29,155	£23,687	£29,248	£7,624	£120,146
Other biologic therapies*	-£30,432	-£11,368	-£13,428	-£13,874	-£6,495	-£75,598
Conventional care (NSAIDs)	£0	£0	£0	£0	£0	£0
Total Cost	**-£1,534,259**	**-£1,396,577**	**-£1,086,131**	**-£1,326,722**	**-£222,928**	**-£5,566,617**

NSAID: Non-steroidal anti-inflammatory drug
* Adalimumab, etanercept, golimumab

Table 9-11: Budget Impact: nr-axSpA subpopulation

	2014	2015	2016	2017	2018	Total
Medication acquisition cost	**-£1,825,378**	**-£754,653**	**-£906,839**	**-£877,858**	**£1,201,222**	**-£3,165,456**
Biologic therapies	-£1,825,378	-£750,056	-£892,981	-£855,911	£1,232,054	-£3,092,272
Certolizumab pegol	£4,874,305	£9,555,275	£14,900,392	£21,773,860	£24,656,785	£75,760,617
Other biologic therapies*	-£6,699,683	-£10,305,331	-£15,793,372	-£22,629,771	-£23,424,731	-£78,852,888
Conventional care (NSAIDs)	£0	-£6,548	-£13,858	-£21,947	-£30,831	-£73,185
Medication administration cost	**£0**	**£1,961**	**£5,949**	**£13,460**	**£3,098**	**£24,467**
Biologic therapies	£0	£1,961	£5,949	£13,460	£3,098	£24,467
Certolizumab pegol	£36,968	£24,315	£36,384	£46,217	£15,789	£159,673
Other biologic therapies*	-£36,968	-£22,354	-£30,435	-£32,757	-£12,691	-£135,206
Conventional care (NSAIDs)	£0	£0	£0	£0	£0	£0
Disease management cost	**£0**	**-£48,698**	**-£103,064**	**-£163,222**	**-£229,297**	**-£544,281**
Total Cost	**-£1,825,378**	**-£803,342**	**-£1,003,954**	**-£1,027,620**	**£975,023**	**-£3,685,270**

NSAID: Non-steroidal anti-inflammatory drug
* Adalimumab

9.7.2 Sensitivity Analyses

9.7.2.1 Sensitivity analysis on prevalence

In the sensitivity scenario where a greater prevalence of axSpA patients was assumed, a much greater budgetary savings resulted. Table 9-12 presents the number of AS and nr-axSpA patients eligible for biologic therapies; number treated with CZP; and budget impact associated with medication acquisition, administration, disease management, and total by subpopulation. The table also provides the total budget impact by year for overall axSpA population. Under the higher prevalence assumption, the estimated 5 year total budget savings due to the introduction of CZP as an alternative treatment for axSpA is -£36,035,518 (savings of £21,424,767 in the AS subpopulation and of £14,610,751 in nr-axSpA).

Table 9-12: Budget impact summary for overall axSpA and AS and nr-axSpA populations sensitivity analysis where prevalence is 0.52%

	2014	2015	2016	2017	2018	Total
AS Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	28,981	29,236	29,492	29,747	30,002	147,458
Uptake of certolizumab pegol	8.0%	15.0%	20.0%	26.0%	26.0%	-
Number of patients on certolizumab pegol	**2,318**	**4,385**	**5,898**	**7,734**	**7,801**	**28,137**
Budget impact						
Medication acquisition cost	-£5,905,047	-£5,443,597	-£4,219,780	-£5,165,452	-£862,349	-£21,596,225
Medication administration cost	£0	£68,460	£39,483	£59,172	£4,344	£171,458
Total Cost	**-£5,905,047**	**-£5,375,137**	**-£4,180,297**	**-£5,106,280**	**-£858,005**	**-£21,424,767**
nr-axSpA Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	29,011	30,776	32,566	34,383	36,227	162,964
Uptake of certolizumab pegol	10.0%	15.0%	22.0%	30.0%	30.0%	-
Number of patients on certolizumab pegol	**2,901**	**4,616**	**7,165**	**10,315**	**10,868**	**35,865**
Budget impact						
Medication acquisition cost	-£7,236,957	-£2,999,659	-£3,595,285	-£3,480,385	£4,762,408	-£12,549,878
Medication administration cost	£0	£7,774	£23,585	£53,362	£12,281	£97,002
Disease management cost	£0	-£193,072	-£408,611	-£647,114	-£909,078	-£2,157,874
Total Cost	**-£7,236,957**	**-£3,184,957**	**-£3,980,311**	**-£4,074,138**	**£3,865,611**	**-£14,610,751**
Overall axSpA Population						
Budget impact						
Total Cost	**-£13,142,004**	**-£8,560,094**	**-£8,160,608**	**-£9,180,418**	**£3,007,606**	**-£36,035,518**

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

9.7.2.2 Sensitivity analysis on comparators – Inclusion of IFX in AS subpopulation

A sensitivity scenario analysis was conducted assuming IFX and CZP were both newly available to patients with AS. The scenario assumed that the new market share of CZP from the base-case would now be shared by both IFX and CZP such that IFX assumes 1%, 2%, 3%, 4% and 4% market share from years 1 to 5 respectively, whilst CZP assumes 7%, 13%, 17%, 22%, 22% respectively. In this way, IFX assumes part of the market share of CZP whilst ETA, ADA and GOL are unchanged relative to the base-case.

Table 9-13 presents the number of AS patients eligible for biologic therapies; number treated with CZP; and budget impact associated with medication acquisition, administration, disease management, and total by AS and nr-axSpA. Results specific to the nr-axSpA subpopulation are unchanged from the base case. The total 5 year budget savings in the axSpA population is reduced to -£2,418,627 compared to -£9,251,887 in the base-case, due to the higher drug acquisition and administration costs associated with IFX.

Table 9-13: Budget impact summary for AS and nr-axSpA subpopulations and total net budget impact for axSpA for sensitivity analysis where IFX is included as a comparator in AS

	2014	2015	2016	2017	2018	Total
AS Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	7,530	7,596	7,663	7,729	7,795	38,313
Uptake of certolizumab pegol	7.0%	13.0%	17.0%	22.0%	22.0%	–
Number of patients on certolizumab pegol	**527**	**988**	**1,303**	**1,700**	**1,715**	**6,233**
Budget impact						
Medication acquisition cost	-£891,201	-£587,379	-£82,435	-£138,128	£507,237	-£1,191,906
Medication administration cost	£202,665	£378,773	£532,293	£701,185	£643,634	£2,458,549
Total Cost	**-£688,536**	**-£208,606**	**£449,858**	**£563,057**	**£1,150,871**	**£1,266,643**
nr-axSpA Subpopulation						
Total Cost (base case)	**-£1,825,378**	**-£803,342**	**-£1,003,954**	**-£1,027,620**	**£975,023**	**-£3,685,270**
Overall axSpA Population						
Budget impact						
Total Cost	**-£2,513,914**	**-£1,011,948**	**-£554,096**	**-£464,563**	**£2,125,894**	**-£2,418,627**

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

9.7.2.3 Sensitivity analysis on comparators – Inclusion of ETA in nr-axSpA subpopulation

A sensitivity scenario analysis was conducted assuming ETA and CZP were both newly available to patients with nr-axSpA. The scenario assumed that both ETA and CZP would share the new market share of CZP from the base-case equally, such that ETA and CZP each assumes 5%, 7.5%, 11%, 15% and 15% market share from years 1 to 5 respectively. Thus, ETA assumes half of the market share of CZP whilst displacement of ETA, ADA and GOL are unchanged relative to the base-case.

Table 9-14 presents the results specific to this scenario. Results for the AS subpopulation are unchanged from the base case. The total 5 year budget savings in the axSpA population is reduced to -£5,101,272 compared to -£9,251,887 in the base case, due primarily to the reduced number of CZP patients who benefit from the PAS.

Table 9-14: Budget impact summary for AS and nr-axSpA subpopulations and total net budget impact for axSpA for sensitivity analysis where ETA is included as a comparator in nr-axSpA

	2014	2015	2016	2017	2018	Total
AS Subpopulation						
Total Cost (base case)	**-£1,534,259**	**-£1,396,577**	**-£1,086,131**	**-£1,326,722**	**-£222,928**	**-£5,566,617**
nr-axSpA Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	7,318	7,763	8,214	8,673	9,138	41,104
Uptake of certolizumab pegol	5.0%	7.5%	11.0%	15.0%	15.0%	-
Number of patients on certolizumab pegol	**366**	**582**	**904**	**1,301**	**1,371**	4,523
Budget impact						
Medication acquisition cost	-£861,510	-£123,179	£40,553	£325,174	£1,610,128	£991,165
Medication administration cost	-£922	£186	£3,183	£9,422	-£1,449	£10,420
Disease management cost	£0	-£48,698	-£103,064	-£163,222	-£229,297	-£544,281
Total Cost	**-£862,432**	**-£171,691**	**-£59,328**	**£171,375**	**£1,379,382**	**£457,305**
Overall axSpA Population						
Budget impact						
Total Cost	**-£2,396,691**	**-£1,568,268**	**-£1,145,460**	**-£1,155,347**	**£1,156,454**	**-£5,109,312**

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

9.7.2.4 Sensitivity analysis on treatment discontinuation

A sensitivity scenario analysis was conducted assuming 15% annual discontinuation of treatment applied to all TNFs and to both patients with AS and nr-axSpA. Table 9-15 presents the results specific to this scenario. The total 5 year budget savings in the axSpA population is increased to -£12,311,623 compared to -£9,251,887 in the base case analysis.

Table 9-15: Budget impact summary for AS and nr-axSpA subpopulations and total net budget impact for axSpA for sensitivity analysis with treatment discontinuation of 15%

	2014	2015	2016	2017	2018	Total
AS Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	7,530	7,596	7,663	7,729	7,795	38,313
Uptake of certolizumab pegol	8.0%	15.0%	20.0%	26.0%	26.0%	-
Number of patients on certolizumab pegol	602	1,139	1,533	2,010	2,027	7,311
Budget impact						
Medication acquisition cost	-£1,624,707	-£1,615,598	-£1,383,524	-£1,720,527	-£628,953	-£6,973,310
Medication administration cost	£0	£14,679	£4,060	£10,374	£0	£29,114
Total Cost	**-£1,624,707**	**-£1,600,919**	**-£1,379,464**	**-£1,710,153**	**-£628,953**	**-£6,944,196**
nr-axSpA Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	7,318	7,763	8,214	8,673	9,138	41,104
Uptake of certolizumab pegol	10.0%	15.0%	22.0%	30.0%	30.0%	-
Number of patients on certolizumab pegol	**732**	**1,164**	**1,807**	**2,602**	**2,741**	**9,046**
Budget impact						
Medication acquisition cost	-£1,935,251	-£968,061	-£1,236,457	-£1,358,959	£659,405	-£4,839,323
Medication administration cost	£0	£2,073	£2,593	£7,762	£3,749	£16,177
Disease management cost	£0	-£48,698	-£103,064	-£163,222	-£229,297	-£544,281
Total Cost	**-£1,935,251**	**-£1,014,687**	**-£1,336,928**	**-£1,514,419**	**£433,857**	**-£5,367,427**
Overall axSpA Population						
Budget impact						
Total Cost	**-£3,559,957**	**-£2,615,606**	**-£2,716,392**	**-£3,224,571**	**-£195,096**	**-£12,311,623**

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

9.7.2.5 Sensitivity analysis on market share of CC

A sensitivity scenario analysis was conducted that assumes a greater proportion of patients with nr-axSpA who initiate treatment with CZP were displaced from CC. The scenario assumes that up to 10% of patients eligible for treatment with anti-TNF were receiving CC (0%, 2.5%, 5%, 7.5%, 10% in years 1 to 5 respectively), all of whom receive CZP under the new market share assumption. Table 9-16 presents the results specific to this scenario. The total 5-year budget impact in the axSpA population is £4,205,185 compared to savings of £9,251,887 in the base case analysis, due to the greater number of patients who were receiving CC whose drug acquisition price by comparison with anti-TNFs is considerably less costly.

Table 9-16: Budget impact summary for AS and nr-axSpA subpopulations and total net budget impact for axSpA for sensitivity analysis with greater CZP market share drawn from CC

	2014	2015	2016	2017	2018	Total
AS Subpopulation						
Total Cost (base case)	**-£1,534,259**	**-£1,396,577**	**-£1,086,131**	**-£1,326,722**	**-£222,928**	**-£5,566,617**
nr-axSpA Subpopulation						
Epidemiological summary						
Number of patients eligible for biologic therapies	7,318	7,763	8,214	8,673	9,138	41,104
Uptake of certolizumab pegol	10.0%	15.0%	22.0%	30.0%	30.0%	-
Number of patients on certolizumab pegol	**732**	**1,164**	**1,807**	**2,602**	**2,741**	**9,046**
Budget impact						
Medication acquisition cost	-£1,825,378	£638,629	£2,045,990	£3,798,517	£7,770,677	£12,428,435
Medication administration cost	£0	£9,804	£15,226	£24,252	£15,488	£64,771
Disease management cost	£0	-£243,492	-£515,320	-£816,108	-£1,146,483	-£2,721,404
Total Cost	**-£1,825,378**	**£404,941**	**£1,545,897**	**£3,006,661**	**£6,639,681**	**£9,771,802**
Overall axSpA Population						
Budget impact						
Total Cost	**-£3,359,636**	**-£991,636**	**£459,766**	**£1,679 ,939**	**£6,416,753**	**£4,205,185**

AS: Ankylosing spondylitis; **axSpA**: Axial spondyloarthritis; **nr-axSpA**: Non-radiographic axial spondyloarthritis

10 References

1. European Medicines Agency. Summary of Product Characteristics (CIMZIA). 28th July 2014.
2. British National Formulary. British National Formulary (BNF) 67: Pharmaceutical Press, 2014.
3. National Institute for Health and Care Excellence. NICE technology appraisal guidance 186 Certolizumab pegol for the treatment of rheumatoid arthritis. February 2010.
4. Scottish Medicines Consortium. Certolizumab pegol, 200 mg/mL solution for injection in prefilled syringe (Cimzia®) SMC No. (960/14) 12 May 2014.
5. Scottish Medicines Consortium. Certolizumab pegol, 200 mg/mL solution for injection (prefilled syringe) (Cimzia®) SMC No. (590/09) 10 September 2010.
6. Scottish Medicines Consortium. Certolizumab pegol, 200 mg/mL solution for injection in prefilled syringe (Cimzia®) SMC No. (973/14) 07 July 2014.
7. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68(6):777-83.
8. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum 2008;58(7):1981-91.
9. Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? Arthritis Care Res (Hoboken) 2012;64(9):1415-22.
10. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum 2009;60(3):717-27.
11. van den Berg R, de Hooge M, Rudwaleit M, et al. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the SPondyloArthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. Ann Rheum Dis 2013;72(10):1646-53.
12. Rudwaleit M, Landewe R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68(6):770-6.
13. Boonen A, van der Linden SM. The burden of ankylosing spondylitis. J Rheumatol Suppl 2006;78:4-11.
14. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999;12(4):247-55.
15. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis 2013;72(6):815-22.
16. 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(1):20-6.
17. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009;60(4):946-54.
18. 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.
19. Sieper J, Rudwaleit M, Van der Heijde D, 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. Abstract SAT0351. Ann Rheum Dis 2014;73(Suppl 2):719-720.
20. 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. Abstract SAT0362. Ann Rheum Dis 2014;73(Suppl 2):724-725.
21. Rudwaleit M, Landewé R, Marzo-Ortega H, et al. Observed incidence rates of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. Abstract SAT0355. Ann Rheum Dis 2014;73(Suppl 2):721-722.
22. van der Heijde D, Braun J, Rudwaleit M, et al. Improvements in Productivity at Paid Work and Within Household, and Increased Participation in Daily Activities After 24 Weeks of Certolizumab Pegol Treatment of Axial Spondyloarthritis Patients, Including Patients With Ankylosing Spondylitis: Results of a Phase 3 Double-blind Randomized Placebo-Controlled Study. Poster session presentedat the American

College of Rheumatology (ACR) Annual Meeting, November 9-14, 2012: Washingtom DC, USA. Poster 1372.
23. UCB. Data on File. AS001 Trial: Certolizumab Pegol in Subjects with Active Axial Spondyloarthritis. 2013.
24. National Institute for Health and Care Excellence. NICE technology appraisal guidance 143 Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008.
25. National Institute for Health and Care Excellence. NICE technology appraisal guidance 233 Golimumab for the treatment of ankylosing spondylitis. August 2011.
26. European Medicines Agency. Summary of Product Characteristics (Humira). 4th August 2014.
27. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Summary of Opinion. Enbrel (Etanercept). EMA/CHMP/366512/2014. 2014.
28. Reveille JD, Weisman MH. The epidemiology of back pain, axial spondyloarthritis and HLA-B27 in the United States. Am J Med Sci 2013;345(6):431-6.
29. Poddubnyy D, Rudwaleit M, Haibel H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70(8):1369-74.
30. Sampaio-Barros PD, Bortoluzzo AB, Conde RA, et al. Undifferentiated spondyloarthritis: a longterm followup. J Rheumatol 2010;37(6):1195-9.
31. Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? Arthritis Rheum 2013;65(3):543-51.
32. Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol 2012;8(5):262-8.
33. 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(7):2136-46.
34. Wallis D, Haroon N, Ayearst R, et al. Ankylosing spondylitis and nonradiographic axial spondyloarthritis: part of a common spectrum or distinct diseases? J Rheumatol 2013;40(12):2038-41.
35. van der Heijde D, Purcaru O, Kavanaugh A. High economic burden of axial spondyloarthritis related to paid work and household productivity at baselin in the RAPID-axSpA study: difference and similarities between ankylosing spondylitis an non-radiographic axial spondyloarthritis. Poster session presentedat the European League Against Rheumatism (EULAR) Annual Meeting, June 12-15, 2013: Madrid, Spain. Poster FRI0439.
36. Ara RM, Packham JC, Haywood KL. The direct healthcare costs associated with ankylosing spondylitis patients attending a UK secondary care rheumatology unit. Rheumatology 2008;47(1):68-71.
37. Rafia R, Ara R, Packham J, et al. Healthcare costs and productivity losses directly attributable to ankylosing spondylitis. Clin Exp Rheumatol 2012;30(2):246-53.
38. National Institute for Health and Care Excellence. Ankylosing spondylitis - adalimumab, etanercept and infliximab: review decision. Last updated 15th November 2012. [Accessed online at http://guidance.nice.org.uk/TA143/ReviewDecision on 16th October 2013].
39. European Medicines Agency. Summary of Product Characteristics (Remicade). 22nd July 2014.
40. European Medicines Agency. Summary of Product Characteristics (Simponi). 18th August 2014.
41. European Medicines Agency. Summary of Product Characteristics (Enbrel). 3rd February 2014.
42. Parton T, King L, Parker G, et al. The PEG moiety of Certolizumab Pegol is rapidly cleared from the blood of humans by the kidneys once it is cleaved from the Fab'. Abstract THU00051. Ann Rheum Dis 2009;68(Suppl 3):189.
43. Palframan R, Airey M, Moore A, et al. Use of biofluorescence imaging to compare the distribution of certolizumab pegol, adalimumab, and infliximab in the inflamed paws of mice with collagen-induced arthritis. J Immunol Methods 2009;348(1-2):36-41.
44. Carron P, Lambert B, De Vos F, et al. Scintigraphic Detection Of TNFα With a Radiolabeled Anti-TNFα In Patients With Active Peripheral Spondyloarthritis and Rheumatoid Arthritis. Abstract 1113. Arthritis Rheum 2013;65(Suppl 10):S472.
45. Stephens S, Browns D, Nesbitt A, et al. Lack of Placental Transfer and Accumulation in Milk of an Anti-TNF PEGylated Fab' Fragment in Rats. European Crohn's and Colitis Organisation (ECCO) Annual Meeting, March 1-3, 2007. Innsbruck, Austria. Abstract P152.
46. Porter C, Kopotsha T, Smith B, et al. No Significant Transfer of Certolizumab Pegol Compared with IgG in the Perfused Human Placenta In Vitro. Abstract W1208. Ann Rheum Dis 2010;69(Suppl10):S674.
47. Wolf D, Mahadevan U. Certolizumab pegol use in pregnancy: low levels detected in cord blood. Abstract 718. Arthritis Rheum 2010;62(Suppl 10):S299.
48. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11(3):286-92; quiz e24.

49. Red Dot Design Award. Red Dot Award: Communication Design. Design Innovations 2009 Competition, Design Zentrum Nordrhein Westfalen, Germany. Cimzia Packaging. [Accessed online at http://www.oxo.com/Ourawards.aspx on 1st August 2014].
50. Red Dot Design Award. Red Dot Award: Product Design. Design Innovations 2010 Competition, Design Zentrum Nordrhein Westfalen, Germany. Cimzia Syringe. [Accessed online at http://www.oxo.com/Ourawards.aspx on 1st August 2014].
51. Takeuchi T, Yamamoto K, Yamanaka H, et al. Post–Hoc Analysis Showing Better Clinical Response With The Loading Dose Of Certolizumab Pegol In Japanese Patients With Active Rheumatoid Arthritis. Abstract 2322. Arthritis Rheum 2013;65(Suppl 10):S989.
52. Lacroix BD, Lovern MR, Stockis A, et al. A pharmacodynamic Markov mixed-effects model for determining the effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis. Clin Pharmacol Ther 2009;86(4):387-95.
53. van der Heijde D, Deodhar A, Davies O, et al. Disease activity and clinical response early in the course of treatment predict long-term outcomes in axial spondyloarthritis patients treated with certolizumab pegol. Abstract SAT0338. Ann Rheum Dis 2014;73(Suppl 2):714-715.
54. Landewé R, Rudwaleit M, van der Heijde D, et al. Effect of Certolizumab Pegol on Signs And Symptoms of Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis: 24 Week Results of a Double-Blind Randomized Placebo-Controlled Phase 3 Axial Spondyloarthritis Study. Abstract 777. Arthritis Rheum 2012;64(Suppl 10):S336-337.
55. 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 Spondyltitis and Non-Radiographic Axial Spondyloarthritis: 24 week results of a phase 3 double blind randomized placebo-controlled study. Abstract 558. Arthritis Rheum 2012;64(Suppl 10):S243.
56. Landewé RB, 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. Abstract 1799. Arthritis Rheum 2013;65(Suppl 10):S767.
57. Kiltz U, Baraliakos X, Karakostas P, et al. The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. Ann Rheum Dis 2012;71(7):1207-11.
58. National Institute for Health and Care Excellence. Ankylosing spondylitis and axial spondyloarthritis (non-radiographic) - adalimumab, certolizumab pegol, etanercept infliximab and golimumab (inc rev TA143 and TA233). 2014.
59. 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(4):361-8.
60. Blachier M, Canoui-Poitrine F, Dougados M, et al. Factors associated with radiographic lesions in early axial spondyloarthritis. Results from the DESIR cohort. Rheumatology (Oxford) 2013;52(9):1686-93.
61. Expert opinion. Dr Alexander N Bennett. Rheumatologist practicing in England. 2014.
62. 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.
63. van der Heijde D, Calin A, Dougados M, et al. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. J Rheumatol 1999;26(4):951-4.
64. Anderson JJ, Baron G, van der Heijde D, et al. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44(8):1876-86.
65. Calin A, Fries JF. Striking prevalence of ankylosing spondylitis in "healthy" w27 positive males and females. N Engl J Med 1975;293(17):835-9.
66. Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromso, northern Norway. Ann Rheum Dis 1985;44(6):359-67.
67. Mease PJ, van Tubergen A, Deodhar A, et al. Comparing Health-Related Quality of Life Across Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis: Analyses from Certolizumab Pegol Clinical Trial Baseline Data. Abstract SAT0545. Ann Rheum Dis 2013;72(Suppl 3):766-767.
68. 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. J Rheumatol 1994;21(12):2286-91.
69. Schoels MM, Braun J, Dougados M, et al. Treating axial and peripheral spondyloarthritis, including psoriatic arthritis, to target: results of a systematic literature search to support an international treat-to-target recommendation in spondyloarthritis. Ann Rheum Dis 2013;73(1):238-242.
70. Brandt J, Listing J, Sieper J, et al. Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis. Ann Rheum Dis 2004;63(11):1438-44.
71. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68(12):1811-8.

72. Braun J, Baraliakos X, Listing J, et al. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum 2005;52(8):2447-51.
73. Insertional mutagenesis and oncogenesis: update from non-clinical and clinical studies. Gene Therapy Expert Group of the Committee for Proprietary Medical Products (CPMP), European Agency for the Evaluation of Medical Products - June 2003 meeting. J Gene Med 2004;6(1):127-9.
74. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331(7521):897-900.
75. Barkham N, Coates LC, Keen H, et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. Ann Rheum Dis 2010;69(11):1926-8.
76. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359(9313):1187-93.
77. Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346(18):1349-56.
78. 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(4):358-65.
79. 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(2):582-91.
80. 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(6):1065-74.
81. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70(6):905-8.
82. Bao C, Huang F, Khan MA, et al. Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. Rheumatology (Oxford) 2014.
83. Calin A, Dijkmans BA, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 2004;63(12):1594-600.
84. Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48(11):3230-6.
85. 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(11):1437-40.
86. 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(3):587-594.
87. 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 2008;58(11):3402-12.
88. 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):4005-14.
89. van der Heijde D, Da Silva JC, Dougados M, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis 2006;65(12):1572-7.
90. Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2014;66(8):2091-102.
91. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and Safety of Adalimumab in Patients with Non-Radiographic Axial Spondyloarthritis Results From a Phase 3 Study. Abstract 2486A. Arthritis Rheum 2011;63(Suppl 10):S970-971.
92. European Medicines Agency. Public Assessment Report: CIMZIA in axSpA. Procedure no. EMEA/H/C/001037/II/29, 2013.
93. Keystone E, Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58(11):3319-29.

94. Smolen J, Landewé RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68(6):797.
95. Expert opinion. Dr David McCarey. Rheumatologist practicing in Scotland. 2014.
96. Expert opinion. Dr Sara Carty. Rheumatologist practicing in Wales. 2014.
97. Bansback N, Maetzel A, Drummond M, et al. Considerations and preliminary proposals for defining a reference case for economic evaluations in ankylosing spondylitis. J Rheumatol 2007;34(5):1178-83.
98. Wailoo A, Bansback N, Chilcott J. Infliximab, etanercept and adalimumab for the treatment of ankylosing spondylitis: cost-effectiveness evidence and NICE guidance. Rheumatology (Oxford) 2008;47(2):119-20.
99. 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(28):1-158, iii-iv.
100. 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) 2005;44(7):939-47.
101. 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. Ann Rheum Dis 2006;65(2):201-8.
102. 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(8):1320-8.
103. Jansen JP, Pellissier J, Choy EH, et al. Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of ankylosing spondylitis in the UK. Curr Med Res Opin 2007;23(12):3069-78.
104. 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(3):368-75.
105. Muszbek N, Punekar Y, Buchanan J, et al. Cost-effectiveness of golimumab in ankylosing spondylitis from the UK payer perspective. Abstract PSY38. Value Health 2010;13(7):A467.
106. 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(5):979-86.
107. Jois RN, Gaffney K, Keat A. Anti-tumour necrosis factor therapy for ankylosing spondylitis--unresolved issues. Rheumatology (Oxford) 2007;46(6):899-901.
108. 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.
109. 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(9):1158-66.
110. Robertson LP, Davis MJ. A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis. Rheumatology (Oxford) 2004;43(12):1565-8.
111. Dougados M, Dijkmans B, Khan M, et al. Conventional treatments for ankylosing spondylitis. Ann Rheum Dis 2002;61 Suppl 3:iii40-50.
112. Poddubnyy D, Haibel H, Listing J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72(8):1430-2.
113. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70(11):1921-5.
114. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 1993;52(3):174-6.
115. Radford EP, Doll R, Smith PG. Mortality among patients with ankylosing spondylitis not given X-ray therapy. N Engl J Med 1977;297(11):572-6.
116. Office for National Statistics. Interim Life Tables, 1980-82 to 2010-2012. Last updated 2013. [Accessed online at http://www.ons.gov.uk/ons/datasets-and-tables/index.html?pageSize=25&sortBy=none&sortDirection=none&display=releases&content-type=Dataset&content-type=Reference+table&newquery=life+table+dx on 2013].
117. Eurostat - Selected Statistics - Prices (HICP).
118. Personal Social Services Research Unit (PSSRU). Unit Costs for Health and Social Care. Last updated 2012. [Accessed online at http://kar.kent.ac.uk/32408/1/full-with-covers.pdf on 27th August 2013].
119. Poddubnyy D, Haibel H, Listing J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum 2012;64(5):1388-98.

120. National Institute for Health and Care Excellence. Assumptions used in estimating a population benchmark. Last updated 16th October 2012. [Accessed online at http://www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/AssumptionsUsedInEstimatingAPopulationBenchmark.jsp on 15th November 2013].
121. Saraux A, Guillemin F, Guggenbuhl P, et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis 2005;64(10):1431-5.
122. Kaipiainen-Seppanen O, Aho K, Heliovaara M. Incidence and prevalence of ankylosing spondylitis in Finland. J Rheumatol 1997;24(3):496-9.
123. Carter ET, McKenna CH, Brian DD, et al. Epidemiology of ankylosing spondylitis in rochester, minnesota, 1935–1973. Arthritis Rheum 1979;22(4):365-370.
124. Gomor B, Gyodi E, Bakos L. Distribution of HLA B27 and ankylosing spondylitis in the Hungarian population. J Rheumatol Suppl 1977;3:33-5.
125. Saraux A, Guedes C, Allain J, et al. Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. Societe de Rhumatologie de l'Ouest. J Rheumatol 1999;26(12):2622-7.
126. Braun J, Bollow M, Remlinger G, et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41(1):58-67.
127. Carbone LD, Cooper C, Michet CJ, et al. Ankylosing spondylitis in Rochester, Minnesota, 1935-1989. Is the epidemiology changing? Arthritis Rheum 1992;35(12):1476-82.
128. Bakland G, Nossent HC, Gran JT. Incidence and prevalence of ankylosing spondylitis in Northern Norway. Arthritis Rheum 2005;53(6):850-5.
129. British Society for Rheumatology. BSR Guideline for PrescribingTNFα Blockers in Adults with Ankylosing Spondylitis. 2004.
130. Haute Autorité de Santé. Commision de la Transparence: HUMIRA 40 mg, solution injectable en seringue préremplie; HUMIRA 40 mg, solution injectable en stylo prérempli. 20 February 2013.
131. Kaprove RE, Little AH, Graham DC, et al. Ankylosing spondylitis: survival in men with and without radiotherapy. Arthritis Rheum 1980;23(1):57-61.
132. Smith PG, Doll R. Mortality among patients with ankylosing spondylitis after a single treatment course with x rays. Br Med J (Clin Res Ed) 1982;284(6314):449-60.
133. Department of Health. Policy paper: NHS reference costs: financial year 2011 to 2012. . Last updated 2012. [Accessed online at https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 on 27th August 2013].
134. Haroon N IR, Learch TJ, Weisman MH, Ward MM, Reveille JD, Gensler LS. TNF-inhibitors Slow Radiographic Progression in Ankylosing Spondylitis. Abstract 782. Arthritis Rheum 2012;64(Suppl 10):S339-340.
135. 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(6):896-904.
136. Smolen JS, Braun J, Dougados M, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis 2014;73(1):6-16.
137. 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(12):2281-5.
138. van der Heijde D, Braun J, Landewe R, et al. ASessment in Ankylosing Spondylitis (ASAS) international working group: a model for psoriatic arthritis and psoriasis? Ann Rheum Dis 2005;64 Suppl 2:ii108-9.
139. Van Tubergen A, Debats I, Ryser L, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 2002;47(3):242-8.
140. 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(6):1050-7.
141. 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(6):922-9.
142. Osterhaus JT, Purcaru O, Richard L. Discriminant validity, responsiveness and reliability of the rheumatoid arthritis-specific Work Productivity Survey (WPS-RA). Arthritis Res Ther 2009;11(3):R73.
143. Osterhaus JT, Purcaru O. Discriminant validity, responsiveness and reliability of the arthritis-specific Work Productivity Survey assessing workplace and household productivity in patients with psoriatic arthritis. Arthritis Res Ther 2014;16(4):R140.
144. Osterhaus JT, Purcaru O. Discriminant validity, responsiveness and reliability of the arthritis-specific Work Productivity Survey assessing workplace and household productivity within and outside the home in

patients with axial spondyloarthritis, including non-radiographic axial spondyloarthritis and ankylosing spondylitis. Arthritis Res Ther 2014;16(4):R164.
145. 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(6):1543-51.
146. Inman RD, Maksymowych WP. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. J Rheumatol 2010;37(6):1203-10.
147. Li EK, Griffith JF, Lee VW, et al. Short-term efficacy of combination methotrexate and infliximab in patients with ankylosing spondylitis: a clinical and magnetic resonance imaging correlation. Rheumatology (Oxford) 2008;47(9):1358-63.
148. Dougados M, Tsai W-C, Saaibi DL, et al. Patient-Reported Outcomes of Etanercept in Early Non-Radiographic Axial Spondyloarthritis: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Abstract 1516. Arthritis Rheum 2013;65(Suppl 10):S642-643.
149. Song IH, Hermann K, Haibel H, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70(4):590-6.
150. 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(11):1568-75.
151. Pedersen SJ, Sorensen IJ, Loft AG, et al. Efficacy of Adalimumab in Patients with Axial Spondyloarthritis: Results of an Investigator-Initiated 12-Weeks Randomized Double-Blind Placebo Controlled Trial with a 12 Weeks Extension Phase. Abstract THU0366. Ann Rheum Dis 2013;72(Suppl 3):289.
152. Mulleman D, Lauferon F, Wendling D, et al. Infliximab in ankylosing spondylitis: alone or in combination with methotrexate? A pharmacokinetic comparative study. Arthritis Res Ther 2011;13(3):R82.
153. 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(5):799-804.
154. National Institute for Health and Care Excellence. Ankylosing spondylitis commissioning algorithm. Last updated 2011. [Accessed online at http://www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/home.jsp?domedia=1&mid=F1847F0D-19B9-E0B5-D444A7781B1764F1 on 20th March 2014].