Adalimumab

(HUMIRA®)

National Institute for Health and Care Excellence (NICE)

Multiple Technology Appraisal

TNF-alpha inhibitors for severe active ankylosing spondylitis and severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

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Submission by AbbVie

abbvie

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DECLARATION

This submission does not omit any relevant evidence of which AbbVie is aware of and is not currently in the public domain, which could reasonably be considered to be related to the appraisal of adalimumab (HUMIRA®).

Information within this dossier considered as academic in confidence is underlined and highlighted in yellow and information considered commercial-in-confidence is underlined and highlighted in blue

FOREWARD

The aim of this multiple technology appraisal is twofold: 1) to evaluate adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab within their licensed indications for the treatment of severe active ankylosing spondylitis (including a review of TA143 and TA 233); and 2) to appraise adalimumab and certolizumab pegol within their licensed indications for the treatment of severe axial spondylitis without radiographic evidence of ankylosing spondylitis.

NICE technology appraisal 143 recommends adalimumab and etanercept as treatment options for adults with severe active ankylosing spondylitis only if certain criteria are fulfilled, but it does not recommend infliximab for ankylosing spondylitis. Golimumab is also recommended in NICE technology appraisal 233 as an option for the treatment of severe, active ankylosing spondylitis in adults only if it is used as described for adalimumab and etanercept in NICE technology appraisal 143.

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Executive Summary

Axial SpA is a chronic inflammatory disease that primarily affects the axial skeleton (SI joints and spine). At presentation all axial SpA patients have chronic back pain and may also have peripheral manifestations involving the joint and surrounding structures including arthritis, enthesitis and dactylitis and/or extra-articular manifestations such as uveitis, inflammatory bowel disease, or psoriasis, and patients often have the genetic marker, human leukocyte antigen (HLA)-B27. Historically, patients with axial SpA were only identified when there was x-ray evidence of structural damage of the SI joints (radiographic sacroiliitis), and such patients were diagnosed as having AS. Advances in the knowledge of axial SpA have led to the understanding that some patients who have the clinical manifestations typical of this disease may not have evidence of radiographic sacroiliitis at presentation, and such patients are now diagnosed as having nr-axSpA. Therefore, both Ankylosing Spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) represent the same chronic, debilitating, systemic, multi-faceted disease, axial SpA, with the presence or absence of radiographic sacroiliitis being the only differentiating feature.

Both AS and nr-axSpA affect young male and female patients in their thirties and forties, often considered the most productive period of life. A survey of UK National Ankylosing Spondylitis Society (NASS) members reported a mean age of onset for AS of 28.7 years and data from ABILITY-1 show that the average age of onset of symptoms for nr-axSpA was 28.3 years. Patients with nr-axSpA and AS share a similarly high burden of disease, as shown by comparable levels of pain, disease activity, fatigue, morning stiffness, health-related quality of life (HRQoL) and work productivity impairments.

Adalimumab has been shown to be effective in the treatment of AS in the ATLAS randomised controlled trial and in the M03-606 randomised controlled trial. As these studies have been presented in detail in the previous 2006 MTA submission, the present submission focuses on the long term follow up data. In the ATLAS study of patients with active AS, the efficacy and safety of adalimumab were maintained through 5 years, with about half of the patients experiencing sustained remission at any time during the study. Early achievement of remission was the best predictor of long-term and sustained remission. Adalimumab has also been shown to be effective in the treatment of nr-axSpA in ABILITY-1. In this study adalimumab therapy resulted in improvements in pain, disease activity, health-related quality of life, and work outcomes in patients with severe nr axSpA who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs compared to placebo.

Extra Articular Manifestations (EAM) associated with axial SpA include; anterior uveitis (25–30%), psoriasis (10–25%) or inflammatory bowel disease (IBD) (5–10%) and cardiovascular manifestations. Adalimumab has been shown to be efficacious in the treatment of anterior uveitis associated with AS, IBD and psoriasis. As such, the ASAS/ EULAR recommendations in 2010 highlighted that the choice of biologic treatment for patients with AS should take into account not only the axial manifestations, but given the high prevalence of uveitis, IBD, psoriasis etc., also take account of any EAM and the benefit different drugs confer on these co-morbidities.

An economic model to estimate the cost effectiveness of adalimumab vs. conventional therapy and other licensed anti-TNF agents for axial spondyloarthritis (nr-axSpA and AS) patients was developed for the two indications separately.

In the base-case analysis (40 year time horizon) for AS under a £30,000 per QALY willingness-to-pay (WTP) threshold, adalimumab yielded the highest net monetary benefit (NMB) (£168,411) and the lowest ICER (£16,391/QALY) followed by golimumab (£16,535/QALY), etanercept (£16,897/QALY) and certolizumab (£17,067/QALY), when compared to conventional therapy. Infliximab (£44,448/QALY) was the least cost-effective therapy across all WTP thresholds.

In nr-axSpA, certolizumab had the highest NMB (£162,194) and the lowest ICER (£12,866 /QALY) comparing to conventional therapy, followed by adalimumab (£13,228 /QALY versus conventional therapy). Scenario analyses indicated that the AS and nr-axSpA results were sensitive to the same parameter changes.

The definition of response in the model was based on the ASAS response criteria. The choice of the ASAS40 for nr-axSpA was made on the basis that this measure is consistent with the primary endpoint of the ABILITY-1 trial and ASAS20 for AS, as this measure was the primary endpoint in the ATLAS trial. However, alternative definitions have been used in past economic analyses of AS. Nevertheless the results of the present analysis were not affected substantially by the use of these alternative methods.

Given the limited numbers of trials available for synthesis in the network meta-analyses, the different populations considered, differential use of early escape arms, and relatively small populations there is uncertainty regarding the estimates of relative effectiveness obtained in the network meta-analysis conducted in this submission for anti-TNF drugs. Therefore, it is difficult to draw strong conclusions on the cost effectiveness of the anti-TNF drugs when compared to each other when these differences are generated by response rate estimates from the NMA. Cost savings due to adalimumab may be underestimated versus conventional therapy and versus other anti-TNF drugs. It is possible that the cost equation used in the base case and most other scenarios, which links costs to BASDAI scores, ignores the cost associated with extra-articular manifestations of nr-axSpA (e.g. uveitis or IBD), since the BASDAI may not correlate well with these manifestations. Therefore, the cost effectiveness results presented do not take account of the impact of adalimumab therapy on extra-articular manifestations which are common in clinical practice when treating AS and nr-axSpA patients. The results of the model also show that, from a societal perspective when direct non-medical and indirect costs were included, the use of adalimumab resulted in cost savings (in addition to QALY gains) for both AS and nr-axSpA.

Section 1: Background and Context

1.1 Axial spondyloarthritis (Axial SpA)

Spondyloarthritis (SpA) is a group of inflammatory diseases that share common clinical, radiographic, and genetic features. Included in this group are ankylosing spondylitis (AS), psoriatic arthritis, arthritis associated with inflammatory bowel disease, reactive arthritis and undifferentiated SpA. Diseases in the SpA group were previously described by their individual diagnostic entity; however there is an overlap of signs and symptoms among these diseases such that when evaluating patients for a diagnosis of SpA, rheumatologists usually first determine if patients have either predominantly axial or predominantly peripheral manifestations. Therefore the ASAS classification of SpA groups the diseases into two broad categories based on their predominant clinical manifestations (axial or peripheral).

Axial SpA encompasses a spectrum of inflammatory involvement of the axial skeleton which has been arbitrarily split into two categories – AS and non-radiographic axial SpA (nr-axSpA; axial SpA without radiographic evidence of AS) - due to the 1984 modified New York criteria which requires the presence of sacroiliitis on plain radiographs for the classification of AS. The ASAS axial SpA criteria reflect the recent advances in the field of SpA – the acknowledgement that axial SpA patients may present with (AS) or without (nr-axSpA) radiographic sacroiliitis and the use of magnetic resonance imaging (MRI) as an additional imaging modality to assess for sacroiliitis that represents acute inflammation.

Axial SpA is a chronic inflammatory disease that primarily affects the axial skeleton (SI joints and spine). At presentation all axial SpA patients have chronic back pain and may also have peripheral manifestations involving the joint and surrounding structures including arthritis, enthesitis and dactylitis and/or extra-articular manifestations such as uveitis, inflammatory bowel disease, or psoriasis, and patients often have the genetic marker human leukocyte antigen (HLA)-B27. Historically, patients with axial SpA were only identified when there was x-ray evidence of structural damage of the SI joints (radiographic sacroiliitis), and such patients were diagnosed as having AS. Advances in the knowledge of axial SpA has led to the understanding that some patients who have the clinical manifestations typical of this disease may not have evidence of radiographic sacroiliitis at presentation, and such patients are now diagnosed as having nr-axSpA. Therefore, both AS and nr-axSpA represent the same chronic, debilitating, systemic, multi-faceted disease, axial SpA, with the presence or absence of radiographic sacroiliitis being the only differentiating feature.

The presence of radiographic sacroiliitis is the hallmark of AS. To be classified as having AS, patients must have a minimum degree of abnormality on their AP pelvic x-ray as demonstrated by erosions, sclerosis, alterations in joint width, and/or ankylosis (joint fusion). These radiographic changes are the consequence of prior inflammation and represent permanent bony damage. In contrast, patients with nr-axSpA may have no changes or minimal changes on plain x-ray which do not meet the modified New York criteria definition of AS. Both AS and nr-axSpA patients may have active inflammation visible as bone marrow edema/osteitis on MRI and may have fatty infiltration of bone, however MRI changes are not universally present. In addition, some axial SpA patients may develop syndesmophytes in their spine (bony growths which connect 1 vertebra to another). In advanced stages of AS, patients may develop fusion of the spine due to many syndesmophytes forming a bony column referred to as ‘bamboo spine’.

Over time, some patients with nr-axSpA may progress to AS, although others may never develop radiographic sacroiliitis.[1] Although there have not been any studies specifically following nr-axSpA patients using the ASAS criteria over a long period of time, Mau *et al* [2] showed that inn mixed cohorts of axial and peripheral SpA, approximately 60% of patients have historically progressed to develop radiographic changes consistent with AS after ≥ 10 years of follow-up (Table 1.1.1).

Table 1.1.1: Rate of progression from SpA without radiographic evidence of sacroiliitis to AS

	0 – 2 Years[a,b]	2 – 9 Years[a,c-f]	≥ 10 Years[a,g]
% Progression	8% – 12%	20% – 45%	36% – 59%

a. N = 111; undifferentiated SpA by the ESSG (European Spondyloarthropathy Study Group) and Amor criteria.
b. N = 95; nr-axSpA defined by slightly modified ESSG criteria.
c. N = 119; human leukocyte antigen (HLA)-B27 positive oligoarthritis.
d. N = 23; seronegative unclassified HLA-B27 inflammatory rheumatologic disease.
e. N = 23; HLA-B27 positive patients with inflammatory low back pain by Calin criteria.
f. N = 40; patients with IBP by Calin criteria of < 2 years duration (36 patients fulfilled ESSG criteria at Baseline).
g. N = 88; SpA defined by low back pain > 3 months plus peripheral arthritis, heel pain, anterior uveitis, or a raised erythrocyte sedimentation rate adjusted for age and sex (11 patients without low back pain were included due to having 3 of the other symptoms).
Note: Presented are longitudinal studies of patients that are ≥ 17 years of age at baseline. None of the patients met modified New York criteria for AS at study entry.

Both AS and nr-axSpA affect young male and female patients in their thirties and forties,[3] often considered the most productive period of life. A survey of UK National Ankylosing Spondylitis Society (NASS) members reported a mean age of onset for AS of 28.7 years[4], and data from ABILITY-1 show that the average age of onset of symptoms was 28.3 years.[8] Men are afflicted with AS approximately two to three times more frequently than women. In the UK survey of NASS members 71% of patients were male[4]. Whereas non-radiographic axial spondyloarthritis affects approximately equal numbers of men and women, but men are more likely to develop radiographically evident disease. German data indicate that the diagnosis of axial SpA patients as nr-axSpA or AS is correlated with duration of disease at the time of diagnosis; thus, the likelihood that a patient is identified as having AS is higher with longer symptom duration. In a cross-sectional referral cohort of ASAS criteria-defined axial SpA patients, 67.3% with ≤ 1 year of symptoms were diagnosed as nr-axSpA and 28.6% were diagnosed with nr-axSpA after > 12 years of symptoms. This implies that a considerable number of axial SpA patients would have a delayed diagnosis if relying on radiographic damage of the SI joints.[5]

Patients with nr-axSpA and AS share a similarly high burden of disease, as shown by comparable levels of pain, disease activity, fatigue, morning stiffness, health-related quality of life (HRQoL) and work productivity impairments[6,1]. Registry and clinical trial data are presented in Table 1.1.2 illustrating the comparable burden of disease between AS and nr-axSpA6,[7,8,9,10]

Table 1.1.2: Baseline disease activity data from registries and axSpA RCTs

Source	Registry data					RCT data		
	GESPIC[a]			Kiltz et al [b]		ATLAS[9]	ABILITY-1[42]	Haibel[10]
Disease state	**All AS**	**AS ≤5 years**	**nr-axSpA ≤5 years**	**AS**	**nr-axSpA**	**AS**	**nr-axSpA**	**nr-axSpA**
Number of patients	236	119	226	56	44	315	185	46
BASDAI, (0-10)	4.0	4.0	3.9	4.2	3.6	6.3	6.5	6.3
PtGA of disease activity VAS (0-10)	5.0	5.0	4.9	4.6	4.0	6.3	6.8	6.6
PGA of disease activity VAS (0-10)	4.5	4.4	3.6	3.5	2.7	5.7	5.7	5.9
Total pain VAS, (0-10)	5.0	4.8	4.8	4.7	4.0	-	6.8	7.2

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; GESPIC: German Spondyloarthritis Inception Cohort; IBP: inflammatory back pain; nr-axSpA: non-radiographic axial spondyloarthritis; PGA: physician's global assessment of disease; PtGA: patient global assessment; RCT: randomised controlled trial; SF-36: Short-Form 36-item questionnaire mental component summary; VAS: visual analogue scale

a. Values are means. Patients with a definite clinical diagnosis of axial SpA classified as AS, if fulfilling the modified New York criteria for AS with disease duration restricted to ≤ 10 years or as nr-axSpA if fulfilling ESSG criteria, but not the modified New York criteria for AS, with disease duration limited to ≤ 5 years.

b. Values are medians. Prospective cohort of TNF-naïve patients meeting ASAS criteria for axial SpA; classified as AS or nr-axSpA based on the modified New York criteria for AS.

1.2 Treatment goals

The overall objectives of management and treatment in patients with AS and nr-axSpA are five-fold[11].

- Early and accurate diagnosis;
- Control of symptoms, i.e. pain, stiffness, and fatigue;
- Maintenance of posture and flexibility;
- Detection and management of complications and associated conditions as soon as possible;
- Minimisation and management of disabilities.

Current treatment options

Conventional therapy for AS and nr-axSpA includes[12]

- Non pharmacological treatment (e.g. exercise, physiotherapy)

- Non-steroidal anti-inflammatory drugs (NSAIDs)

- Simple analgesics

- Corticosteroids (e.g. prednisolone, methylprednisolone) - Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. However, the use of systemic glucocorticoids for axial disease is not supported by the evidence.

- Tradional disease modifying antirheumatic drugs (tDMARDs) in RA: e.g. sulfasalazine and methotrexate. However, there is no evidence for the efficacy of these DMARDs for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis.

- Anti-TNF agents (updated International ASAS recommendations for the use of anti-TNF agents in patients with axial SpA.)[13]

Assessment of response to drug therapy

A number of tools are available that provide measures of aspects of the disease such as reduction of signs and symptoms, disease controlling clinical response and patient reported outcomes.

1.2.1 Reduction of signs and symptoms

ASAS

Assessment of SpondyloArthritis international Society (ASAS) has derived a number of composite measures based on domains that are of importance in assessing symptomatic outcome in AS. Based on the core set of clinical trials with NSAIDs, ASAS has devised a preliminary definition of short-term improvement in AS[14]. The improvement criteria consist of four outcome domains:

1. patient global assessment (measured on a 100 mm visual analogue scale [VAS]);
2. spinal pain (measured on a 100 mm VAS);
3. physical function (measured using the Bath AS Functional Index (BASFI);
4. inflammation (mean of the last two questions from the Bath AS Disease Activity Index (BASDAI), concerning the intensity and duration of morning stiffness).

Scores on each domain range from 0 (best) to 100 (worst). The ASAS-IC defines improvement as follows:

- An improvement of > 20% and > 10 VAS points on the 0–100 scale in at least three of the four domains. On the fourth domain there must be no worsening of > 20% and > 10 VAS points.

This is otherwise known as the ASAS 20 response, which is the standard primary efficacy criterion to define short term improvement in AS. Other definitions of ASAS response (ASAS 50 and ASAS 70) based on improvements of 50% and 70%, respectively, are also used to measure symptomatic outcome in clinical studies. In nr-axSpA, the ASAS criteria of response are also used in clinical studies to assess improvements in signs and symptoms. The primary endpoint in the adalimumab nr-axSpA trials was a 40% improvement in the ASAS criteria (ASAS40). ASAS 40 is defined as at least 40% improvement and 20 units of absolute change in three of four domains using the same domains as the ASAS 20 response criteria without any worsening in the fourth domain.

BASDAI[15]

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a validated tool which records patients' responses to six questions pertaining to the five major symptoms of AS and nr-axSpA during the preceding week: fatigue/tiredness; neck, back and hip pain; joint pain / swelling (excluding neck, back and hip); discomfort from areas of localized tenderness (to touch or pressure); morning stiffness - two questions: degree and duration from the time of waking up.

The responses are each documented on a 10 cm VAS, where 0 cm = none and 10 cm = very severe (0 to 2 or more hours for duration of stiffness). To give each symptom equal weighting, the mean of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final BASDAI score ranging from 0 – 10. Therefore; the higher the score, the greater the degree of measured disease activity; with reductions from baseline denoting improvement. The BASDAI is user friendly (usually taking less than 2 minutes to complete), reflects the core spectrum of disease features, and is sensitive to clinical changes in AS and nr-axSpA. However, one of its main drawbacks relates to the subjectivity of measurement using patient-assessed VAS scales alone.

BASFI[16]

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated tool, which as for the BASDAI records patients' responses on a series of 10 cm VAS scales. It consists of ten questions designed to determine the degree of functional limitation in those with axial SpA. The first eight questions consider activities related to functional anatomy. The final two questions assess the patient's ability to cope with everyday life. On the VAS, the anchor for 0 cm = easy and for 10 cm = nearly impossible. Therefore; the higher the score, the greater the degree of functional impairment, with reductions from baseline score denoting improvement. A BASDAI20, BASDAI50, BASDAI70 refers to 20%, 50% and 70% improvements in BASDAI, respectively.

ASDAS[17]

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a continuous disease activity index comprised of the following components (back pain, duration of morning stiffness, patient global assessment, peripheral pain/swelling and CRP) formulated in to the equation below:

ASDAS-CRP= 0.12 × back pain + 0.06 × duration of morning stiffness + 0.11 × patient global + 0.07 × peripheral pain/ swelling + 0.58 × ln(CRP + 1)

This is used much more routinely in clinical practice. Furthermore, the ASDAS can be categorised in to disease activity states such that ASDAS less than 1.3 is used to define 'inactive disease', ASDAS $\geq$ 1.3 and < 2.1 equates to 'moderate disease activity', an ASDAS $\geq$ 2.1 and $\leq$ to 3.5 defines 'high disease activity', and an ASDAS > 3.5 equates to 'very high disease activity.

1.2.2 Disease controlling clinical response

The ASAS Working Group also defined a set of criteria to assess a low disease activity state and remission of disease[14]. These are referred to as ASAS partial remission criteria. ASAS partial remission is defined as a value of < 20 on a 0–100 scale in each of the four ASAS 20 domains (patient's global assessment, pain, function, and inflammation).

The ASAS Working Group also suggests the use of ASAS 5/6 response criteria to assess disease modifying capabilities[18]. The ASAS 5/6 adds two further domains - spinal mobility and acute phase reactants - to the four domains covered by the other ASAS responses (i.e. ASAS 20, 40, 50 and 70). These two domains were omitted from the original core criteria as they were not sensitive to the changes induced by NSAIDs, on which the original criteria were developed. For ASAS 5/6, improvement is defined as 20% improvement in 5 of the 6 domains encompassed. As described by the ASAS Working Group the clinical implications of a 20% change in these two further domains are not yet known, but their inclusion has the advantage of adding objective measures to the patient-reported outcomes encompassed by the core four domains. A Minimal Clinically Important State (MCIS) exists which queries the subject on his/her level of satisfaction, asking if the subject were to stay in his/her current state for the next month, would he/she be satisfied with the current state.

1.2.3 Patient reported outcomes

Short Form-36 Health Status Survey (SF-36)

The SF-36 Health Survey is a generic health status instrument developed for application in primary care and chronic disease populations. The SF-36 contains two summary scores, the physical component and mental component summary scores (PCS and MCS), and eight domain scales: physical function, bodily pain, role limitations-physical, general health, vitality, social function, role limitations-emotional and mental health. Domain scale scores range from 0 to 100, with higher scores reflecting better health status, and the summary scores are constructed as T-scores with a mean of 50 and standard deviation of 10, with higher scores indicating better health status. MID criteria have been defined as 2.5-5.0 in the PCS and MCS scores and 5-10 point change in the subscale scores based on information from studies in RA [19].

Ankylosing Spondylitis Quality of Life questionnaire (ASQoL)

The ASQoL is a disease-specific instrument designed to measure health-related quality of life in subjects with AS developed based on a needs-based model[20]. The ASQoL has a total score ranging from 0 to 18, with lower scores representing better AS-specific quality of life. Differences of 1 to 2 points are considered to be clinically relevant[21,22]. In addition, research has shown that a magnitude of change of ≥10% of the total score could be considered clinically meaningful[23].

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale

The FACIT-F is a frequently used instrument measuring fatigue and its effect on functioning and daily activities. It is a subset of the longer Functional Assessment of Cancer Therapy Anaemia (FACT-An) Scale. The FACIT-F has 13 items answered on a 5 point rating scale. Subjects answer how true each item has been over the past 7 days. Scores range from 0 to 52, with higher scores reflecting less fatigue. Differences $\geq$ 3.0 points exceed the *a priori* MID criteria and are considered to be clinically meaningful.

Health Utility Index Mark 3 (HUI-3)

The Health Utilities Index-3 (HUI-3) is a multi-attribute utility theory based index ranging from 0 to 1.0, with higher scores representing better health status. It consists of 15 self-administered items measuring health status. The recall period is the past 4 weeks. Items assess a subject's functional capacity rather than performance in eight domains or attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). Subjects choose from either five or six levels of functioning (normal functioning to severe impairment) within each attribute. An increase in HUI-3 score represents an improvement.

Work Productivity and Activity Impairment Questionnaire (WPAI-SHP)

The WPAI is a patient-reported outcome that measures a subject's ability to work and perform regular activities, based on evaluation of absenteeism, presenteeism, work productivity loss, and activity impairment for a specific health problem. A decrease in score represents improvement.

1.2.4 Additional outcomes collected in AS and nr-axSpA

CRP

A laboratory measurement to evaluate levels of an acute phase reactant as a marker of inflammation. A decrease in the level of CRP indicates reduction in inflammation.

BASMI[24]

The Bath AS Metrology Index (BASMI) is a validated tool for assessment of axial status that is sensitive to changes in spinal movement. Five clinical measurements are included in this index: cervical (i.e. neck) rotation; tragus to wall distance; lumbar side flexion; modified Schober's (lumbar forward flexion); intermalleolar distance. The magnitude of each of the five measures in cm is assigned a score based on a BASMI specific scoring table (i.e. the data are not continuous). There are two BASMI scoring tables. In one, scores range from 0-2 (corresponding to mild, moderate or severe); in the other (developed subsequently) scores range from 0-10 for each of the five measurements. The higher the BASMI score the more severe the patient's limitation of movement due to their AS or nr-axSpA.

Chest Expansion

Measures the excursion between full inspiration and full expiration. An increase in the Chest Expansion score indicates improvement in the severity of Chest Expansion which may have declined in active AS.

EDASMI

A composite index with four measures: cervical rotation, lumbar side flexion, chest expansion and internal hip rotation.

MASES[25]

The MASES assesses a total of 13 entheses; 1st costochondral joint left/right; 7th costochondral joint left/right; posterior superior iliac spine left/right; anterior superior iliac spine left/right; iliac crest left/right; 5th lumbar spinous process and proximal insertion of Achilles tendon left/right.

BAS-G[26]

This consists of two questions that ask the subject to indicate, on a 10 cm VAS, the effect AS has had on their well-being over the 1) last week and 2) last 6 months. The mean of the two scores gives a BAS-G score of 0-10. The higher the score, the greater the perceived effect of the disease on the patient's well-being.

Nocturnal Pain

This measures the amount of back pain at night that the subject experienced over the past week prior to the subject's study visit on a 100 mm VAS scale, with a score of 0 indicating "no pain" and a score of 100 indicating "worst possible pain."

Physician's Global Assessment of Disease Activity

This assesses the subject's current disease activity made by the physician using a 100 mm horizontal VAS. The left end of the VAS (0 mm) indicates absence of disease activity and the right end of the VAS (100 mm) indicates extreme disease activity.

Swollen Joint Count for 66 Joints (SJC 66)

This measure assesses 44 joints by physical examination. The joints examined for swelling were the same as those examined for tenderness, except that hip joints were excluded. Joint swelling was classified as present ("1"), absent ("0") or injected/replaced ("9").

Tender Joint Count for 68 Joints (TJC 68)

This measure assesses 46 joints by physical examination. Joint tenderness/pain was classified as present ("1"), absent ("0") or injected/replaced ("9").

1.3 Adalimumab (Humira®)

1.3.1 Licensed Indications

Rheumatoid arthritis

Adalimumab in combination with methotrexate is indicated 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.
- The treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Adalimumab 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.

Polyarticular juvenile idiopathic arthritis

Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see section 5.1). Adalimumab has not been studied in children aged less than 2 years.

Axial spondyloarthritis comprising the following two indications:

Ankylosing spondylitis (AS)

Adalimumab is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

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

Adalimumab is indicated for the treatment of adults with severe 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 non-steroidal anti-inflammatory drugs.

Psoriatic arthritis

Adalimumab is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as

measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see Section 5.1) and to improve physical function.

Psoriasis

Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.

Crohn's disease

Adalimumab is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

Paediatric Crohn's Disease

Adalimumab is indicated for the treatment of severe active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Adalimumab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

1.3.2 Mechanism of Action

Adalimumab is a fully human monoclonal antibody that binds specifically to the pro-inflammatory cytokine TNF-α and neutralises the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF-α, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1 [endothelial leukocyte adhesion molecule-1], VCAM-1 [vascular cell adhesion molecule-1], and ICAM-1 [intracellular adhesion molecule-1] with an IC_{50} of 1-2 X 10^{-10} M).

1.3.3 Presentation and Cost

Adalimumab is available in the following three presentations:

- A 40mg solution for injection in a single-use pre-filled syringe (type I glass) for patient use: packs of 2 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister are provided.

- A single-use automatic injection device with needle-guard that delivers 40mg adalimumab by pushbutton (Humira Pen). Packs of: 1 pre-filled syringe with needle-guard (0.8 ml sterile solution) in a blister, and 1 alcohol pad are provided.

- 40 mg solution for injection in single-use vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals: 1 pack of 2 boxes each containing: 1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe, 1 needle, 1 vial adapter and 2 alcohol pads.

The list price for all three presentations of adalimumab is £352.14[27]

Adalimumab is available for delivery via a homecare delivery provider. Patients and their carers can be trained in injection technique to allow delivery of the drug direct to their home. This reduces burden on NHS services and reduces the impact of receiving treatment on work productivity or activities of daily living for those who are not working. VAT is also not payable on any drug not delivered in the inpatient setting.

Section 2: Clinical Effectiveness

2.0 Overview of clinical evidence

The aim of this MTA review is to evaluate the clinical- and cost-effectiveness of five anti-TNFs: adalimumab, etanercept, infliximab, golimumab and certolizumab pegol for the treatment of patients with severe ankylosing spondylitis; in addition the review will evaluate adalimumab and certolizumab for the treatment of non-radiographic axial spondyloarthritis. Given the quantity of clinical evidence available for these drugs, providing a detailed account of each study would quadruple the size of this submission. Therefore, AbbVie has instead provided a series of summary tables (Section 2.1) containing the following information: type of population, the intervention(s), baseline characteristics and results, from an extensive systematic literature review of RCTs evaluating biologics in AS and nr-axSpA (see Appendix 1 for further details of the search strategy and literature review).

Given this is a review of the TNF inhibitors for AS, AbbVie has previously provided a detailed description of the two randomised controlled trials of adalimumab for the treatment of AS in its January 2006 submission (ATLAS[28] and M03-606 [M03-606]). Furthermore, a summary of these trials including design, study characteristics and results are presented in Section 2.1 alongside the other anti-TNFs. Therefore, Section 2.2.1 focuses on the long-term, open-label safety and efficacy data for adalimumab from these trials that have been published since the 2006 AS NICE appraisal. In addition, efficacy data from other open-label studies and country registries have also been included in this section (Section 2.2.2). AbbVie is happy to provide a copy of the 2006 submission if the Appraisal Committee or the Assessment Group require any additional information about the design of ATLAS and the M03-606 trial.

This MTA review also aims to assess the clinical and cost-effectiveness of adalimumab and certolizumab for the treatment of nr-axSpA. NICE has yet to review an intervention for this indication; therefore Section 2.3 provides a detailed account of the adalimumab nr-axSpA clinical trials including study design, baseline characteristics, and results. Sections 2.3.1, 2.3.2, and 2.3.4 describes the randomised controlled trials, whilst Section 2.3.3 focuses on the long-term open label data showing sustained adalimumab response.

Section 2.4 summarises safety data of interest from the adalimumab RCTs in AS and nr-axSpA. In addition, the Cochrane review of safety for the biologics has also been summarised and the most recent global safety publication for adalimumab across multiple indications including AS and nr-axSpA has also been included in this section.

Section 2.5 briefly describes the evidence synthesis, the methodology, results and sensitivity analyses for the mixed treatment comparison. A more detailed description of the MTC including the code, box-plots, estimates of model fit and convergence etc. can be found in Appendix 1.

Section 2.6 discusses issues relating to the interpretation of the clinical data, particularly focusing on issues around the following: comparability of the biologic RCTs (heterogeneity), burden of illness, extra-articular manifestations and sequential use of anti-TNFs.

Section 2.7 summarises all the ongoing AbbVie sponsored clinical trials in axial spondyloarthritis (i.e. to include both AS and nr-axSpA).

2.1 Summary of RCT data for all the anti-TNFs

The following tables provide summary information from a comprehensive systematic literature review looking at randomised controlled trials of all the biologics licensed for use in patients with ankylosing spondylitis and non-radiographic axial spondylitis.

The data have been summarised in the following format: Tables 2.1.1, 2.1.2 and 2.1.3 list the main study characteristics including population, design and enrolment criteria. Table 2.1.4 details patient characteristics e.g. age, gender, ethnicity at baseline for individual arms from the included studies. Table 2.1.5 reports the mean (SD) baseline data for a variety of clinical measures *e.g.* BASDAI, BASFI, and BASMI by study arm. Table 2.1.6 highlights changes in treatment during the trial by individual study arms. Table 2.1.7 comprises a summary of outcomes reported and the weeks of follow-up for each included study. Table 2.1.8 reports the number and percentage of ASAS20/40 and BASDAI50 responders from all the trials. Tables 2.1.9 – 2.1.13 detail change in BASDAI score, change in BASMI score, change in BASFI score, change in spinal pain and change in nocturnal pain, respectively. Table 2.1.14 details results from studies that report SF-36 data. Finally Table 2.1.15 reports any other measure of functional capacity not reported in the aforementioned tables.

Table 2.1.1: General study characteristics

Author, Year [Trial name]; Study setting; Study duration (publication type)	Population	Interventions (randomised, n)	Background tx during trial	Number of previous tx and duration	Prior tx (%)
Bao, 2012; Multicentre, China; 24 wks. (abstract & CTR)	Chinese adults with active AS	GOL 50mg/mth (108); PLA (105)	NR	NR	NR[a]
Barkham, 2009; single centre; UK; 16 wks. (full-text)	Adults with active nr-axSpA	IFX iv 5mg/kg/6-8wks (20); PLA (20)	+/- NSAIDs at stable dose	≥ 1 NSAID; No cDMARDs	NSAIDs (90%)
Barkham, 2010; single centre; UK; 12 wks. (full-text)	Adults with active AS	ETN 2x25mg/1wk (20); PLA (20)	+/- NSAID or cDMARD (MTX or SUL) at stable dose	≥ 1 NSAID; ≥ 0 cDMARD	NSAIDs or cDMARDs [MTX, SUL]
Braun 2002; Multicentre; Germany; 12 wks. (full-text)	Adults with active AS	IFX iv 5mg/kg/6-8wks (35); PLA (35)	+/- NSAIDs at stable or reduced dose	≥ 1 NSAID; ≥ 0 cDMARD	NSAIDs, CS or cDMARDs
Braun, 2011 [ASCEND]; Multicentre, International (Asia, Europe, Latin America, Australia, Middle East); 16 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs +/- DMARD	ETN 1x50mg/1wk (379); SUL 2-3gm/day (187)	+/- NSAIDs, oral CS or cDMARD (MTX, HCQ) at stable dose	≥ 1 NSAID at least 3 mths at max tolerated dose; up to 1 previous cDMARD	NSAIDs (88.4%; 85.0%); oral CSs (10.8%; 9.1%); cDMARDs (28.0%; 28.3% [SUL (17.7%; 20.9%)])
Calin, 2004; Multicentre, European; 12 wks. (full-text)	Adults with active AS	ETN 2x25mg/1wk (45); PLA (39)	+/- NSAIDs, CS, cDMARD (MTX, SUL, HCQ)	1 patient in each group took > 1 cDMARD	NSAIDs (89%; 85%); CSs (16%; 15%); cDMARD (36%; 41% [MTX (13%; 13%); SUL (24%; 28%); HCQ (0%, 3%)])
Davis, 2003; Multicentre; International (North America, Europe); 24 wks. (full-text)	Adults with (moderate to severe) active AS	ETN 2x25mg/1wk (138); PLA (139)	+/- NSAIDs, cDMARD (MTX,SUL) or CS +/- standard doses of analgesics at stable dose[a]	≥ 1 NSAID; ≥ 0 cDMARD	NSAIDs (91%; 92%); CSs (13%; 14%); cDMARDs (32%, 31% [MTX (11%; 12%); SUL (21%; 22%); HCQ (2%, 1%)])
Dougados, 2011 [SPINE]; Multicentre; European; 12 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs	ETN 1x50mg/1wk (39); PLA (43)	+ NSAIDs +/- cDMARD (MTX,SUL) at stable dose	≥ 2 NSAIDs for > 3 mths at max recommended / tolerated dose; ≥ 0 cDMARD	NSAID(s); cDMARDs
Dougados, 2013 [AS EARLY]; Multicentre; International (South America, Europe, Asia); 24 wks. = 12 wks. RCT + 12 wks. extension (abstract & CTR)	Adults with active nr-axSpA and inadequate response to NSAIDs	ETN 1x50mg/1wk (106); PLA (109)[b]	+ NSAIDs	≥ 2 NSAIDs	NSAID(s)
Giardina, 2010; Italy; 102 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs	ETN 1x50mg/1wk (25); IFX iv 5mg/kg/6-8wks (25)	+ NSAIDs	≥ 1 NSAID; No cDMARDs	NSAID(s)

Author, Year [Trial name]; Study setting; Study duration (publication type)	Population	Interventions (randomised, n)	Background tx during trial	Number of previous tx and duration	Prior tx (%)
[GO-AHEAD]; Multicentre; 48 wks. =16 wks. RCT + 32 wks. extension (CTR)	Adults with active nr-axSpA	GOL 50mg/mth (NR); PLA (NR)	+ NSAIDs	≥ 1 NSAID at least 30 days at optimal dose	NSAID(s)
Gorman, 2002; Multicentre; USA; 40 wks. = 16 wks.[c] RCT + 24 wks. extension (full-text)	Adults with active AS	ETN 2x25mg/1wk (20); PLA (20)	+/- NSAID, cDMARD (MTX,SUL), gold injections or CSs at stable dose	≥ 0 NSAID; ≥ 0 cDMARD;	NSAIDs (80%; 95%); CSs (25%; 10%); cDMARDs(40%; 35% [MTX or SUL]);
Haibel, 2008; Multicentre; Germany; 52 wks. = 12 wks. + 40 wks. extension (full-text)	Adults with active nr-axSpA and inadequate response /intolerance to NSAIDs	ADA 40mg/2wks (22); PLA (24)	+/- NSAID	≥ 1 NSAID at max dose; 1 patient had previously received short-term IFX	NSAID(s)
Hu, 2012; single centre; China; 24 wks. = 12 wks. RCT + 12 wks. extension (full-text)	Adults with active AS and inadequate response /intolerance to NSAIDs	ADA 40mg/2wks (26); PLA (20)	+/- NSAIDs, oral CS or cDMARD (MTX, SUL) at stable dose	≥ 1 NSAID	NSAIDs, oral CS, cDMARDs (MTX, SUL)
Huang, 2014; Multicentre; China; 24 wks. =12 wks. RCT + 12 wks. extension (full-text)	Chinese adults with active AS and inadequate response /intolerance to NSAIDs	ADA 40mg/2wks (229); PLA (115)	+/- NSAIDs, oral CS or cDMARD (MTX, SUL) or standard analgesics at stable dose	≥ 1 NSAID	NSAIDs (79.5%; 78.3%); CS (3.5%, 4.3%); cDMARDs (58.5%; 60.9% [MTX (22.7%; 21.7%); SUL (52.4%; 56.5%)])
Inman, 2008 [GO-RAISE]; Multicentre; International (North America, Europe, and Asia); 24 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs (+/- cDMARD)	GOL 50mg/mth (138); GOL 50-100mg/mth (140); PLA (78)	+/- NSAIDs, CS or cDMARD (MTX, SUL, HCQ)	≥ 1 NSAID taken for ≥ 3 mths at max tolerated dose; ≥ 0 cDMARD	NSAIDs (89.9%; 87.9%; 92.3%); CSs (18.8%; 12.9%; 16.7%); cDMARDs ([MTX (21.0%; 20.0%; 19.2%); SUL (23.9%; 26.4%; 30.8%); HCQ (1.4%; 0.7%; 2.6%)])
Landewe, 2014 [RAPID-axSpA]; Multicentre; International (Europe, North America, Latin America); 24 wks. Phase 1 of RCT[d] (full-text)	Adults with active axSpA (subgroups: AS and nr-axSpA)	CTZ 200 mg/2wks (111); CTZ 400 mg/4wks (107); PLA(107)	+/- NSAIDs, cDMARDs	≥ 1 NSAID at least 30 days at max tolerated dose; or ≥ 2 wks. each for ≥ 2 NSAIDs	All patients: NSAIDs (87.4%; 88.8%; 86.0%); cDMARDs (27.9%; 29.0%; 35.5%); AS subgroup NSAIDs (91.0%); cDMARDs (35.4%); nr-axSpA subgroup NSAIDs (83.7%); cDMARDs (25.2%)
Maksymowych, 2008 [M03-606]; Multicentre; Canada; 24 wks. (full-text)	Adults with active AS and inadequate response /intolerance to NSAIDs (+/- cDMARD)	ADA 40mg/2wks (38); PLA (44)	+/- NSAIDs, CS or cDMARD (MTX, SUL) at stable dose	≥ 1 NSAID; ≥ 0 cDMARD	NSAIDs (89.5%; 90.9%); CSs (13.2%; 15.9%); cDMARDs (15.8%; 20.5% [MTX (10.5%; 9.1%); SUL (7.9%; 11.4%)]);

Author, Year [Trial name]; Study setting; Study duration (publication type)	Population	Interventions (randomised, n)	Background tx during trial	Number of previous tx and duration	Prior tx (%)
Marzo-Ortega, 2005; Single centre; UK; 30 wks. (full-text)	Adults with active AS	IFX iv 5mg/kg/6-8wks + MTX 10mg/wk. (28); PLA + MTX 10mg (14)	+/- NSAIDs or oral CS at stable dose	≥ 0 NSAID; ≥ 0 cDMARD;	NSAIDs (89%; 86%); cDMARDs (36%; 21%); CSs (18%; 25%)
Mulleman, 2011 [SPAXIM]; Multicentre; France; 18 wks. (full-text)	Adults with AS	IFX iv 5mg/kg/6-8wks + MTX 10mg/wk. (14); IFX iv 5mg/kg/6-8wks (12)	+/- NSAIDs	≥ 0 NSAID	NSAIDs (86%; 67%)
Navarro, 2011 [LOADET]; Multicentre; Spain; 12 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs/CS /cDMARD	ETN 1x50mg/1wk (54); ETN 2x50mg/1wk (54)	+/- NSAIDs, cDMARDs or CSs at stable dose	≥ 2 NSAIDs at max recommended doses for ≥ 3 mths	NSAIDs (88.89%; 83.33%); cDMARDs (27.8%; 29.63%); CSs (9.26%; 11.11%)
Pedersen, 2013; 24 wks. = 12 wks. RCT + 12 wks. extension (abstract)	Adults with active nr-axSpA	ADA 40mg/2wks (27); PLA (25)	+ NSAIDs	≥ 1 NSAID	NSAID(s)
Sieper, 2013 [ABILITY-1]; Multicentre; International (Australia, Europe, North America); 156 wks. = 12 wks. RCT + 144 wks. extension (full-text)	Adults with active nr-axSpA and inadequate response/ contraindication to NSAIDs	ADA 40mg/2wks (95); PLA (97) ATP subgroup[f]: ADA 40mg/2wks (71); PLA (76)	+/- NSAIDs, oral CS, cDMARD (MTX, SUL, HCQ) or AZA at stable dose	≥ 1 NSAID	NSAIDs (79%; 79%); cDMARDs (19%; 17%)
Sieper, 2014 [INFAST]; Multicentre; International (Europe, Asia); 28 wks. (full-text)	Adults with (moderate to severe) active nr-axSpA	IFX iv 5mg/kg/6-8wks (106); PLA (52)	NSAID (NPX oral 1000mg/day)	NSAID naïve or NSAID at sub-optimal dose (<2/3 max dose)	NSAIDs (94.3%; 84.6%)
Song, 2011; Multicentre; Germany; 48 wks. (full-text)	Adults with active SpA and inadequate response to NSAIDs	ETN 2x25mg/1wk (40); SUL 2-3gm/day (or, if intolerance, oral MTX 15-20mg/wk.) (36)	NSAIDs	≥ 1 NSAID; ≥ 0 cDMARD	NSAID(s)
Tam, 2014; Single centre; Hong Kong; 52 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs	GOL 50mg/mth (20); PLA (21)	+/- NSAIDs, oral CS, or cDMARD (MTX, SUL)	≥ 2 NSAIDs for ≥ 3 mths	NSAIDs or COX-2 inhibitors (85%; 100%); oral CS (5%; 0%); cDMARD ([MTX (15%; 14%); SUL (20%; 19%)])
van der Heijde, 2005 [ASSERT]; Multicentre; International (North America, Europe); 96 wks. = 24 wks. RCT + 72 wks. extension (full-text)	Adults with active AS and inadequate response /intolerance to NSAIDs	IFX iv 5mg/kg/6-8wks (201); PLA (78)	+/- NSAIDs +/- analgesics (paracetamol or tramadol)	≥ 1 NSAID	NSAID(s)
van der Heijde, 2006a [ATLAS]; Multicentre; International (USA, Europe); 26 wks. (full-text)	Adults with active AS and inadequate response to NSAIDs (+/- cDMARD)	ADA 40mg/2wks (208); PLA (107)	+/- NSAIDs, oral CS or cDMARD (MTX, SUL, HCQ) at stable dose	≥ 1 NSAID; ≥ 0 cDMARD	NSAIDs (79.8%; 78.5%); oral CSs (12.0%; 5.6%); cDMARDs (19.2%; 20.6% [SUL (12.5%; 14.0%); MTX (9.6%; 7.5%); Other (0%, 0.9%)])

Author, Year [Trial name]; Study setting; Study duration (publication type)	Population	Interventions (randomised, n)	Background tx during trial	Number of previous tx and duration	Prior tx (%)
van der Heijde, 2006b; Multicentre; European; 12 wks. (full-text)	Adults with active AS	ETN 1x50mg/1wk (155); ETN 2x25mg/1wk (150); PLA (51)	+/- NSAIDs, oral CS or cDMARD (MTX, SUL, HCQ) at stable dose	≥ 0 NSAID; ≥ 0 cDMARD	NSAIDs (80.0%; 84.7%; 78.4%); oral CSs (12.3%; 10.7%; 17.6%); cDMARDs (41.9%; 36.7%; 33.3% [MTX, SUL, HCQ])

cDMARD = conventional disease modifying anti-rheumatic drug; CS = corticosteroid; HCQ = hydroxychloroquine; mths = months; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; SUL = sulfasalazine; tx = treatment; wk. = week; wks. = weeks

[a] No detail of background tx reported in the abstract nor on Clinical Trials Register
[b] Standard doses of analgesics (paracetamol, codeine, hydrocodone, oxycodone, tramadol)
[c] Modified intent-to-treat (mITT) numbers
[d] 112 days
[e] Extension to 204 wks. is ongoing but not yet reported in publications
[f] A post-hoc analysis for was also conducted for the Adalimumab Target Population (ATP) i.e. all subjects who had objective evidence of inflammation at Baseline based on a positive MRI (e.g., SPARCC MRI score at Baseline of at least 2 for either the SI joints or the spine) or an elevated CRP at Baseline. Data for the ATP subgroup is from the CSR.

Table 2.1.2: Study design

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Bao, 2012 (abs)	Randomised, placebo-controlled, double-blind, parallel (24 wks.); EE 16 wks.	NR	NR	EE at 16 wks.: PLA patients who had <20% improvement from baseline in both total back pain and morning stiffness measures switched to blinded GOL 50mg/4wks	ITT (all randomised patients)	NR	NR
Barkham, 2009	Randomised, placebo-controlled, double-blind, parallel (16 wks.)	None	Infusions were given at 0, 2, 6 and 12 wks.	None	ITT (all randomised patients)	NR	LOCF used for imputation of missing data
Barkham, 2010	Randomised, placebo-controlled, double-blind, parallel (12 wks.)	None	None	None	ITT (all randomised patients)	ITT (all randomised patients)	ANCOVA with BL value as covariable. Ordinal AS-WIS data was Rasch-transfomed to interval scaling prior to ANCOVA. LOCF used for imputation of missing data
Braun, 2002	Randomised, placebo-controlled, double-blind, parallel (12 wks.)	cDMARDs / oral CSs withdrawn at least 4wks before screening	Infusions were given at 0, 2, 6 and 12 wks.	None	mITT (1 randomised patient who failed to meet the radiographic criteria of the mNYC was excluded)	mITT (1 randomised patient who failed to meet the radiographic criteria of the mNYC was excluded)	Means were compared by ANCOVA with BL as covariable. LOCF used for imputation of missing data

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Braun, 2011 [ASCEND]	Randomised, active-controlled, double-blind, parallel (16 wks.)	Screening period up to 4 wks. (2 wks. to ensure stable NSAIDs or CSs; 4 wks. to ensure stable MTX or HCQ)	Initial dose of 0.5 gm of SUL given orally in 1st wk. of study; dose ↑ increments of 0.5 gm/wk. until target daily dose of 3 gm achieved	Rescue: Patients unable to tolerate daily doses of SUL 2–3 gm, dose ↓ 0.5 gm as needed. Patients in whom ≥ 1.5 gm of SUL/day could not be consistently tolerated were withdrawn from study	mITT (randomised and received ≥ 1 dose; ≥ 1 assessment post-BL)	mITT (randomised and received ≥ 1 dose)	Between-group differences were determined using ANCOVA with BL, tx and pooled site as predictors; LOCF used for imputation of missing data
Calin, 2004	Randomised, placebo-controlled, double-blind, parallel (12 wks.)	Screening period for 4 wks.	None	None	mITT (randomised and received ≥ 1 dose)	mITT (randomised and received ≥ 1 dose)	LOCF used for imputation of missing pts. and ordinal data. Patients who withdrew prematurely were treated as non-responders thereafter for ASAS and other patient reported responses
Davis, 2003	Randomised, placebo-controlled, double-blind, parallel (24 wks.)	None	None	None	mITT (randomised and received ≥ 1 dose)	mITT (randomised and received ≥ 1 dose)	LOCF used for imputation of missing data
Dougados, 2011 [SPINE]	Randomised, placebo-controlled, double-blind, parallel (12 wks.)	Screening period up to 6 wks.	None	Rescue: In case of a painful episode, analgesics such as paracetamol, with or without codeine or dextropropoxyphen, could be used and patient continue on the trial	mITT (randomised, received ≥ 1 dose of study medication and ≥ 1 efficacy measurement post BL)	NR	Mixed model ANCOVA with autoregressive correlation structure with tx groups, visits and their interaction as fixed factors and BL scores as covariate used to analyse cts variables. For binary efficacy variables, generalised estimating equation model with a logit link, a binominal distribution and autoregressive correlation structure was used, with tx groups, visits and their interaction as fixed factors. LOCF used to impute missing data
Dougados, 2013 [AS EARLY] (abs)	Randomised, placebo-controlled, double-blind, parallel (12 wks.); subsequent 12 wks. open-label ETN	NR	NR	Post-RCT extension: After 12 wks. patients switched to open-label ETN	mITT (NR)	NR	ANCOVA models used with BL score, tx, region and sacroiliac joints status at BL (MRI) as variables. LOCF used to impute missing data

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Giardina, 2010	Randomised, placebo-controlled, double-blind, parallel (102 wks.)	None	Infusions were given at 0, 2, 6 wks. and every 6 wks. after for a period of 102 wks.	None	ITT (all randomised patients)	ITT (all randomised patients)	No adjustment reported
GO-AHEAD	Randomised, placebo-controlled, double-blind, parallel (16 wks.), subsequent 32 wks. open-label GOL	NR	NR	Post-RCT extension: After 16 wks. patients switched to open-label GOL	NR	NR	NR
Gorman, 2002	Randomised, placebo-controlled, double-blind, parallel (16 wks.) subsequent 24 wks. open-label ETN	None	None	Post-RCT extension: After 16 wks. patients switched to open-label ETN	ITT (all randomised patients)	ITT (all randomised patients)	No adjustment reported
Haibel, 2008	Randomised placebo-controlled, double-blind, parallel (12 wks.); subsequent 40 wks. open-label ADA	None	None	Post-RCT extension: After 12 wks. patients switched to open-label ADA	ITT (all randomised patients)	ITT (all randomised patients)	ANCOVA models used with BL score as covariable. LOCF used to impute missing data
Hu, 2012	Randomised placebo-controlled, double-blind, parallel (12 wks.); subsequent 12 wks. open-label ADA	None	None	Post-RCT extension: After 12 wks. patients switched to open-label ADA	NR	NR	ANOVA for group comparisons

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Huang, 2014	Randomised placebo-controlled, double-blind, parallel (12 wks.); subsequent 12 wks. open-label ADA	None	None	Post-RCT extension: After 12 wks. patients switched to open-label ADA	mITT (randomised and received ≥ 1 dose)	mITT (randomised and received ≥ 1 dose)	For the primary end-point and other categorical variables, an NRI approach was used at wk. 12 for missing data. Patients without data at wk. 12 were treated as non-responders. For cts variables at wk. 12, missing data were imputed using the LOCF. Differences from BL between ADA and PLA groups were compared using ANCOVA, adjusting for BL score
Inman, 2008 [GO-RAISE]	Randomised, placebo-controlled, double-blind, parallel (24 wks.); EE at 16 wks.	None	None	EE at 16 wks.: patients with < 20% improvement from BL in both total back pain and morning stiffness switched treatment in a double-blind manner: PLA switched to GOL 50 mg; GOL 50mg switched to GOL 100 mg; GOL 100mg continued at the same dose	ITT (all randomised patients)	mITT (excluding one PLA patient who received a GOL 50-mg dose in error)	Changes from BL in cts variables were compared between tx groups using ANOVA on the normal van der Waerden test scores. Logistic regression analysis of ASAS20 response at wk. 14 performed based on tx group, screening CRP level, DMARD use, body weight and duration of AS. LOCF used to impute missing ASAS components for patients who had data for ≥ 1 ASAS component at wk. 14. Patients without data for any of the ASAS components at wk. 14 were considered non-responders. In addition, patients were considered non-responders if before wk. 14 they initiated new DMARDs, or biologic agents, or systemic immunosuppressives; or increased their MTX, SUL, or HCQ dose above BL level; or initiated tx with or increased dose of CSs; or discontinued study tx due to an unsatisfactory therapeutic effect

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Landewe, 2014 [RAPID-axSpA]	Randomised, placebo-controlled, double-blind, parallel (24 wks.); EE at 16 wks.	None	For the CTZ groups, CTZ 400 mg given at wks. 0, 2 and 4 (loading dose) followed by either CTZ 200 mg/2 wks. or CTZ 400 mg every 4 wks.	EE at wks. at 16: patients who did not achieve ASAS20 response at wk. 14 and 16 switched treatment in a blind manner; PLA switched to CTZ; CTZ groups continued on their original randomised treatment	ITT (all randomised patients)	ITT (all randomised patients)	ANCOVA used to analysis changes from BL in quantitative efficacy measures. Tx arm and each of the stratification criteria were included as factors with BL value as a covariate. Missing data due to study withdrawal, any other reason, and all post 16 wk. data for PLA patients escaping were imputed using NRI for ASAS responses and LOCF for BASFI, BASDAI, BASMI linear and ASDAS
Maksymowych, 2008 [M03-606]	Randomised, placebo-controlled, double-blind, parallel (24 wks.); EE at 12, 16 or 20 wks.	None	None	EE at wks. 12, 16 or 20: Patients who failed to achieve ASAS20 response at wks. 12, 16 or 20 switched to open-label ADA	ITT (all randomised patients)	NR	LOCF for 24 wk. data if patient had EE
Marzo-Ortega, 2005	Randomised, placebo-controlled, double-blind, parallel (30 wks.)	Other cDMARDs discontinued at least 4 wks. before BL visit	IFX or PLA infusions were given at 0, 2, 6, 14 and 22 wks. At wk. 0, patients were given a prescription for oral MTX at dose of 7.5mg, which would be increased to 10mg during study	Rescue: Patients who required IA or IM injections of CSs because of an unacceptably high level of disease activity, subjects could be dropped from the study at investigator's discretion	ITT (all randomised patients)	ITT (all randomised patients)	ANCOVA used to analysis change in BASDAI from BL in the two tx groups, using BL BASDAI as a covariate. LOCF used to impute missing data
Mulleman, 2011 [SPAXIM]	Randomised, active-controlled, open-label, parallel (18 wks.)	None	IFX or PLA infusions were given at 0, 2, 6, 12 and 18 wks.	None	ITT (all randomised patients)	NR	No adjustment reported
Navarro, 2011 [LOADET]	Randomised, active-controlled, double-blind, parallel (12 wks.)	Screening period up to 6 wks.	None	Rescue: Suspension of treatment for up to 2 wks. in response to adverse events	mITT (randomised, received ≥ 1 dose of study medication and ≥ 1 efficacy measurement post BL)	mITT (randomised, received ≥ 1 dose of study medication and ≥ 1 efficacy measurement post BL)	No adjustment reported

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
Pedersen, 2013 (abs)	Randomised placebo-controlled, double-blind, parallel (12 wks.); subsequent 12 wks. open-label ADA	NR	NR	Post-RCT extension: After 12 wks. patients switched to open-label ADA	ITT (all randomised patients)	NR	NR
Sieper, 2013 [ABILITY-1]	Randomised placebo-controlled, double-blind, parallel (12 wks.); subsequent 144 wks. open-label ADA	None	None	Rescue: background tx dose reduction as medically required due to an adverse event. Post-RCT extension: After 12 wks. patients switched to open-label ADA	mITT (randomised and received ≥ 1 dose, exclusion of 7 patients from 1 site due to investigator non-compliance)	mITT (randomised and received ≥ 1 dose)	For categorical variables, patients with missing data at wk. 12 were considered to be non-responders using NRI. LOCF imputed values were used for cts variables. ANCOVA adjusting for BL score was used to compare change from BL at wk. 12 between ADA and PLA tx groups
Sieper, 2014 [INFAST]	Randomised, placebo-controlled, double-blind, parallel (28 wks.)	Previous NSAID washed-out ≥ 3 days before BL (increase in total back pain ≥ 30%)	IFX or PLA infusions were given at 0, 2, 6, 12, 18 and 24 wks.	None	mITT (randomised, received ≥ 1 dose of study medication and ≥ 1 efficacy measurement post BL)	mITT (randomised and received ≥ 1 dose)	ANCOVA used to analysis change in cts variables, adjusted for BL. Analyses included observed data. For the primary efficacy analysis, patients who withdrew before wk. 28 were categorised as not achieving partial remission
Song, 2011 [ESTHER]	Randomised, active-controlled, open-label, parallel (48 wks.)	Previous DMARDs or prednisone ≥ 7.5mg/day (or equivalent) discontinued ≥ 4 wks. before initiation of study	None	None	ITT (all randomised patients)	NR	ANCOVA model used, adjusted for BL. LOCF used to impute missing data
Tam, 2014	Randomised, placebo-controlled, double-blind, parallel (52 wks.); EE at 24 wks.	None	None	EE at 24 wks.: patients who failed to achieve an ASAS20 response switched to open-label treatment. PLA switched to open-label GOL. GOL continued on original dose	mITT (randomised and ≥ 1 assessment post-BL)	NR	ANCOVA used to analysis early / delayed GOL vs. PLA; LOCF used to impute missing data

Author, Year [Trial name]	Study design	Trial run-in/ wash-out	Titration	Other protocol-driven change in tx	Efficacy analysis population	Safety population	Endpoint adjustment methods
van der Heijde, 2005 [ASSERT]	Randomised, placebo-controlled, double-blind, parallel (24 wks.) subsequent 72 wks. IFX	None	IFX or PLA infusions were given at 0, 2, 6, 12, and 18 wks.	Rescue: Patients who initiated prohibited anti-inflammatory medications (e.g., systemic CSs, cytotoxic drugs, or cDMARDs) were assessed for tx response based on actual observed values at wk. 24. Post-RCT extension: After 24 wks. patients switched to open-label IFX	ITT (all randomised patients)	mITT (randomised and received ≥ 1 dose)	ANCOVA used for cts measures, covariable not specified. LOCF was used to impute missing data. Patients in whom non–study-related anti-TNF therapy was initiated or who prematurely discontinued study treatment due to lack of efficacy were considered to be non-responders
van der Heijde, 2006a [ATLAS]	Randomised, placebo-controlled, double-blind, parallel (24 wks.); EE at 12, 16 or 20 wks.	Screening period for 2 wks.	None	EE at wks. 12, 16 or 20: Patients who failed to achieve ASAS20 response at wks. 12, 16 or 20 switched to open-label ADA	mITT (randomised and received ≥ 1 dose)	mITT (randomised and received ≥ 1 dose)	ANCOVA used to analysis change in cts variables, adjusted for BL. LOCF used to impute missing data
van der Heijde, 2006b	Randomised, placebo-controlled, double-blind, parallel (12 wks.)	None	None	None	mITT (randomised and received ≥ 1 dose)	mITT (randomised and received ≥ 1 dose)	Demographic and baseline characteristics were analysed using one-way analysis of variance for cts variables. LOCF used to impute missing data

ANOVA = analysis of variance; ANCOVA = analysis of covariance; BL = baseline; cDMARD = conventional disease modifying anti-rheumatic drug; CS = corticosteroid; cts = continuous; EE = early escape; IA = intra-articular; IM = intramuscular; ITT = intent-to-treat; LOCF = last observation carried forward; mITT = modified intent-to-treat; MTX = methotrexate; NRI = non-responder imputation; NSAID = non-steroidal anti-inflammatory drug; tx = treatment; wk. = week; wks. = weeks

Table 2.1.3: Enrolment criteria: definition of active disease

Author, Year [Trial name]	AS (nr-axSpA) criteria[a]	Active disease criteria[b]	(1) BASDAI VAS (0-10)	(2) BASFI VAS (0-10)	(3) Back pain VAS (0-10)	(4) Patient's global assessment of disease activity	(5) Morning stiffness	(6) Other
Bao, 2012 (abs)	NR	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
Barkham, 2009	Calin	(1), (3) & (5)	4 ≤	NR	4 ≤	NR	45 mins ≤	NR
Barkham, 2010	mNYC	2 from (1), (3), (5)	4 ≤	NR	4 ≤	NR	45 mins ≤	NR
Braun, 2002	mNYC	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
Braun, 2011 [ASCEND]	mNYC	(1) & (5) & 2 from (2), (3) & (4)	3 ≤	30 ≤	3 ≤	3 ≤	Composite of duration and intensity VAS 30 ≤	NR
Calin, 2004	mNYC	(5) and 2 from (3), (4), (6)	NR	NR	3 ≤	3 ≤	Composite of duration and intensity VAS 30 ≤	Physical function (VAS) 30 ≤
Davis, 2003	mNYC	(5) and 2 from (2), (3), (4)	NR	30 ≤	3 ≤	3 ≤	Composite of duration and intensity VAS 30 ≤	NR
Dougados, 2011 [SPINE]	mNYC	(1) & (6)	4 ≤	NR	NR	NR	NR	Neck, back or hip VAS 30 ≤
Dougados, 2013 [AS EARLY] (abs)	ASAS	(1) & (6)	4 ≤	NR	NR	NR	NR	Despite tx with NSAIDs
Giardina, 2010	mNYC	(1), (3) & (6)	4 <	NR	4 <	NR	NR	Despite tx with NSAIDs
[GO-AHEAD]	NR	(6)	NR	NR	NR	NR	NR	Chronic back pain ≥3 mths; inadequate response to 30 days of optimal daily doses of ≥ 1 NSAID
Gorman, 2002	mNYC	(5) & (6)	NR	NR	NR	NR	45 mins ≤	Presence of inflammatory back pain (stiffness and pain that worsened with rest and improved with exercise); at least moderate disease activity as assessed by patient 3≤ and physician (VAS 40 ≤)

Author, Year [Trial name]	AS (nr-axSpA) criteria[a]	Active disease criteria[b]	(1) BASDAI VAS (0-10)	(2) BASFI VAS (0-10)	(3) Back pain VAS (0-10)	(4) Patient's global assessment of disease activity	(5) Morning stiffness	(6) Other
Haibel, 2008	See page 22 of NMA report appendix document for more details	(1) & (6)	4 ≤	NR	NR	NR	NR	Despite treatment with NSAIDs
Hu, 2012	mNYC	2 from (1), (3), (5)	4 ≤	NR	4 ≤	NR	60 mins ≤	NR
Huang, 2014	mNYC	2 from (1), (3), (5)	4 ≤	NR	4 ≤	NR	60 mins ≤	NR
Inman, 2008 [GO-RAISE]	mNYC	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
Landewe, 2014 [RAPID-axSpA]	ASAS	(1), (3) & (6)	4 ≤	NR	4 ≤	NR	NR	Chronic back pain ≥ 3 mths; CRP levels > upper limit of normal (ULN=7.9 mg/L) and/or sacroiliitis on MRI according to ASAS/OMERACT definition; previously had an inadequate response, or been intolerant, to ≥ 1 NSAID during ≥ 30 days of continuous therapy (highest tolerated dose) or ≥ 2 wks. each for ≥ 2 NSAIDs
Maksymowych, 2008 [M03-606]	mNYC	2 from (1), (3), (5)	4 ≤	NR	4 ≤	NR	60 mins ≤	NR
Marzo-Ortega, 2005	mNYC	(3) & (6)	NR	NR	3 ≤	NR	NR	CRP > 10mg/l despite optimal dosing with NSAIDs or DMARDs
Mulleman, 2011 [SPAXIM]	mNYC	NR	NR	NR	NR	NR	NR	NR
Navarro, 2011 [LOADET]	mNYC	(1) & at least 1 of (3), (4) or (6).	4 ≤	NR	4 ≤	4 ≤	NR	↑ ESR and/or CRP above normal lab levels
Pedersen, 2013 (abs)	ESSG	(1) & (6)	4 ≤	NR	NR	NR	NR	Despite treatment with NSAIDs

Author, Year [Trial name]	AS (nr-axSpA) criteria[a]	Active disease criteria[b]	(1) BASDAI VAS (0-10)	(2) BASFI VAS (0-10)	(3) Back pain VAS (0-10)	(4) Patient's global assessment of disease activity	(5) Morning stiffness	(6) Other
Sieper, 2013 [ABILITY-1]	ASAS	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	Despite treatment with NSAIDs
Sieper, 2014 [INFAST]	ASAS	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
Song, 2011 [ESTHER]	NR	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
Tam, 2014	mNYC	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
van der Heijde, 2005 [ASSERT]	mNYC	(1) & (3)	4 ≤	NR	4 ≤	NR	NR	NR
van der Heijde, 2006a [ATLAS]	mNYC	2 from (1), (3), (5)	4 ≤	NR	4 ≤	NR	60 mins ≤	NR
van der Heijde, 2006b	mNYC	(5) and 2 from (2), (4), (6)	NR	3 ≤	NR	30 ≤	Composite of duration and intensity VAS 30 ≤	Mean of nocturnal and total pain VAS score 30 ≤

CRP = C-reactive protein; cDMARD = conventional disease modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; ESSG, European Spondyloarthropathy Study Group; mNYC = modified New York criteria; NSAID = non-steroidal anti-inflammatory drug; tx = treatment; VAS = visual analogue scale; wk. = week

[a] Modified New York criteria for AS

- Patients normally fulfilling modified New York criteria (1984) for definitive AS.
- Radiological criterion: Sacroiliitis, grade II bilaterally or grade III to IV unilaterally
- Clinical criteria (two of the following three): low back pain and stiffness for more than three months which improves with exercise but is not relieved by rest; limitation of motion of the lumbar spine in both the sagittal and frontal planes; limitation of chest expansion relative to normal values correlated for age and sex.

[b] BSR criteria for active AS: BSR guidelines for eligibility for treatment with anti-TNFα agents require demonstration of active AS, where:

- Active spinal disease should be defined as BASDAI at least 4 cm and spinal pain VAS (within last week) at least 4 cm. Both recorded on two occasions at least 4 weeks apart, without any change of treatment.
- Failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks

Table 2.1.4: Patient characteristics at baseline by study arm

Author, Year [Trial name]	Study arm	Baseline, n	Age, mean (SD) [SE]	Male, n (%)	White, n (%)	Hispanic, n (%)	Asian, n (%)	Other, n (%)	Duration of disease, years (SD) [SE]
Bao, 2012 (abs)	PLA	105	29	177 (83.1%)	0 (0%)	0 (0%)	105 (100%)	0 (0%)	NR[a]
Bao, 2012 (abs)	GOL 50mg/mth	108	-	-	0 (0%)	0 (0%)	108 (100%)	0 (0%)	NR[a]
Barkham, 2009	PLA	20	28.2	15 (75%)	NR	NR	NR	NR	1.12
Barkham, 2009	IFX iv 5mg/kg/6-8wks	20	29.5	15 (75%)	NR	NR	NR	NR	1.43
Barkham, 2010	PLA	20	39.4 (10.1)	17 (85%)	NR	NR	NR	NR	Median 20 (range 0.6-30)
Barkham, 2010	ETN 2x25mg/1wk	20	40.8 (9.7)	15 (75%)	NR	NR	NR	NR	Median 11 (range 2.1-45)
Braun, 2002	PLA	35	39.0 (9.1)	22 (63%)	NR	NR	NR	NR	14.9 (9.3)
Braun, 2002	IFX iv 5mg/kg/6-8wks	35	40.6 (8.0)	23 (68%)[b]	NR	NR	NR	NR	16.4 (8.3)
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	187	40.9 (12.2)	140 (74.9%)	162 (86.6%)	NR	NR	25 (13.4%)	8.0 (8.9)
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	379	40.7 (11.7)	279 (73.6%)	331 (87.3%)	NR	NR	48 (12.7%)	7.5 (9.5)
Calin, 2004	PLA	39	40.7 (11.4)	30 (77%)	37 (95%)	NR	NR	2 (5%)	9.7 (8.2)
Calin, 2004	ETN 2x25mg/1wk	45	45.3 (9.5)	36 (80%)	42 (93%)	NR	NR	3 (7%)	15.0 (8.8)
Davis, 2003	PLA	139	41.9 (range 18-65)	105 (75.5%)	127 (91.4%)	6 (4.3%)	3 (2.2%)	3 (2.2%)	10.5 (range 0-35.3)
Davis, 2003	ETN 2x25mg/1wk	138	42.1 (range 24-70)	105 (76.1%)	130 (94.2%)	3 (2.2%)	3 (2.2%)	2 (1.4%)	10.1 (range 0-30.7)
Dougados, 2011 [SPINE]	PLA	43	48 (10)	39 (90.7%)	NR	NR	NR	NR	23 (11)
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	39	46 (11)	37 (94.9%)	NR	NR	NR	NR	19 (10)
Dougados, 2013 [AS EARLY] (abs)	PLA	109[c]	32 (range 18-49)	131 (61%)	NR	NR	NR	NR	2.4 (median 2.3; range 0-16.0)
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	106[c]	-	-	NR	NR	NR	NR	-
Giardina, 2010	ETN 1x50mg/1wk	25	32.6 (6.8)	20 (80%)	NR	NR	NR	NR	15.7 (6.5)
Giardina, 2010	IFX iv 5mg/kg/6-8wks	25	31.9 (9.2)	19 (76%)	NR	NR	NR	NR	15.4 (10.6)
[GO-AHEAD]	PLA	NR	NR	NR	NR	NR	NR	NR	NR
[GO-AHEAD]	GOL 50mg/mth	NR	NR	NR	NR	NR	NR	NR	NR
Gorman, 2002	PLA	20	Median 39 (10)	18 (90%)	14 (70%)	NR	NR	6 (30%)	Median 12 (9)
Gorman, 2002	ETN 2x25mg/1wk	20	Median 38 (10)	13 (65%)	15 (75%)	NR	NR	5 (25%)	Median 15 (10)
Haibel, 2008	PLA	24	37 (range 26-54)	12 (50%)	NR	NR	NR	NR	8 (range 1-24)

Author, Year [Trial name]	Study arm	Baseline, n	Age, mean (SD) [SE]	Male, n (%)	White, n (%)	Hispanic, n (%)	Asian, n (%)	Other, n (%)	Duration of disease, years (SD) [SE]
Haibel, 2008	ADA 40mg/2wks	22	38 (range 25-64)	9 (41%)	NR	NR	NR	NR	7 (range 2-16)
Hu, 2012	PLA	20	27.4 (7.2)	20 (100%)	0 (0%)	0 (0%)	20 (100%)	0 (0%)	7.6 (4.6)
Hu, 2012	ADA 40mg/2wks	26	28.2 (6.9)	24 (92.3%)	0 (0%)	0 (0%)	26 (100%)	0 (0%)	7.4 (5.7)
Huang, 2014	PLA	115	29.6 (7.5)	95 (82.6%)	0 (0%)	0 (0%)	115 (100%)	0 (0%)	3.0 (3.2)
Huang, 2014	ADA 40mg/2wks	229	30.1 (8.7)	185 (80.8%)	0 (0%)	0 (0%)	229 (100%)	0 (0%)	3.0 (3.8)
Inman, 2008 [GO-RAISE]	PLA	78	41.0 (range 31.0-50.0)	55 (70.5%)	57 (73.1%)	0 (0%)	18 (23.1%)	3 (3.8%)	16.0 (range 5.0-25.0)
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	138	38.0 (range 30.0-47.0)	102 (73.9%)	103 (74.6%)	0 (0%)	32 (23.2%)	3 (2.2%)	11.0 (range 6.0-18.0)
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	140	38 (range 29.0-46.0)	98 (70.0%)	102 (72.9%)	0 (0%)	35 (25.0%)	3 (2.1%)	9.5 (range 4.0-18.0)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	PLA	107	39.9 (12.4)	65 (60.7%)	NR	NR	NR	NR	7.7 (range 0.3-50.9)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 200 mg/2wks	111	39.1 (11.9)	67 (60.4%)	NR	NR	NR	NR	6.9 (range 0.3-34.2)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 400 mg/4wks	107	39.8 (11.9)	68 (63.6%)	NR	NR	NR	NR	7.9 (range 0.3-44.8)
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*PLA*	*57*	*41.6 (12.8)*	*41 (71.9%)*	*NR*	*NR*	*NR*	*NR*	*10.2 (range 0.3-50.9)*
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*CTZ 200 mg/2wks*	*65*	*41.0 (10.8)*	*47 (72.3%)*	*NR*	*NR*	*NR*	*NR*	*8.8 (range 0.3-32.7)*
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*CTZ 400 mg/4wks*	*56*	*41.9 (11.5)*	*41 (73.2%)*	*NR*	*NR*	*NR*	*NR*	*8.8 (range 0.3-44.8)*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA sub-pop)	*PLA*	*50*	*38.0 (11.8)*	*24 (48.0%)*	*NR*	*NR*	*NR*	*NR*	*4.5 (range 0.5-41.5)*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA sub-pop)	*CTZ 200 mg/2wks*	*46*	*36.6 (13.0)*	*20 (43.5%)*	*NR*	*NR*	*NR*	*NR*	*4.8 (range 0.3-34.2)*
Landewe, 2014	*CTZ 400 mg/4wks*	*51*	*37.5 (10.8)*	*27 (52.9%)*	*NR*	*NR*	*NR*	*NR*	*7.3*

Author, Year [Trial name]	Study arm	Baseline, n	Age, mean (SD) [SE]	Male, n (%)	White, n (%)	Hispanic, n (%)	Asian, n (%)	Other, n (%)	Duration of disease, years (SD) [SE]
[RAPID-axSpA] (nr-axSpA sub-pop)									*(range 0.3-25.3)*
Maksymowych, 2008 [M03-606]	PLA	44	40.0 (10.87)	36 (81.8%)	NR	NR	NR	NR	12.1 (8.65)
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	38	41.9 (11.14)	29 (76.3%)	NR	NR	NR	NR	14.5 (9.02)
Marzo-Ortega, 2005	MTX 10mg/1wk	14	39 (range 30-56)	11 (78.6%)	NR	NR	NR	NR	Median 10 (range 0-35)
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	28	41 (range 28-74)	23 (82.1%)	NR	NR	NR	NR	Median 8 (range 0-41)
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	12	Median 42.5 (range 27-59)	9 (75%)	NR	NR	NR	NR	Median 4.0 (range 0-28)
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	14	Median 45.5 (range 29-55)	11 (79%)	NR	NR	NR	NR	Median 4.5 (range 1-19)
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	54	42.63 (10.66)	43 (79.63%)	NR	NR	NR	NR	7.28 (7.06) (median 4.93)
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	54	40.22 (10.36)	43 (79.63%)	NR	NR	NR	NR	7.03 (6.83) (median 4.76)
Pedersen, 2013 (abs)	PLA	25	Median 37 (Range 23-54)	19 (76%)	NR	NR	NR	NR	Median 6 (range 1-25)
Pedersen, 2013 (abs)	ADA 40mg/2wks	27	Median 41 (Range 23-65)	21 (78%)	NR	NR	NR	NR	Median 13 (range 1-35)
Sieper, 2013 [ABILITY-1]	PLA	97[d]	38.4 (10.4)	40 (43%)	91 (97%)	NR	NR	3 (4%)	10.1 (8.8)
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	95[d]	37.6 (11.3)	44 (48%)	91 (100%)	NR	0 (0%)	0 (0%)	10.1 (9.0)
Sieper, 2013 [ABILITY-1] (ATP subgroup)	PLA	73	38.3 (10.49)	33 (45.2%)	71 (97.3%)	-	0 (0%)	2 (2.7%)	10.5 (9.2)
Sieper, 2013 [ABILITY-1] (ATP subgroup)	ADA 40mg/2wks	69	38.3 (11.70)	32 (46.4%)	69 (100%)	-	0 (0%)	0 (0%)	10.7(9.6)
Sieper, 2014 [INFAST]	PLA	52[e]	30.7 (7.34)	40 (78.4%)	45 (88.2%)	0 (0%)	5 (9.8%)	1 (2.0%)	0.69 (0.647)
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	106[f]	31.7 (8.51)	72 (68.6%)	91 (86.7%)	0 (0%)	14 (13.3%)	0 (0%)	0.84 (0.814)

Author, Year [Trial name]	Study arm	Baseline, n	Age, mean (SD) [SE]	Male, n (%)	White, n (%)	Hispanic, n (%)	Asian, n (%)	Other, n (%)	Duration of disease, years (SD) [SE]
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	40	34.5 (8.6)	23 (57.5%)	NR	NR	NR	NR	2.6 (1.7)
Song, 2011 [ESTHER]	SUL 2-3 gm/day	36	32.8 (8.4)	21 (58.3%)	NR	NR	NR	NR	3.0 (1.8)
Tam, 2014	PLA	21	34.2 (10.0)	19 (90%)	0 (0%)	0 (0%)	21 (100%)	0 (0%)	Median 11.0 (IQR 6.0-17.5)
Tam, 2014	GOL 50mg/mth	20	35.6 (9.93)	18 (90%)	0 (0%)	0 (0%)	20 (100%)	0 (0%)	Median 8.0 (IQR 3.0-17.0)
van der Heijde, 2005 [ASSERT]	PLA	78	Median 41.0 (IQR 34.0-47.0)	68 (87.2%)	76 (97.4%)	NR	NR	NR	Median 13.2 (IQR 3.7-17.9)
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	201	Median 40.0 (IQR 32.0-47.0)	157 (78.1)	197 (98.0%)	NR	NR	NR	Median 7.7 (IQR 3.3-14.9)
van der Heijde, 2006a [ATLAS]	PLA	107	43.4 (11.32)	79 (73.8%)	99 (92.5%)	NR	NR	NR	10.0 (8.34)
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	208	41.7 (11.69)	157 (75.5%)	202 (97.1%)	NR	NR	NR	11.3 (9.99)
van der Heijde, 2006b	PLA	51[e]	40.1 (10.9)	40 (78.4%)	NR	NR	NR	NR	8.5 (6.8)
van der Heijde, 2006b	ETN 2x25mg/1wk	150	39.8 (10.7)	114 (76.0%)	NR	NR	NR	NR	10.0 (9.1)
van der Heijde, 2006b	ETN 1x50mg/1wk	155	41.5 (11.0)	108 (69.7%)	NR	NR	NR	NR	9.0 (8.7)

[a] Diagnosis of active AS for >=3 months prior to screening
[b] 1 patient excluded, n = 34
[c] BL from 215 randomised [215 patients were randomized and included in the mITT population (ETN=106; placebo=109)]
[d] 7 randomised subjects were excluded due to investigator non-compliance, 94 (PLA) and 91 (ADA) treated
[e] 52 were randomised. 1 had no efficacy assessment, so analysis pop was 51
[f] 106 were randomised. 1 did not receive tx, so analysis population was 105
[g] 361 were randomised but no detail given of breakdown into txs; mITT population (356 pts.) received at least one dose of tx
Data in blue: potential imbalance in study arms (See main report [Appendix 1] for discussion)

Table 2.1.5: Patient clinical measures at baseline by study arm

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Bao, 2012 (abs)	PLA	Median 6.65 (IQR: 5.16-7.54)	105 (100%)	Median 4.82 (IQR: 3.19-6.87)	Median 3.57 (IQR: 2.38-4.62)	NR	NR	NR	NR
Bao, 2012 (abs)	GOL 50mg/mth	Median 6.58 (IQR: 5.74-7.40)	108 (100%)	Median 5.26 (IQR: 3.04-6.80)	Median 3.89 (IQR: 2.40-5.36)	NR	NR	NR	NR
Barkham, 2009	PLA	5.76	NR	4.11	NR	NR	NR	Median 11.5	20 (100%)
Barkham, 2009	IFX iv 5mg/kg/6-8wks	5.85	NR	4.42	NR	NR	NR	Median 5	20 (100%)
Barkham, 2010	PLA	5.46 (1.74)	NR	5.27 (1.81)	NR	NR	NR	NR	NR
Barkham, 2010	ETN 2x25mg/1wk	6.05 (1.71)	NR	5.60 (1.98)	NR	NR	NR	NR	NR
Braun, 2002	PLA	6.3 (1.4)	35 (100%)	5.1 (2.2)	3.7 (2.2)	NR	6.9 (1.9)	Median 18 (range 1-74)	27 (88%)
Braun, 2002	IFX iv 5mg/kg/6-8wks	6.5 (1.2)	35 (100%)	5.4 (1.8)	3.7 (2.0)	NR	6.9 (1.8)	Median 24 (range 4-131)	31 (91%)
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	5.91 (1.59)	NR	5.5 (2.08)	3.4 (2.19)	6.16 (2.034)	6.56 (1.78)	15.5 (18.4)	469 (83%)
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	5.93 (1.63)	NR	5.5 (2.02)	3.7 (2.25)	6.31 (2.032)	6.52 (1.87)	17.0 (20.8)	-
Calin, 2004	PLA	5.86	34 (87.18%)	5.72	NR	Nocturnal & total pain 5.61	6.34	Median 97	NR

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Calin, 2004	ETN 2x25mg/1wk	6.1	41 (91.11%)	6.02	NR	Nocturnal & total pain 6	6.56	Median 154	NR
Davis, 2003	PLA	5.96 [0.14]	NR	5.63 (range 1.15-9.70)	NR	6.35 (range 0-9.9)	6.29 (range 0.9-10)	20 (2)	109 (84%)
Davis, 2003	ETN 2x25mg/1wk	5.81 [0.15]	NR	5.17 (range 0.43-9.77)	NR	6.11 (range 0.7-10)	6.29 (range 1.6-10)	19 (2)	108 (84%)
Dougados, 2011 [SPINE]	PLA	5.8 (1.5)	NR	5.7 (1.9)	5.8 (1.3)	6.1 (2.0)	NR	17 (19)	36 (86%)
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	6.4 (1.2)	NR	6.3 (2.0)	5.7 (1.4)	7.0 (1.6)	NR	25 (31)	31 (79%)
Dougados, 2013 [AS EARLY] (abs)	PLA	NR	109 (100%)	NR	NR	NR	NR	NR	NR
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	NR	106 (100%)	NR	NR	NR	NR	NR	NR
Giardina, 2010	ETN 1x50mg/1wk	6.6 (1.1)	25 (100%)	6.5 (1.1)	3.9 (1.7)	6.3 (1.2)	6.7 (1.4)	22.9 (10.5)	24 (96%)
Giardina, 2010	IFX iv 5mg/kg/6-8wks	6.5 (1.2)	25 (100%)	6.1 (0.9)	3.7 (1.6)	6.0 (1.5)	6.4 (1.4)	25 (12.1)	23 (92%)
[GO-AHEAD]	PLA	NR	NR	NR	NR	NR	NR	NR	NR
[GO-AHEAD]	GOL 50mg/mth	NR	NR	NR	NR	NR	NR	NR	NR
Gorman, 2002	PLA	NR	NR	Median 3.2 (2.5)	NR	Median nocturnal 4.65 (2.53)	Median 6.0 (1.4)	Median 15 (12)	18 (90%)
Gorman, 2002	ETN 2x25mg/1wk	NR	NR	Median 4.5 (2.1)	NR	Median nocturnal 6.50 (2.39)	Median 6.0 (1.4)	Median 20 (18)	19 (95%)

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Haibel, 2008	PLA	6.3 (range 4.2-8.9)	NR	4.9 (1.6)	1.3 (1.6)	NR	6.7 (1.5)	7.8 (7.0)	18 (75%)
Haibel, 2008	ADA 40mg/2wks	6.7 (range 4.2-7.9)	NR	5.4 (2.0)	1.3 (1.2)	NR	6.6 (1.7)	6.2 (5.8)	13 (59%)
Hu, 2012	PLA	6.2 (1.1)	NR	3.9 (2.0)	NR	NR	NR	32.1 (29.1)[b]	19 (95.0%)
Hu, 2012	ADA 40mg/2wks	5.9 (1.4)	NR	3.7 (2.1)	NR	NR	NR	24.6 (23.2)	25 (96.2%)
Huang, 2014	PLA	6.2 (1.4)	NR	4.4 (2.3)	3.4 (1.5)	6.7 (1.6)	6.6 (1.9)	High sensitivity CRP 23.0 mg/ml (30.0)	109 (94.8%)
Huang, 2014	ADA 40mg/2wks	6.0 (1.4)	NR	4.3 (2.3)	3.4 (1.4)	6.8 (1.5)	6.4 (1.9)	High sensitivity CRP 22.4 mg/ml (24.0)	219 (95.6%)
Inman, 2008 [GO-RAISE]	PLA	Median 6.6 (range 5.7-7.7)	78 (100%)	Median 4.9 (range 3.5-6.8)	Median 4.0 (range 2.0-5.0)	Median 7.6 (range 6.6-8.8)	Median 7.2 (range 6.2-8.4)	Median 11.5 (range 3.0-24.0)	66 (84.6%)
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	Median 6.6 (range 5.6-7.6)	138 (100%)	Median 5.0 (range 3.2-6.7)	Median 3.0 (range 2.0-4.0)	Median 7.5 (range 5.7-8.2)	Median 7.0 (range 5.9-8.0)	Median 11.0 (range 5.0-25.0)	112 (81.8%)
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	Median 7.0 (range 6.0-7.9)	140 (100%)	Median 5.4 (range 3.4-7.3)	Median 3.0 (range 2.0-5.0)	Median 7.9 (range 6.5-8.8)	Median 7.2 (range 6.0-8.6)	Median 9.0 (range 4.0-25.0)	118 (84.3%)

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	PLA	6.4 (1.7)	NR	5.5 (2.1)	4.0 (1.8)	NR	NR	Median 15.0 min/max (0.1, 156.2)	87 (81.3%)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 200 mg/2wks	6.5 (1.6)	NR	5.3 (2.3)	3.7 (1.6)	NR	NR	Median 12.7 min/max (0.1, 174.8)	87 (78.4%)
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 400 mg/4wks	6.4 (1.5)	NR	5.4 (2.3)	3.8 (1.6)	NR	NR	Median 12.3 min/max (0.1, 159.9)	81 (75.7%)
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*PLA*	*6.4 (1.9)*	*NR*	*6.0 (2.0)*	*4.7 (1.6)*	*NR*	*NR*	*Median 16.6 min/max (1.4, 155.6)*	*48 (84.2%)*
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*CTZ 200 mg/2wks*	*6.5 (1.7)*	*NR*	*5.6 (2.3)*	*4.2 (1.6)*	*NR*	*NR*	*Median 14.0 min/max (0.1, 174.8)*	*53 (81.5%)*
Landewe, 2014 [RAPID-axSpA] (AS sub-pop)	*CTZ 400 mg/4wks*	*6.2 (1.3)*	*NR*	*5.7 (2.3)*	*4.3 (1.8)*	*NR*	*NR*	*Median 12.9 min/max (0.7, 159.9)*	*44 (78.6%)*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA sub-pop)	*PLA*	*6.4 (1.5)*	*NR*	*4.9 (2.2)*	*3.1 (1.6)*	*NR*	*NR*	*Median 13.5 min/max (0.2, 156.2)*	*39 (78.0%)*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA sub-pop)	*CTZ 200 mg/2wks*	*6.5 (1.4)*	*NR*	*4.8 (2.2)*	*3.1 (1.4)*	*NR*	*NR*	*Median 10.0 min/max (2.0, 52.0)*	*34 (73.9%)*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA sub-pop)	*CTZ 400 mg/4wks*	*6.6 (1.6)*	*NR*	*5.1 (2.4)*	*3.3 (1.5)*	*NR*	*NR*	*Median 12.1 min/max (0.1, 120.0)*	*37 (72.5%)*

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Maksymowych, 2008 [M03-606]	PLA	6.5 (1.6)	NR	5.6 (2.2)	3.6 (2.1)	7.17 (1.48)	6.78 (1.91)	23 (26)	36 (81.8%)
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	6.2 (1.7)	NR	5.3 (2.0)	4.0 (2.2)	6.72 (1.67)	6.61 (1.89)	18 (17)	33 (86.8%)
Marzo-Ortega, 2005	MTX 10mg/1wk	Median 6.4 (range 3-10)	NR	Median 6.0 (range 3.8-10)	NR	Day 6.6 (2.4-100) and night 7.65 (3.3-100)	NR	Median 30 (range 13-60)	12 (86%)
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	Median 6.9 (range 2.11-9.26)	NR	Median 6.7 (range 1.9-9.63)	NR	Day 5.75 (1.7-9.6) and night 6.35 (1.1-100)	NR	30.5 (range 10-153)	27 (96%)
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	Median 5.8 (range 3.9-8.4)	NR	NR	NR	NR	NR	Median 3.6 (range 0.5-18.0)	9 (75%)
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	Median 7.0 (range 5.0-8.2)	NR	NR	NR	NR	NR	Median 2.7 (range 0.5-31.2)	10 (71%)
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	6.48 (1.61)	54 (100%)	5.66 (2.04)	3.10 (2.24)	6.30 (2.31)	6.97 (2.02)	20.95 (31.85)	40 (74.07%)
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	6.10 (1.70)	54 (100%)	5.87 (1.96)	3.40 (2.10)	6.74 (2.31)	6.75 (2.05)	17.05 (20.54)	48 (90.57%)
Pedersen, 2013 (abs)	PLA	Median 6.2 (IQR: 4.6-7.2)	25 (100%)	NR	NR	NR	NR	Median 5.3 (range 1.2-131)	17 (77%)
Pedersen, 2013 (abs)	ADA 40mg/2wks	Median 6.0 (IQR: 5.0-6.8)	27 (100%)	NR	NR	NR	NR	Median 10 (range 1.6-50)	26 (96%)

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
Sieper, 2013 [ABILITY-1]	PLA	6.5 (1.6)	91 (96.8%)	4.9 (2.3)	2.7 (1.2)	7.0 (1.7)	6.8 (1.9)	7.6 (10.2)	70 (74%)
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	6.4 (1.5)	88 (96.7%)	4.5 (1.9)	2.7 (1.3)	6.9 (1.8)	6.8 (1.8)	6.8 (11.8)	75 (82%)
Sieper, 2013 [ABILITY-1] (ATP subgroup)	PLA	6.4 (1.5)	71 (97.3%)	4.8 (2.3)	2.7 (1.2)	6.7 (1.7)	6.6 (1.9)	9.3 (10.9)	58 (43.8%)
Sieper, 2013 [ABILITY-1] (ATP subgroup)	ADA 40mg/2wks	6.4 (1.55)	66 (95.7%)	4.5 (2.1)	2.7 (1.4)	7.0 (1.9)	7.0 (1.8)	8.6 (13.1)	56 (81.2%)
Sieper, 2014 [INFAST]	PLA	6.3	52 (100%)	5.4	3.1	7.66	7.23	16.5	47 (90.4%)
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	6.4	106 (100%)	5.3	3.1	7.67	7.35	20.2	87 (82.1%)
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	5.5 (1.3)	40 (100%)	4.3 (2.3)	1.9 (1.7)	NR	6.7 (2.1)	11.9 (13.2)	34 (85%)
Song, 2011 [ESTHER]	SUL 2-3 gm/day	6.0 (1.2)	36 (100%)	4.3 (1.8)	1.7 (1.4)	NR	7.1 (1.6)	10.6 (14.9)	28 (77.8%)
Tam, 2014	PLA	6.17 (1.52)	21 (100%)	4.1 (2.32)	Median 3.0 (IQR 2.0-5.5)	Median 7 (IQR 6-8)	6.38 (1.75)	19.9 (14.0)	NR
Tam, 2014	GOL 50mg/mth	6.15 (1.02)	20 (100%)	4.61 (1.85)	Median 5.0 (IQR 4.0-7.0)	Median 7 (IQR 6.25-8)	6.15 (1.98)	23.9 (18.6)	NR
van der Heijde, 2005 [ASSERT]	PLA	Median 6.5 (IQR 5.2-7.1)	78 (100%)	Median 6.0 (IQR 4.1-7.2)	Median 4.0 (IQR 2.0-6.0)	Night median 6.7 (IQR 4.7-7.9)	Median 6.7 (IQR 5.8-7.7)	Median 17 (IQR 7-33)	69 (88.5%)
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	Median 6.6 (IQR 5.3-7.6)	201 (100%)	Median 5.7 (IQR 4.5-7.1)	Median 4.0 (IQR 2.0-5.0)	Night median 6.6 (IQR 4.8-8.1)	Median 6.9 (IQR 5.7-8.0)	Median 15 (IQR 7-32)	173 (86.5%)

Author, Year [Trial name]	Study arm	BASDAI score, mean (SD) [SE]	BASDAI >=4, n (%)[a]	BASFI score, mean (SD) [SE]	BASMI score, mean (SD) [SE]	Spinal pain VAS, mean (SD) [SE]	Global Assessment, mean (SD) [SE]	CRP (mg/L),* mean (SD) [SE]	HLA-B27 +ve, n (%)
van der Heijde, 2006a [ATLAS]	PLA	6.3 (1.7)	NR	5.6 (2.2)	4.2 (2.1)	6.7 (2.2)	6.5 (2.0)	22 (29)	85 (79.4%)
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	6.3 (1.7)	NR	5.2 (2.2)	3.8 (2.2)	6.4 (2.1)	6.3 (2.2)	18 (22)	163 (78.4%)
van der Heijde, 2006b	PLA	6.11 (1.37)	NR	5.97 (1.93)	NR	6.31 (1.84)	6.62 (1.63)	22.0 (22.9)	NR
van der Heijde, 2006b	ETN 2x25mg/1wk	5.94 (1.67)	NR	5.77 (2.01)	NR	6.35 (2.11)	6.54 (1.81)	19.8 (20.8)	NR
van der Heijde, 2006b	ETN 1x50mg/1wk	6.24 (1.70)	NR	6.06 (2.03)	NR	6.39 (1.92)	6.81 (1.89)	21.7 (24.6)	NR

[a] If the trial entry criteria state that patients were required to have BASDAI>=4cm and no other data provided, then it is assumed 100% were in this category
[b] CRP labelled as mg/L, but it was noted that these figures are much higher than other studies
Note that for studies where any of BASDAI, BASFI, Spinal pain VAS or Global assessment were reported on a 0-100 (mm) scale, the data were converted to a 0-10 (cm) scale. Similarly for studies reporting CRP in mg/dL, the data were converted to mg/L; blue cells, characteristic is noticeably different between study arms

* Please note that elevated CRP at BL has been shown to be the best predictor of response. As normal vs abnormal CRP is determined by a specific assay and these studies did not all use the same assay mean/median CRP may be difficult to understand in the context of this table as these values do not indicate how many subjects had elevated CRP levels above normal.

Table 2.1.6: Summary of change in treatment during trial by study arm

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
Bao, 2012 (abs)	PLA	105	EE at 16 weeks: Patient with <20% improvement from BL in both total back pain and morning stiffness	PLA switch to GOL 50mg/4wks at wk. 16	NR	None	NR
Bao, 2012 (abs)	GOL 50mg/mth	108		GOL 50mg/4wks no switch at wk. 16	NR	None	NR
Barkham, 2009	PLA	20	None	None	None	None	NR
Barkham, 2009	IFX iv 5mg/kg/6-8wks	20	None	None	None	None	NR
Barkham, 2010	PLA	20	None	None	None	None	NR
Barkham, 2010	ETN 2x25mg/1wk	20	None	None	None	None	NR
Braun, 2002	PLA	35	None	None	None	None	NR
Braun, 2002	IFX iv 5mg/kg/6-8wks	35	None	None	None	None	NR
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	187	Rescue: Patients unable to tolerate daily doses of SUL 2–3 gm,	SUL: dose ↓ 0.5 gm as needed; Patient withdrawn if ≥ 1.5 gm of SUL/day not tolerated	NR	None	NR
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	379		ETN: No rescue	0 (0%)	None	NR
Calin, 2004	PLA	39	None	None	None	None	NR

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
Calin, 2004	ETN 2x25mg/1wk	45	None	None	None	None	NR
Davis, 2003	PLA	139	None	None	None	None	NR
Davis, 2003	ETN 2x25mg/1wk	138	None	None	None	None	NR
Dougados, 2011 [SPINE]	PLA	43	Rescue: Painful episode during the study	Analgesics such as paracetamol, with / without codeine or dextropropoxyphene; no withdrawal	NR	None	NR
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	39			NR	None	NR
Dougados, 2013 [AS EARLY] (abs)	PLA	109	None	None	None	After 12 wk. randomised phase, patients switched to open-label ETN for further 12 wks.	108 [41/67]
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	106	None	None	None		105 [53/52]
Giardina, 2010	ETN 1x50mg/1wk	25	None	None	None	None	NA
Giardina, 2010	IFX iv 5mg/kg/6-8wks	25	None	None	None	None	NA
[GO-AHEAD]	PLA	NR	None	None	None	After 16 wk. randomised phase, patients switched to open-label GOL for further 32 wks.	NR
[GO-AHEAD]	GOL 50mg/mth	NR	None	None	None		NR
Gorman, 2002	PLA	20	None	None	None	After 16 wk. randomised phase, patients switched to	18

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
Gorman, 2002	ETN 2x25mg/1wk	20	None	None	None	open-label ETN for further 24 wks[a]	19
Haibel, 2008	PLA	24	None	None	None	After 12 wk. randomised phase, patients switched to open-label ADA for further 40 wks.	24 [6/18]
Haibel, 2008	ADA 40mg/2wks	22	None	None	None		22 [15/7]
Hu, 2012	PLA	20	None	None	None	After 12 wk. randomised phase, patients switched to open-label ADA for further 12 wks.	20
Hu, 2012	ADA 40mg/2wks	26	None	None	None		26
Huang, 2014	PLA	115	None	None	None	After 12 wk. randomised phase, patients switched to open-label ADA for further 12 wks.	229 [154/75]
Huang, 2014	ADA 40mg/2wks	229	None	None	None		115 [35/80]
Inman, 2008 [GO-RAISE]	PLA	78	EE at 16 wks.: patient with < 20% improvement from BL in both total back pain and morning stiffness	PLA switched to GOL 50 mg (double-blind)	41 (53%)	None	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	138		GOL dose ↑ to 100 mg (double-blind)	25 (18%)	None	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	140		GOL continued at same dose (double-blind)	NA	None	NR

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	PLA	107	EE at wks. 16: patients who failed to achieve ASAS20 response	PLA randomised switch to either CTZ 200 mg/2wks or 400 mg/4wks (blinded)	56 (52%)	None	NR
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 200 mg/2wks	111		No switch at wk. 16 (blinded)		None	NR
Landewe, 2014 [RAPID-axSpA] *(All SpA)*	CTZ 400 mg/4wks	107		No switch at wk. 16 (blinded)		None	NR
Maksymowych, 2008 [M03-606]	PLA	44	EE at wks. 12,16 or 20: patients who failed to achieve ASAS20 response	Open label ADA 40mg/2wks	NR	NR	NR
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	38		Open label ADA 40mg/2wks	NR	NR	NR
Marzo-Ortega, 2005	MTX 10mg/1wk	14	Rescue: patients who required IA or IM injections of CSs because of an unacceptably high level of disease activity	Withdrawal from study at investigator's discretion	NR	None	NR
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	28			NR	None	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	12	None	None	None	None	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	14	None	None	None	None	NR
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	54	Rescue: Response to adverse events	Tx suspension for <2 weeks	0 (0%)[b]	None	NR
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	54			1 (1.85%)[c]	None	NR

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
Pedersen, 2013 (abs)	PLA	25	None	None	None	After 12 wks. Randomised phase, patients switched to open-label ADA for further 12 wks.	21 [17/4]
Pedersen, 2013 (abs)	ADA 40mg/2wks	27	None	None	None		25 [11/14]
Sieper, 2013 [ABILITY-1]	PLA	94	None	None	None	After 12 wks. Randomised phase, patients switched to open-label ADA for further 144 wks.	NR
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	91			None		NR
Sieper, 2014 [INFAST]	PLA	51	None	None	None	None	NR
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	105	None	None	None	None	NR
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	40	None	None	None	None	NR
Song, 2011 [ESTHER]	SUL 2-3 gm/day	36	Rescue: Intolerance to SUL	SUL switched to MTX 15mg/week	4 (11.1%)	None	NR
Tam, 2014	PLA	21	EE at 24 weeks: patients who failed to achieve ASAS20 response	PLA switched to open label GOL 50mg/mth	17 (81%)	None	NR
Tam, 2014	GOL 50mg/mth	20		Open label GOL 50mg/mth	8 (40%)	None	NR

Author, Year [Trial name]	Study arm at baseline	Randomised, n	Rescue/ early escape design	Rescue/ switch tx	Rescued/ switched tx, n (%)	Open-label extension	Study extension, n [responders / non-responders]
van der Heijde, 2005 [ASSERT]	PLA	78	Rescue: Patients initiated on prohibited anti-inflammatory medications	Systemic CSs, cytotoxic drugs, or cDMARDs added to background treatment	None	After 24 wk. randomised phase, patients switched to open-label IFX for further 72 wks[d]	76 [*15/61*]
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	201	None	None	None		201 [*123/78*]
van der Heijde, 2006a [ATLAS]	PLA	107	EE at weeks 12,16 or 20: patients who failed to achieve ASAS20 response	PLA switched to open label ADA 40mg/2wks	55 (51.4%)	Up to five years in OLE.	NR
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	208		Open label ADA 40mg/2wks	54 (26.0%)	None	NR
van der Heijde, 2006b	PLA	51	None	None	None	None	NR
van der Heijde, 2006b	ETN 2x25mg/1wk	150	None	None	None	None	NR
van der Heijde, 2006b	ETN 1x50mg/1wk	155	None	None	None	None	NR

BL = baseline; EE = early escape; IA = intra-articular; IM = intramuscular; LEF = Leflunomide
[a] During open-label extension period, dose decreased or discontinued in 66% of patients receiving oral CS, 63% of patients receiving MTX and 73% of patients receiving NSAIDs
[b] 2 patients had tx suspended, they were then withdrawn from the trial
[c] 1 suspended then reintroduced
[d] Sixty-one (78.2%) patients who were randomized to PLA and 166 (82.6%) randomised to IFX completed the study through 102 wks.

Table 2.1.7: Summary of outcomes reported by study and weeks of follow-up

Unique study ID	Comparators	Population	ASAS20	ASAS40	BASDAI50	BASDAI score	BASDAI <4	BASMI score	BASFI score	Spinal pain	Night pain	AEs	Disc
Bao, 2012 (abs)	GOL	AS	**14,** 24	24	24			14	14			24	
Barkham, 2009	IFX	nr-axSpA		**16**		16			16			16	16
Barkham, 2010	ETN	AS		**12**	**12**	12	12		12			12	12†
Braun, 2002	IFX	AS	**12**		**12**	12		12	12			12	12
Braun, 2011 [ASCEND]	ETN v SUL	AS	16	16		16		16	16	16	16	16	16
Calin, 2004	ETN	AS	**12**			12	12		12	Spinal + night pain: 12		12	12
Davis, 2003	ETN	AS	**12**, 24			24			24	24		24	12, 24
Dougados, 2011 [SPINE]	ETN	AS	**12**	**12**	**12**	12		12	12	12		12	12
Dougados, 2013 [AS EARLY] (abs)	ETN	nr-axSpA	**12**	**12**		12		12	12			12	12
Giardina, 2010	ETN v IFX	AS	**12,** 24	**12,** 24		12, 24			12, 24			12	12, 24
[GO-AHEAD]	GOL	nr-axSpA	14 not published										
Gorman, 2002	ETN	AS	**16**						16		16	16	16
Haibel, 2008	ADA	nr-axSpA	**12**	**12**	**12**	12		12	12	12	12	12	12
Hu, 2012	ADA	AS				12			12				
Huang, 2014	ADA	AS	**12**	**12**	**12**				12	12		12	12
Inman, 2008 [GO-RAISE]	GOL	AS	**14,** 24	**14,** 24	**14,** 24	14, 24		14, 24	14, 24	14, 24	14, 24	16, 24	16, 24
Landewe, 2014 [RAPID-axSpA]	CTZ	AS / nr-axSpA	**12**, 24	**12**, 24	**12,** 24	12		12	12			24	24
Maksymowych, 2008 [M03-606]	ADA	AS	**12,** 24			12, 24		12, 24	12, 24	12, 24	12, 24		12, 24
Marzo-Ortega, 2005	IFX + MTX v MTX	AS	10, 30			30			30		30	30	30

Unique study ID	Comparators	Population	ASAS20	ASAS40	BASDAI50	BASDAI score	BASDAI <4	BASMI score	BASFI score	Spinal pain	Night pain	AEs	Disc
Mulleman, 2011 [SPAXIM]	IFX + MTX v IFX	AS	18			18							
Navarro, 2011 [LOADET]	ETN (v u/l ETN)	AS	12	12	12	12	12	12	12	12	12	12	12
Pedersen, 2013 (abs)	ADA	nr-axSpA	**12**	**12**	**12**								12
Sieper, 2013 [ABILITY-1]	ADA	nr-axSpA	**12***	**12**	**12**	12		12	12	12		12	12
Sieper, 2014 [INFAST]	IFX	nr-axSpA	**18**, 28	18, 28	28	18	BASDAI <3	28	18, 28	28	28	28	28
Song, 2011 [ESTHER]	ETN v SUL	AS / nr-axSpA	48	48	48	24, 48		24, 48	24, 48				48
Tam, 2014	GOL	AS	26			26		26	26	26			26
van der Heijde, 2005 [ASSERT]	IFX	AS	**12,** 24	**12,** 24	24	24		24			24	24	24
van der Heijde, 2006a [ATLAS]	ADA	AS	**12,** 24	**12,** 24	**12**, 24	12		12	12	12	12	24	12, 24
van der Heijde, 2006b	ETN	AS	**12**	**12**	**12**	12						12	12

Key: underlined = priority outcomes/time points for the economic model; **bold** = included in the meta-analysis base case; grey, excluded from meta-analysis; u/l unlicensed; † not reported separately by study arm;
*This endpoint also has data from the post-hoc analysis of the ATP subgroup

Table 2.1.8: ASAS20/40 and BASDAI 50

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which BASDAI50 measured	BASDAI50, n	BASDAI50, %	Number in which ASAS measured	ASAS20, n	ASAS20, %	ASAS40, n	ASAS40, %
Bao, 2012 (abs)	PLA	14	NR			105	26	24.8	NR	NR
Bao, 2012 (abs)	GOL 50mg/mth	14	NR			108	53	49.1	NR	NR
Bao, 2012 (abs)	PLA	24	105	14	13.3	105	24	22.9	14	13.3
Bao, 2012 (abs)	GOL 50mg/mth	24	108	36	33.3	108	54	50	36	33.3
Barkham, 2009	PLA	16	NR			17	NR	NR	3	17.6
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR			18	NR	NR	11	61.1
Barkham, 2010	PLA	12	20	1	5	12	NR	NR	0	*0*
Barkham, 2010	ETN 2x25mg/1wk	12	20	7	35	11	NR	NR	4	*36*
Braun, 2002	PLA	12	35	*3*	9	35	10	*28*	NR	NR
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	*18*	53	34	23	*68*	NR	NR
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	NR			187	*99*	52.9	*61*	32.6
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	NR			378	*287*	75.9	*226*	59.8
Calin, 2004	PLA	12	NR			39	9	*23*	NR	NR
Calin, 2004	ETN 2x25mg/1wk	12	NR			45	26	*58*	NR	NR
Davis, 2003	PLA	12	NR			139	39	28	NR	NR
Davis, 2003	ETN 2x25mg/1wk	12	NR			138	82	59	NR	NR
Davis, 2003	PLA	24	NR			139	31	22	NR	NR
Davis, 2003	ETN 2x25mg/1wk	24	NR			138	78	57	NR	NR
Dougados, 2011 [SPINE]	PLA	12	43	10	23.26	43	14	32.56	10	23
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	18	46.15	39	25	66.67	17	44
Dougados, 2013 [AS EARLY] (abs)	PLA	12	NR			108	41	38	17	15.7
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	NR			105	53	50.5	34	32.4
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR			25	19	75	*14*	55
Giardina, 2010	ETN 1x50mg/1wk	12	NR			25	15	60	*11*	43
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR			25	*18*	72.7	*13*	51.8

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which BASDAI50 measured	BASDAI50, n	BASDAI50, %	Number in which ASAS measured	ASAS20, n	ASAS20, %	ASAS40, n	ASAS40, %
Giardina, 2010	ETN 1x50mg/1wk	24	NR			25	*16*	65.0	*12*	46.4
[GO-AHEAD]	PLA	NR	NR			NR				
[GO-AHEAD]	GOL 50mg/mth	NR	NR			NR				
Gorman, 2002	PLA	16	NR			20	6	30	NR	NR
Gorman, 2002	ETN 2x25mg/1wk	16	NR			20	16	80	NR	NR
Haibel, 2008	PLA	12	24	*5*	21	24	*6*	25	*3*	12.5
Haibel, 2008	ADA 40mg/2wks	12	22	*11*	50	22	*15*	68.2	*12*	54.5
Hu, 2012	PLA	NR	NR			NR				
Hu, 2012	ADA 40mg/2wks	NR	NR			NR				
Huang, 2014	PLA	12	115	19	16.5	115	35	30.4	11	9.6
Huang, 2014	ADA 40mg/2wks	12	229	114	49.8	229	154	67.2	102	44.5
Inman, 2008 [GO-RAISE]	PLA	14	78	12	15.4	78	17	*21.79*	12	*15.38*
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	61	45.9	138	82	*59.42*	62	*44.93*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	56	40.9	140	84	*60*	*68*	48.6
Inman, 2008 [GO-RAISE]	PLA	24	78	11	14.7	78	18	*23.08*	*12*	15.0
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	66	50.8	138	77	*55.80*	*60*	43.1
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	66	47.8	140	92	*65.71*	*76*	54.0

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which BASDAI50 measured	BASDAI50, n	BASDAI50, %	Number in which ASAS measured	ASAS20, n	ASAS20, %	ASAS40, n	ASAS40, %
Landewe, 2014 [RAPID-axSpA]	PLA	12	107	*14*	13.2	107	*41*	38.3	*19*	17.8
Landewe, 2014 [RAPID-axSpA]	CTZ 200 mg/2wks	12	111	*50*	45.0	111	*64*	57.7	*48*	43.2
Landewe, 2014 [RAPID-axSpA]	CTZ 400 mg/4wks	12	107	*47*	43.9	107	*68*	63.6	*52*	48.6
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	NR			57	*21*	36.8	*11*	19.3
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	NR			65	*37*	56.9	*26*	40.0
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	NR			56	*36*	64.3	*28*	50.0
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	NR			50	*20*	40.0	*8*	16.0
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	NR			46	*27*	58.7	*22*	47.8
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	NR			51	*32*	62.7	*24*	47.1
Landewe, 2014 [RAPID-axSpA]	PLA	24	107	*19*	17.9	107	*30*	28.0	NR	NR
Landewe, 2014 [RAPID-axSpA]	CTZ 200 mg/2wks	24	111	*56*	50.5	111	*73*	66.0	NR	NR
Landewe, 2014 [RAPID-axSpA]	CTZ 400 mg/4wks	24	107	58	54.2	107	*75*	70.0	NR	NR
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	NR			57	*19*	33.3	*9*	15.8
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	NR			65	*44*	67.7	*31*	47.7
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	NR			56	*39*	69.6	*33*	58.9
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	NR			50	*12*	24.0	*7*	14.0
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	NR			46	*30*	65.2	*26*	56.5
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	NR			51	*36*	70.6	*23*	45.1
Maksymowych, 2008 [M03-606]	PLA	12	NR			44	12	*27.27*	NR	NR
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	NR			38	18	*47.37*	NR	NR
Maksymowych, 2008 [M03-606]	PLA	24	NR			44	7	*15.91*	NR	NR
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	NR			38	13	*34.21*	NR	NR
Marzo-Ortega, 2005	MTX 10mg/1wk	10	NR			14	*4*	28	NR	NR

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which BASDAI50 measured	BASDAI50, n	BASDAI50, %	Number in which ASAS measured	ASAS20, n	ASAS20, %	ASAS40, n	ASAS40, %
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	NR			27	*19*	71	NR	NR
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR			14	*3*	21	NR	NR
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR			27	*14*	50	NR	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	NR			12	7	NR	NR	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	NR			14	10	NR	NR	NR
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	49	*31*[a]	63[a]	49	37	76	25	*51.0*
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	48	*32*	67	48	34	71	25	*52.1*
Pedersen, 2013 (abs)	PLA	12	25	6	24	25	11	44	7	28
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	27	13	48	27	17	63	15	56
Sieper, 2013 [ABILITY-1]	PLA	12	94	14	15	94	29	31	14	15
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	91	32	35	91	47	52	33	36
Sieper, 2013 [ABILITY-1] (ATP subgroup)	PLA	12	73	10	13.7	73	23	31.5	10	13.7
Sieper, 2013 [ABILITY-1] (ATP subgroup)	ADA 40mg/2wks	12	69	27	39.1	69	41	59.4	28	40.6
Sieper, 2014 [INFAST]	PLA	18	NR			51	*39*	76.5	*27*	52.9
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	NR			105	*87*	82.9	*82*	78.1
Sieper, 2014 [INFAST]	PLA	28	51	*26*	51.1	51	*37*	72.5	*29*	56.9
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	105	*81*	77.3	105	*85*	81.0	*79*	75.2
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	36	*10*	28	36	*15*	42	*11*	31
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	40	*26*	65	40	*34*	85	*28*	70
Tam, 2014	PLA	26	NR			21	3	14	NR	NR
Tam, 2014	GOL 50mg/mth	26	NR			20	11	55	NR	NR
Tam, 2014	PLA	52	NR			21	1	*5*	NR	NR
Tam, 2014	GOL 50mg/mth	52	NR			20	18	*90*	NR	NR
van der Heijde, 2005 [ASSERT]	PLA	12	NR			78	15	*19*	*9*	12
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	12	NR			201	126	*63*	*96*	48

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which BASDAI50 measured	BASDAI50, n	BASDAI50, %	Number in which ASAS measured	ASAS20, n	ASAS20, %	ASAS40, n	ASAS40, %
van der Heijde, 2005 [ASSERT]	PLA	24	78	8	10.7	78	15	19.2	9	12.0
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	101	51.0	201	123	61.2	93	47.0
van der Heijde, 2006a [ATLAS]	PLA	12	107	17	15.9	107	22	20.6	*14*	13.1
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	94	45.2	208	121	58.2	*83*	39.9
van der Heijde, 2006a [ATLAS]	PLA	24	107	16	15.0	107	*21*	19.9	*14*	13.1
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	88	42.3	208	*104*	50.2	*82*	39.4
van der Heijde, 2006b	PLA	12	51	*10*	19.6	51	*19*	37.3	*11*	21.6
van der Heijde, 2006b	ETN 2x25mg/1wk	12	150	*87*	58.0	150	*107*	71.3	*80*	53.3
van der Heijde, 2006b	ETN 1x50mg/1wk	12	155	*93*	60.0	155	*115*	74.2	*90*	58.1

[a] It was noted that % reported in text does not correspond to % at week 12 in Fig 3 B
NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.9: BASDAI score

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASDAI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Bao, 2012 (abs)	PLA	14	NR						
Bao, 2012 (abs)	GOL 50mg/mth	14	NR						
Barkham, 2009	PLA	16	19	5.76	NR	-	-	-	-
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	20	5.85	NR	*-2.66*	*0.79*	*-4.21*	*-1.11*
Barkham, 2010	PLA	12	20	5.46	1.74	-	-	-	-
Barkham, 2010	ETN 2x25mg/1wk	12	20	6.05	1.71	*-1.87*	*0.73*	*-3.29*	*-0.45*
Braun, 2002	PLA	12	35	6.30	1.40	-	-	-	-
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	6.50	1.20	-2.70	*0.54*	-3.70	-1.60
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	59.10	15.90	-	-	-	-
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	59.30	16.30	*-1.22*	*0.31*	*-1.83*	*-0.61*
Calin, 2004	PLA	12	39	58.60	NR	-	-	-	-
Calin, 2004	ETN 2x25mg/1wk	12	45	61.00	NR	*-1.63*	*0.48*	*-2.57*	*-0.69*
Davis, 2003	PLA	24	139	59.60	[1.4]	-	-	-	-
Davis, 2003	ETN 2x25mg/1wk	24	138	58.10	[1.5]	*-2.06*	*0.29*	*-2.63*	*-1.49*
Dougados, 2011 [SPINE]	PLA	12	43	58.00	15.00	-	-	-	-
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	64.00	12.00	*-0.80*	*0.29*	*-1.38*	*-0.22*
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	NR	NR	-	-	-	-
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	NR	NR	*-0.70*	*0.38*	*-1.44*	*0.04*
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	25	6.50	1.20	-	-	-	-
Giardina, 2010	ETN 1x50mg/1wk	12	25	6.60	1.10	*2.10*	NR	NR	NR
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	25	6.50	1.20	-	-	-	-
Giardina, 2010	ETN 1x50mg/1wk	24	25	6.60	1.10	*1.07*	NR	NR	NR
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASDAI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Gorman, 2002	PLA	16	NR						
Gorman, 2002	ETN 2x25mg/1wk	16	NR						
Haibel, 2008	PLA	12	24	6.20	1.30	-	-	-	-
Haibel, 2008	ADA 40mg/2wks	12	22	6.50	1.20	*-1.20*	*0.55*	*-2.29*	*-0.11*
Hu, 2012	PLA	12	20	6.20	1.10	-	-	-	-
Hu, 2012	ADA 40mg/2wks	12	26	5.90	1.40	*-1.90*	*0.68*	*-3.23*	*-0.57*
Huang, 2014	PLA	12	NR						
Huang, 2014	ADA 40mg/2wks	12	NR						
Inman, 2008 [GO-RAISE]	PLA	14	78	(6.6)	NR	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	(6.6)	NR	*-2.18*	NR	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	(7)	NR	*-1.64*	NR	NR	NR
Inman, 2008 [GO-RAISE]	PLA	24	78	(6.6)	NR	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	(6.6)	NR	*-2.00*	NR	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	(7)	NR	*-1.90*	NR	NR	NR
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	57	6.40	1.90	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	65	6.50	1.70	*-1.50*	*0.44*	*-2.37*	*-0.63*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	56	6.20	1.30	*-1.40*	*0.41*	*-2.21*	*-0.59*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	50	6.40	1.50	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	46	6.50	1.40	*-1.80*	*0.53*	*-2.84*	*-0.76*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	51	6.60	1.60	*-1.90*	*0.56*	*-3.00*	*-0.80*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	57	6.4	1.90	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	65	6.5	1.70	*-1.90*	*0.56*	*-3.00*	*-0.80*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	56	6.2	1.30	*-1.90*	*0.56*	*-3.00*	*-0.80*

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASDAI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	50	6.4	1.50	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	46	6.5	1.40	*-2.30*	*0.68*	*-3.63*	*-0.97*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	51	6.6	1.60	*-2.20*	*0.65*	*-3.47*	*-0.93*
Maksymowych, 2008 [M03-606]	PLA	12	44	6.50	1.60	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	6.20	1.70	*-1.70*	*0.58*	*-2.84*	*-0.56*
Maksymowych, 2008 [M03-606]	PLA	24	44	6.50	1.60	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	6.20	1.70	*-1.90*	*0.63*	*-3.14*	*-0.66*
Marzo-Ortega, 2005	MTX 10mg/1wk	10	14	6.57	2.05	-	-	-	-
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	28	6.45	1.87	*-1.14*	*0.72*	*-2.55*	*0.27*
Marzo-Ortega, 2005	MTX 10mg/1wk	30	12	(5.8)	NR	-	-	-	-
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	14	(7)	NR	NR	NR	NR	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	49	6.48	1.61	-	-	-	-
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	48	6.10	1.70	*-0.13*	*0.44*	*-0.98*	*0.72*
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR						
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR						
Pedersen, 2013 (abs)	PLA	12	94	6.50	1.60	-	-	-	-
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	91	6.40	1.50	*-0.90*	*0.31*	*-1.51*	*-0.29*
Sieper, 2013 [ABILITY-1]	PLA	12	51	6.30	NR	-	-	-	-
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	105	6.40	NR	*-0.90*	*0.34*	*-1.57*	*-0.23*
Sieper, 2014 [INFAST]	PLA	18	51	6.30	NR	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	6.40	NR	*-1.40*	*0.42*	*-2.22*	*-0.58*
Sieper, 2014 [INFAST]	PLA	28	36	6.00	1.20	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	40	5.50	1.30	*-1.80*	*0.56*	*-2.90*	*-0.70*
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	36	6.00	1.20	-	-	-	-

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASDAI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	40	5.50	1.30	*-1.90*	*0.55*	*-2.99*	*-0.81*
Tam, 2014	PLA	26	21	6.17	1.52	-	-	-	-
Tam, 2014	GOL 50mg/mth	26	20	6.15	1.02	*-1.16*	*0.46*	*-2.05*	*-0.27*
van der Heijde, 2005 [ASSERT]	PLA	24	78	(6.5)	NR	-	-	-	-
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	(6.6)	NR	*-2.50*	*0.27*	*-3.04*	*-1.96*
van der Heijde, 2006a [ATLAS]	PLA	12	107	6.30	1.70	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	6.30	1.70	*-1.80*	*0.28*	*-2.35*	*-1.25*
van der Heijde, 2006a [ATLAS]	PLA	24	107	6.30	1.70	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	6.30	1.70	*-1.80*	*0.28*	*-2.35*	*-1.25*
van der Heijde, 2006b	PLA	12	51.00	61.10	13.70	-	-	-	-
van der Heijde, 2006b	ETN 2x25mg/1wk	12	150.00	59.40	16.70	*-1.72*	*0.66*	*-3.02*	*-0.42*
van der Heijde, 2006b	ETN 1x50mg/1wk	12	155.00	62.40	17.00	*-1.91*	*0.73*	*-3.35*	*-0.47*

* Where data was reported on a 0-100mm VAS scale; data has been rescaled using a 0-10cm scale

NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.10: BASMI score

				Baseline		Follow-up (rescaled[Error! Bookmark not defined.])*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASMI measured**	**Baseline mean (median)**	**Baseline SD**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Bao, 2012 (abs)	PLA	14	105	NR	NR	-	-	-	-
Bao, 2012 (abs)	GOL 50mg/mth	14	108	NR	NR	*-0.16*	*0.09*	*-0.34*	*0.02*
Barkham, 2009	PLA	16	NR						
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR						
Barkham, 2010	PLA	12	NR						
Barkham, 2010	ETN 2x25mg/1wk	12	NR						
Braun, 2002	PLA	12	35	3.70	2.20	-	-	-	-
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	3.70	2.00	*-1.10*	*0.50*	*-2.08*	*-0.12*
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	3.40	2.19	-	-	-	-
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	376	3.70	2.25	-0.64	*0.32*	-0.87	0.40
Calin, 2004	PLA	12	NR						
Calin, 2004	ETN 2x25mg/1wk	12	NR						
Davis, 2003	PLA	24	NR						
Davis, 2003	ETN 2x25mg/1wk	24	NR						
Dougados, 2011 [SPINE]	PLA	12	43	5.80	1.30	-	-	-	-
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	5.70	1.40	*-0.37*	*0.14*	*-0.65*	*-0.09*
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	NR	NR	-	-	-	-
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	NR	NR	*0.00*	*0.20*	*-0.39*	*0.39*
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR						
Giardina, 2010	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR						
Giardina, 2010	ETN 1x50mg/1wk	24	NR						
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						

				Baseline		Follow-up (rescaled[Error! Bookmark not defined.])*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASMI measured**	**Baseline mean (median)**	**Baseline SD**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Gorman, 2002	PLA	16	NR						
Gorman, 2002	ETN 2x25mg/1wk	16	NR						
Haibel, 2008	PLA	12	24	1.30	1.60	-	-	-	-
Haibel, 2008	ADA 40mg/2wks	12	22	1.30	1.20	*-0.40*	*0.43*	*-1.24*	*0.44*
Hu, 2012	PLA	12	NR						
Hu, 2012	ADA 40mg/2wks	12	NR						
Huang, 2014	PLA	12	NR						
Huang, 2014	ADA 40mg/2wks	12	NR						
Inman, 2008 [GO-RAISE]	PLA	14	78	(4)	IQR: 2.0, 5.0	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	(3)	IQR: 2.0, 4.0	*-0.08*	*0.15*	*-0.37*	*0.21*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	(3)	IQR: 2.0, 5.0	*-0.21*	*0.16*	*-0.52*	*0.10*
Inman, 2008 [GO-RAISE]	PLA	24	78	(4)	IQR: 2.0, 5.0	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	(3)	IQR: 2.0, 4.0	*0.00*	*0.11*	*-0.21*	*0.21*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	(3)	IQR: 2.0, 5.0	*-0.20*	*0.10*	*-0.41*	*0.01*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	57	4.70	1.60	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	65	4.20	1.60	*-0.40*	NR	NR	NR
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	56	4.30	1.80	*-0.10*	NR	NR	NR
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	50	3.10	1.60	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	46	3.10	1.40	*-0.60*	*0.18*	*-0.95*	*-0.25*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	51	3.30	1.50	*-0.50*	*0.15*	*-0.79*	*-0.21*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	57	4.70	1.60	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	65	4.20	1.60	*-0.30*	*0.15*	*-0.60*	*0.00*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	56	4.30	1.80	*-0.30*	NR (not significant)		

				Baseline		Follow-up (rescaled[Error! Bookmark not defined.])*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASMI measured**	**Baseline mean (median)**	**Baseline SD**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	50	3.10	1.60	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	46	3.10	1.40	*-0.60*	*0.18*	*-0.95*	*-0.25*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	51	3.30	1.50	*-0.50*	*0.25*	*-0.99*	*-0.01*
Maksymowych, 2008 [M03-606]	PLA	12	44	3.60	2.10	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	4.00	2.20	*0.00*	*0.50*	*-0.98*	*0.98*
Maksymowych, 2008 [M03-606]	PLA	24	44	3.60	2.10	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	4.00	2.20	*0.00*	*0.49*	*-0.96*	*0.96*
Marzo-Ortega, 2005	MTX 10mg/1wk	10	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	NR						
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR						
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	49	3.10	2.24	-	-	-	-
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	48	3.40	2.10	*0.60*	*0.43*	*-0.25*	*1.45*
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR						
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR						
Pedersen, 2013 (abs)	PLA	12	94	2.70	1.20	-	-	-	-
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	91	2.70	1.30	*0.00*	NR	NR	NR
Sieper, 2013 [ABILITY-1]	PLA	12	NR						
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	NR						
Sieper, 2014 [INFAST]	PLA	18	51	3.10	NR	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	3.10	NR	*-0.50*	*0.15*	*-0.79*	*-0.21*
Sieper, 2014 [INFAST]	PLA	28	36	1.70	1.40	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	40	1.90	1.70	*-0.20*	*0.37*	*-0.92*	*0.52*
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	36	1.70	1.40	-	-	-	-

				Baseline		Follow-up (rescaled[Error! Bookmark not defined.])*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASMI measured**	**Baseline mean (median)**	**Baseline SD**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	40	1.90	1.70	*-0.30*	*0.40*	*-1.09*	*0.49*
Tam, 2014	PLA	26	21	(3)	IQR: 2.0, 5.5	-	-	-	-
Tam, 2014	GOL 50mg/mth	26	20	(5)	IQR: 4.0, 7.0	*-1.00*	*0.37*	*-1.72*	*-0.28*
van der Heijde, 2005 [ASSERT]	PLA	24	78	(4)	IQR: 2.0, 6.0	-	-	-	-
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	(4)	IQR: 2.0, 5.0	*-1.00*	*0.10*	*-1.19*	*-0.81*
van der Heijde, 2006a [ATLAS]	PLA	12	107	4.20	2.10	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	3.80	2.20	*-0.60*	*0.14*	*-0.88*	*-0.32*
van der Heijde, 2006a [ATLAS]	PLA	24	107	4.20	2.10	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	3.80	2.20	*-0.60*	*0.14*	*-0.88*	*-0.32*
van der Heijde, 2006b	PLA	12	NR						
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR						
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR						

* Where data was reported on a 0-100mm VAS scale; data has been rescaled using a 0-10cm scale

NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.11: BASFI Score

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASFI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Bao, 2012 (abs)	PLA	14	105	NR	NR	-	-	-	-
Bao, 2012 (abs)	GOL 50mg/mth	14	108	NR	NR	*-0.980*	*0.259*	*-1.488*	*-0.472*
Barkham, 2009	PLA	16	20	4.11	NR	-	-	-	-
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	20	4.42	NR	*-2.230*	*0.729*	*-3.659*	*-0.801*
Barkham, 2010	PLA	12	20	5.27	1.81	-	-	-	-
Barkham, 2010	ETN 2x25mg/1wk	12	20	5.60	1.98	*-1.560*	*0.613*	*-2.762*	*-0.358*
Braun, 2002	PLA	12	35	5.10	2.20	-	-	-	-
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	5.40	1.80	*-1.6*	*0.757*	*-3.084*	*-0.116*
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	55.10	20.80	-	-	-	-
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	55.00	20.20	-1.07	*0.190*	-14.43	-6.97
Calin, 2004	PLA	12	39	57.20	NR	-	-	-	-
Calin, 2004	ETN 2x25mg/1wk	12	45	60.20	NR	*-1.937*	NR	NR	NR
Davis, 2003	PLA	24	139	56.30	[1.7]	-	-	-	-
Davis, 2003	ETN 2x25mg/1wk	24	138	51.70	[1.8]	*-1.87*	*0.265*	*-2.390*	*-1.350*
Dougados, 2011 [SPINE]	PLA	12	43	57.00	19.00	-	-	-	-
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	63.00	20.00	*-1.200*	*0.398*	*-1.980*	*-0.420*
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	NR	NR	-	-	-	-
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	NR	NR	*-0.600*	*0.343*	*-1.273*	*0.073*
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	25	6.10	0.90	-	-	-	-
Giardina, 2010	ETN 1x50mg/1wk	12	25	6.50	1.10	*1.5*	NR	NR	NR
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	25	6.10	0.90	-	-	-	-
Giardina, 2010	ETN 1x50mg/1wk	24	25	6.50	1.10	*0.83*	NR	NR	NR
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASFI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Gorman, 2002	PLA	16	20	(3.2)	2.50	-	-	-	-
Gorman, 2002	ETN 2x25mg/1wk	16	20	(4.5)	2.10	*-0.9*	*0.944*	*-2.750*	*0.950*
Haibel, 2008	PLA	12	24	4.90	1.60	-	-	-	-
Haibel, 2008	ADA 40mg/2wks	12	22	5.40	2.00	*-1.1*	*0.890*	*-2.845*	*0.645*
Hu, 2012	PLA	12	20	3.90	2.00	-	-	-	-
Hu, 2012	ADA 40mg/2wks	12	26	3.70	2.10	*-1.1*	*0.723*	*-2.518*	*0.318*
Huang, 2014	PLA	12	115	NR	NR	-	-	-	-
Huang, 2014	ADA 40mg/2wks	12	229	NR	NR	*-1.280*	*0.203*	*-1.678*	*-0.882*
Inman, 2008 [GO-RAISE]	PLA	14	78	(4.9)	IQR: 3.5, 6.8	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	(5)	IQR: 3.2, 6.7	*-1.470*	*0.947*	*-3.325*	*0.385*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	(5.4)	IQR: 3.4, 7.3	*-1.590*	*1.071*	*-3.689*	*0.509*
Inman, 2008 [GO-RAISE]	PLA	24	78	(4.9)	IQR: 3.5, 6.8	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	(5)	IQR: 3.2, 6.7	*-2.000*	*0.294*	*-2.577*	*-1.423*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	(5.4)	IQR: 3.4, 7.3	*-2.000*	*0.294*	*-2.576*	*-1.424*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	57	6.00	2.00	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	65	5.60	2.30	*-1.100*	*0.556*	*-2.189*	*-0.011*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	56	5.70	2.30	*-1.100*	*0.555*	*-2.188*	*-0.012*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	50	4.90	2.20	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	46	4.80	2.20	*-1.900*	*0.559*	*-2.996*	*-0.804*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	51	5.10	2.40	*-1.900*	*0.559*	*-2.997*	*-0.803*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	57	6.00	2.00	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	65	5.60	2.30	*-1.700*	*0.504*	*-2.688*	*-0.712*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	56	5.70	2.30	*-1.600*	*0.474*	*-2.529*	*-0.671*

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASFI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	50	4.90	2.20	-	-	-	-
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	46	4.80	2.20	*-2.400*	*0.706*	*-3.785*	*-1.015*
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	51	5.10	2.40	*-2.100*	*0.618*	*-3.312*	*-0.888*
Maksymowych, 2008 [M03-606]	PLA	12	44	5.60	2.20	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	5.30	2.00	*-1.3*	*0.764*	*-2.797*	*0.197*
Maksymowych, 2008 [M03-606]	PLA	24	44	5.60	2.20	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	5.30	2.00	*-1.4*	*0.794*	*-2.955*	*0.155*
Marzo-Ortega, 2005	MTX 10mg/1wk	10	14	(6)	Range: 3.84, 10	-	-	-	-
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	28	(6.68)	Range: 1.90, 9.63	*-0.64*	*0.487*	*-1.594*	*0.314*
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR						
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	49	5.66	2.04	-	-	-	-
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	48	5.87	1.96	*0.23*	*0.691*	*-1.124*	*1.584*
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR						
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR						
Pedersen, 2013 (abs)	PLA	12	94	4.90	2.30	-	-	-	-
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	91	4.50	1.90	*-0.500*	*0.253*	*-0.997*	*-0.003*
Sieper, 2013 [ABILITY-1]	PLA	12	51	5.40	NR	-	-	-	-
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	105	5.30	NR	*-0.8*	*0.405*	*-1.594*	*-0.006*
Sieper, 2014 [INFAST]	PLA	18	51	5.40	NR	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	5.30	NR	*-1.00*	*0.506*	*-1.992*	*-0.008*
Sieper, 2014 [INFAST]	PLA	28	36	4.30	1.80	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	40	4.30	2.30	*-1.2*	*0.698*	*-2.569*	*0.169*

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which BASFI measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	36	4.30	1.80	-	-	-	-
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	40	4.30	2.30	*-1.3*	*0.691*	*-2.654*	*0.054*
Tam, 2014	PLA	26	21	41.00	23.20	-	-	-	-
Tam, 2014	GOL 50mg/mth	26	20	46.10	18.50	*-0.300*	*0.167*	*-0.627*	*0.027*
van der Heijde, 2005 [ASSERT]	PLA	24	78	(6)	IQR: 4.1, 7.2	-	-	-	-
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	(5.7)	IQR: 4.5, 7.1	*-1.700*	*0.230*	*-2.150*	*-1.250*
van der Heijde, 2006a [ATLAS]	PLA	12	107	5.60	2.20	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	5.20	2.20	*-1.414*	*0.267*	*-1.937*	*-0.890*
van der Heijde, 2006a [ATLAS]	PLA	24	107	5.60	2.20	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	5.20	2.20	*-1.484*	*0.282*	*-2.038*	*-0.931*
van der Heijde, 2006b	PLA	12	51	59.70	19.30	-	-	-	-
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR						
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR						

* Where data was reported on a 0-100mm VAS scale; data has been rescaled using a 0-10cm scale

NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.12: Spinal pain score

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Spinal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Bao, 2012 (abs)	PLA	14	NR						
Bao, 2012 (abs)	GOL 50mg/mth	14	NR						
Barkham, 2009	PLA	16	NR						
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR						
Barkham, 2010	PLA	12	NR						
Barkham, 2010	ETN 2x25mg/1wk	12	NR						
Braun, 2002	PLA	12	NR						
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	NR						
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	61.60	20.34	-	-	-	-
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	63.10	20.32	-1.46	*0.23*	-1.90	-1.01
Calin, 2004	PLA	12	39	56.10[b]	NR	-	-	-	-
Calin, 2004	ETN 2x25mg/1wk	12	45	60.00[b]	NR	*-2.24*	NR	NR	NR
Davis, 2003	PLA	24	NR						
Davis, 2003	ETN 2x25mg/1wk	24	NR						
Dougados, 2011 [SPINE]	PLA	12	43	61.00	20.00	-	-	-	-
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	70.00	16.00	*-1.40*	*0.53*	*-2.44*	*-0.36*
Dougados, 2013 [AS EARLY] (abs)	PLA	12	NR						
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR						
Giardina, 2010	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR						
Giardina, 2010	ETN 1x50mg/1wk	24	NR						
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Spinal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Gorman, 2002	PLA	16	NR						
Gorman, 2002	ETN 2x25mg/1wk	16	NR						
Haibel, 2008	PLA	12	24	7.10	1.60	-	-	-	-
Haibel, 2008	ADA 40mg/2wks	12	22	7.20	1.10	*-1.40*	*0.79*	*-2.94*	*0.14*
Hu, 2012	PLA	12	NR						
Hu, 2012	ADA 40mg/2wks	12	NR						
Huang, 2014	PLA	12	115	NR	NR	-	-	-	-
Huang, 2014	ADA 40mg/2wks	12	229	NR	NR	*-1.83*	*0.26*	*-2.35*	*-1.31*
Inman, 2008 [GO-RAISE]	PLA	14	78	(7.6)	IQR: 6.6, 8.8	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	(7.5)	IQR: 5.7, 8.2	*-2.70*	*0.41*	*-3.51*	*-1.89*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	(7.9)	IQR: 6.5, 8.8	*-2.80*	*0.43*	*-3.65*	*-1.95*
Inman, 2008 [GO-RAISE]	PLA	24	78	(7.6)	IQR: 6.6, 8.8	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	(7.5)	IQR: 5.7, 8.2	*-3.10*	*0.39*	*-3.87*	*-2.33*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	(7.9)	IQR: 6.5, 8.8	*-3.50*	*0.44*	*-4.37*	*-2.63*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Spinal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	NR						
Maksymowych, 2008 [M03-606]	PLA	12	44	71.70	14.80	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	67.20	16.70	*-2.13*	*0.62*	*-3.34*	*-0.92*
Maksymowych, 2008 [M03-606]	PLA	24	44	71.70	14.80	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	67.20	16.70	*-1.82*	*0.67*	*-3.13*	*-0.51*
Marzo-Ortega, 2005	MTX 10mg/1wk	10	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	NR						
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR						
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	49	6.30	2.31	-	-	-	-
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	48	6.74	2.31	*0.12*	*0.49*	*-0.85*	*1.09*
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR						
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR						
Pedersen, 2013 (abs)	PLA	12	94	7.00	1.70	-	-	-	-
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	91	6.90	1.80	*-1.20*	*0.36*	*-1.90*	*-0.50*
Sieper, 2013 [ABILITY-1]	PLA	12	NR						
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	NR						
Sieper, 2014 [INFAST]	PLA	18	51	76.60	NR	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	76.70	NR	*-1.28*	*0.48*	*-2.22*	*-0.34*
Sieper, 2014 [INFAST]	PLA	28	NR						
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	NR						
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Spinal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	NR						
Tam, 2014	PLA	26	21	(7)	IQR: 6, 8	-	-	-	-
Tam, 2014	GOL 50mg/mth	26	20	(7)	IQR: 6.25, 8	*-3.50*	*0.74*	*-4.95*	*-2.05*
van der Heijde, 2005 [ASSERT]	PLA	24	NR						
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	NR						
van der Heijde, 2006a [ATLAS]	PLA	12	107	6.70	2.20	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	6.40	2.10	*-1.96*	*0.35*	*-2.64*	*-1.27*
van der Heijde, 2006a [ATLAS]	PLA	24	107	6.70	2.20	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	6.40	2.10	*-2.04*	*0.35*	*-2.73*	*-1.36*
van der Heijde, 2006b	PLA	12	51	63.10	18.40	-	-	-	-
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR						
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR						

* Where data was reported on a 0-100mm VAS scale; data has been rescaled using a 0-10cm scale

NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.13: Nocturnal pain

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Nocturnal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Bao, 2012 (abs)	PLA	14	NR						
Bao, 2012 (abs)	GOL 50mg/mth	14	NR						
Barkham, 2009	PLA	16	NR						
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR						
Barkham, 2010	PLA	12	NR						
Barkham, 2010	ETN 2x25mg/1wk	12	NR						
Braun, 2002	PLA	12	NR						
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	NR						
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	63.20	23.13	-	-	-	-
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	63.40	22.63	-1.59	0.23	-2.04	-1.14
Calin, 2004	PLA	12	NR**						
Calin, 2004	ETN 2x25mg/1wk	12	NR**						
Davis, 2003	PLA	24	NR						
Davis, 2003	ETN 2x25mg/1wk	24	NR						
Dougados, 2011 [SPINE]	PLA	12	NR						
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	NR						
Dougados, 2013 [AS EARLY] (abs)	PLA	12	NR						
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR						
Giardina, 2010	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR						
Giardina, 2010	ETN 1x50mg/1wk	24	NR						
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Nocturnal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Gorman, 2002	PLA	16	20	(46.5)	25.30	-	-	-	-
Gorman, 2002	ETN 2x25mg/1wk	16	20	(65)	23.90	*-2.30*	*0.83*	*-3.92*	*-0.68*
Haibel, 2008	PLA	12	24	6.40	2.50	-	-	-	-
Haibel, 2008	ADA 40mg/2wks	12	22	7.00	1.60	*-1.30*	*0.82*	*-2.90*	*0.30*
Hu, 2012	PLA	12	NR						
Hu, 2012	ADA 40mg/2wks	12	NR						
Huang, 2014	PLA	12	NR						
Huang, 2014	ADA 40mg/2wks	12	NR						
Inman, 2008 [GO-RAISE]	PLA	14	78	(7.4)	IQR: 6.0, 8.6	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	(7.1)	IQR: 5.2, 8.1	*-2.70*	*0.42*	*-3.52*	*-1.88*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	(7.6)	IQR: 6.5, 8.8	*-2.80*	*0.43*	*-3.64*	*-1.96*
Inman, 2008 [GO-RAISE]	PLA	24	78	(7.4)	IQR: 6.0, 8.6	-	-	-	-
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	(7.1)	IQR: 5.2, 8.1	*-2.70*	*0.38*	*-3.45*	*-1.95*
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	(7.6)	IQR: 6.5, 8.8	*-3.10*	*0.44*	*-3.96*	*-2.24*
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	NR						
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	NR						

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Nocturnal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	NR						
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	NR						
Maksymowych, 2008 [M03-606]	PLA	12	44	64.30	20.80	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	53.60	25.00	*-1.91*	*0.61*	*-3.11*	*-0.71*
Maksymowych, 2008 [M03-606]	PLA	24	44	64.30	20.80	-	-	-	-
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	53.60	25.00	*-1.61*	*0.66*	*-2.91*	*-0.31*
Marzo-Ortega, 2005	MTX 10mg/1wk	10	14	(76.5)	Range: 33, 100	-	-	-	-
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	28	(63.5)	Range: 11, 100	*-3.65*	NR	NR	NR
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR						
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR						
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	49	6.40	2.55	-	-	-	-
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	48	6.75	2.15	*0.62*	*0.48*	*-0.31*	*1.55*
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR						
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR						
Pedersen, 2013 (abs)	PLA	12	NR						
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	NR						
Sieper, 2013 [ABILITY-1]	PLA	12	NR						
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	NR						
Sieper, 2014 [INFAST]	PLA	18	51	69.30	NR	-	-	-	-
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	70.60	NR	*-1.66*	*0.50*	*-2.64*	*-0.68*

				Baseline		Follow-up (rescaled)*			
Author, Year [Trial name]	**Study arm**	**Follow-up Weeks**	**Number in which Nocturnal Pain measured**	**Baseline mean (median)**	**Baseline SD [SE]**	**Between tx: Difference v control**	**SE: Difference v control**	**Lower CI**	**Upper CI**
Sieper, 2014 [INFAST]	PLA	28	NR						
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	NR						
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	NR						
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	NR						
Tam, 2014	PLA	26	NR						
Tam, 2014	GOL 50mg/mth	26	NR						
van der Heijde, 2005 [ASSERT]	PLA	24	78	(6.7)	IQR: 4.7, 7.9	-	-	-	-
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	(6.6)	IQR: 4.8, 8.1	*-2.60*	*0.33*	*-3.25*	*-1.95*
van der Heijde, 2006a [ATLAS]	PLA	12	107	6.50	2.40	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	6.10	2.40	*-1.80*	*0.36*	*-2.51*	*-1.09*
van der Heijde, 2006a [ATLAS]	PLA	24	107	6.50	2.40	-	-	-	-
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	6.10	2.40	*-1.80*	*0.36*	*-2.51*	*-1.09*
van der Heijde, 2006b	PLA	12	NR						
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR						
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR						

* Where data was reported on a 0-100mm VAS scale; data has been rescaled using a 0-10cm scale

** Reported as nocturnal and total pain combined

NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

Table 2.1.14: QoL - SF-36 physical and mental component scores

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean (median)	Follow-up SD	Change in score at follow-up, mean (median) [mean %]	Change in score at follow-up, SD [IQR]	Additional QoL measure reported
Bao, 2012 (abs)	PLA	14	NR							
Bao, 2012 (abs)	GOL 50mg/mth	14	NR							
Barkham, 2009	PLA	16	NR							ASQoL; HAQ-DI
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR							ASQoL; HAQ-DI
Barkham, 2010	PLA	12	NR							ASQoL; HAQ-DI
Barkham, 2010	ETN 2x25mg/1wk	12	NR							ASQoL; HAQ-DI
Braun, 2002	PLA	12	35	PCS 47.6%	23.40%	46.00%	25.20%	NR	NR	NR
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	PCS 46.5%	22.60%	61.50%	24.30%	NR	NR	NR
Braun, 2002	PLA	12	35	MCS 56.8%	19.40%	63.00%	17.10%	NR	NR	NR
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	MCS 51.5%	18.40%	65.40%	17.10%	NR	NR	NR
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	NR							
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	NR							
Calin, 2004	PLA	12	NR							
Calin, 2004	ETN 2x25mg/1wk	12	NR							
Davis, 2003	PLA	24	NR							
Davis, 2003	ETN 2x25mg/1wk	24	NR							
Dougados, 2011 [SPINE]	PLA	12	NR							
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	NR							
Dougados, 2013 [AS EARLY] (abs)	PLA	12	NR							
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	NR							
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR							HAQ
Giardina, 2010	ETN 1x50mg/1wk	12	NR							HAQ

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean (median)	Follow-up SD	Change in score at follow-up, mean (median) [mean %]	Change in score at follow-up, SD [IQR]	Additional QoL measure reported
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR							HAQ
Giardina, 2010	ETN 1x50mg/1wk	24	NR							HAQ
[GO-AHEAD]	PLA	NR	NR							
[GO-AHEAD]	GOL 50mg/mth	NR	NR							
Gorman, 2002	PLA	16	20	PCS 61.0	NR	NR	NR	[9.5%]	NR	NR
Gorman, 2002	ETN 2x25mg/1wk	16	20	PCS 41.8	NR	NR	NR	[38.0%]	NR	NR
Gorman, 2002	PLA	16	20	NR	NR	NR	NR	[-8%]	NR	NR
Gorman, 2002	ETN 2x25mg/1wk	16	20	NR	NR	NR	NR	[8%]	NR	NR
Haibel, 2008	PLA	12	24	PCS 30.7	6.0	34.9	9.6	NR	NR	NR
Haibel, 2008	ADA 40mg/2wks	12	22	PCS 28.8	7.6	38.8	11.8	NR	NR	NR
Haibel, 2008	PLA	12	24	MCS 43.6	11.1	43.9	11.8	NR	NR	NR
Haibel, 2008	ADA 40mg/2wks	12	22	MCS 41.3	12.5	44.6	12.7	NR	NR	NR
Hu, 2012	PLA	12	NR							
Hu, 2012	ADA 40mg/2wks	12	NR							
Huang, 2014	PLA	12	113	NR	NR	NR	NR	PCS 4.0	6.31	NR
Huang, 2014	ADA 40mg/2wks	12	226	NR	NR	NR	NR	PCS 6.6	6.43	NR
Inman, 2008 [GO-RAISE]	PLA	14	78	PCS (28.3)	[23.8, 34.1]	NR	NR	(2.4)	[-1.4, 7.8]	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	PCS (29.7)	[22.5, 35.3]	NR	NR	(7.3)	[1.5, 15.3]	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	PCS (29.8)	[25.2, 35.5]	NR	NR	(8.4)	[2.3, 14.1]	NR
Inman, 2008 [GO-RAISE]	PLA	14	78	MCS (46.2)	[37.1, 54.8]	NR	NR	(0.1)	[-4.3, 5.3]	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	MCS (46.5)	[36.8, 54.1]	NR	NR	(1.5)	[-2.2, 7.8]	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	MCS (43.1)	[33.5, 53.5]	NR	NR	(3.7)	[-3.2, 12.1]	NR
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	NR							

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean (median)	Follow-up SD	Change in score at follow-up, mean (median) [mean %]	Change in score at follow-up, SD [IQR]	Additional QoL measure reported
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	NR							
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	NR							
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	NR							
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	NR							
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	NR							
Maksymowych, 2008 [M03-606]	PLA	12	NR							
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	NR							
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR							ASQoL
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR							ASQoL
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	NR							
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	NR							
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	49	PCS 30.23 (26.25)	13.79	45.75 (44.38)	16.42	NR	NR	EuroQOL
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	47	PCS 33.37 (32.81)	14.61	45.03 (44.38)	16.45	NR	NR	EuroQOL
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	49	MCS 45.02 (46.06)	17.87	56.43 (61.63)	13.63	NR	NR	NR
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	47	MCS 49.22 (55.75)	16.86	57.88 (61.88)	13.81	NR	NR	NR

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean (median)	Follow-up SD	Change in score at follow-up, mean (median) [mean %]	Change in score at follow-up, SD [IQR]	Additional QoL measure reported
Pedersen, 2013 (abs)	PLA	12	NR							
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	NR							
Sieper, 2013 [ABILITY-1]	PLA	12	94	PCS 33.1	8.3	NR	NR	2.0	NR	NR
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	91	PCS 33.9	7.7	NR	NR	5.5	v PLA 0.001	NR
Sieper, 2014 [INFAST]	PLA	18	NR							
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	NR							
Sieper, 2014 [INFAST]	PLA	28	51	PCS 32.4	NR	40.3	NR	8.6 [29.4%]	8.93	EQ-5D
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	105	PCS 34.0	NR	46.6	NR	12.6 [42.5%]	10.31	EQ-5D
Sieper, 2014 [INFAST]	PLA	28	51	MCS 37.7	NR	45.7	NR	7.6 [27.1%]	11.10	NR
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	105	MCS 40.0	NR	49.0	NR	9.0 [33.5%]	10.96	NR
Song, 2011 [ESTHER]	SUL 2-3 gm/day	24	NR							ASQoL; EQ-5D
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	24	NR							ASQoL; EQ-5D
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	NR							ASQoL; EQ-5D
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	NR							ASQoL; EQ-5D
Tam, 2014	PLA	26	NR							
Tam, 2014	GOL 50mg/mth	26	NR							
van der Heijde, 2005 [ASSERT]	PLA	24	78	PCS (30.1)	[24.9, 36.2]	NR	NR	(0.8)	[-1.9, 6.0]	NR
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	PCS (28.8)	[23.8, 33.7]	NR	NR	(10.2)	[3.9, 17.1]	NR
van der Heijde, 2005 [ASSERT]	PLA	24	78	MCS (45.0)	[33.7, 55.5]	NR	NR	(2.0)	[-2.6, 7.5]	NR
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	MCS (47.6)	[37.6, 54.9]	NR	NR	(2.7)	[-2.9, 8.8]	NR

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean (median)	Follow-up SD	Change in score at follow-up, mean (median) [mean %]	Change in score at follow-up, SD [IQR]	Additional QoL measure reported
van der Heijde, 2006a [ATLAS]	PLA	12	NR							
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	NR							
van der Heijde, 2006b	PLA	12	NR							
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR							
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR							

Table 2.1.15: Other measures of functional capacity

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Measurement description	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean	Follow-up SD	Change in score at follow-up, mean (median)	Change in score at follow-up SE {SD} (95% CI) [IQR]
Bao, 2012 (abs)	PLA	14	NR							
Bao, 2012 (abs)	GOL 50mg/mth	14	NR							
Barkham, 2009	PLA	16	NR							
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	NR							
Barkham, 2010	PLA	12	20	AS-WIS	14.18	3.57	NR	NR	-0.68	(-2.56, 1.21)
Barkham, 2010	ETN 2x25mg/1wk	12	20	AS-WIS	15.32	3.55	NR	NR	-2.75	(-4.63, -0.87)
Braun, 2002	PLA	12	NR							
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	NR							
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	NR							
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	NR							
Calin, 2004	PLA	12	NR							
Calin, 2004	ETN 2x25mg/1wk	12	NR							
Davis, 2003	PLA	24	NR							
Davis, 2003	ETN 2x25mg/1wk	24	NR							
Dougados, 2011 [SPINE]	PLA	12	43	ASDAS - CRP	3.63	0.76	3.18	0.95	-0.49	0.87
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	ASDAS - CRP	3.9	0.71	2.3	0.97	-1.51	0.87
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	BAS-G	NR	NR	NR	NR	-1.4	(-1.9, -0.9)
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	BAS-G	NR	NR	NR	NR	-1.9	(-2.4, -1.3)
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	ASDAS - CRP	NR	NR	NR	NR	-0.5	(-0.7, -0.3)
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	ASDAS - CRP	NR	NR	NR	NR	-1.1	(-1.3, -0.9)
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR							
Giardina, 2010	ETN 1x50mg/1wk	12	NR							

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Measurement description	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean	Follow-up SD	Change in score at follow-up, mean (median)	Change in score at follow-up SE {SD} (95% CI) [IQR]
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR							
Giardina, 2010	ETN 1x50mg/1wk	24	NR							
[GO-AHEAD]	PLA	NR	NR							
[GO-AHEAD]	GOL 50mg/mth	NR	NR							
Gorman, 2002	PLA	16	NR							
Gorman, 2002	ETN 2x25mg/1wk	16	NR							
Haibel, 2008	PLA	12	NR							
Haibel, 2008	ADA 40mg/2wks	12	NR							
Hu, 2012	PLA	12	NR	ASDAS	4.0cm	0.9cm	3.2cm	1.2cm	NR	NR
Hu, 2012	ADA 40mg/2wks	12	NR	ASDAS	3.7cm	0.8cm	1.5cm	1.2cm	NR	NR
Huang, 2014	PLA	12	NR							
Huang, 2014	ADA 40mg/2wks	12	NR							
Inman, 2008 [GO-RAISE]	PLA	14	NR							
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	NR							
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	NR							
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	57	ASDAS - CRP	NR	NR	NR	NR	-0.6	NR
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	65	ASDAS - CRP	NR	NR	NR	NR	-1.8	v PLA p<0.001
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	56	ASDAS - CRP	NR	NR	NR	NR	-1.6	v PLA p<0.001
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	50	ASDAS - CRP	NR	NR	NR	NR	-0.6	NR
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	46	ASDAS - CRP	NR	NR	NR	NR	-1.9	v PLA p<0.001
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	51	ASDAS - CRP	NR	NR	NR	NR	-1.7	v PLA p<0.001
Maksymowych, 2008 [M03-606]	PLA	12	NR							
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	NR							
Marzo-Ortega, 2005	MTX 10mg/1wk	30	NR							

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Measurement description	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean	Follow-up SD	Change in score at follow-up, mean (median)	Change in score at follow-up SE {SD} (95% CI) [IQR]
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	NR							
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	NR							
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	NR							
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	NR							
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	NR							
Pedersen, 2013 (abs)	PLA	12	NR							
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	NR							
Sieper, 2013 [ABILITY-1]	PLA	12	91	ASDAS - CRP	3.4	0.8	NR	NR	NR	NR
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	87	ASDAS - CRP	3.2	0.8	NR	NR	NR	NR
Sieper, 2014 [INFAST]	PLA	18	51	ASDAS	3.9	NR	2.3	NR	NR	NR
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	105	ASDAS	3.8	NR	1.5	NR	NR	v PLA p< 0.001
Sieper, 2014 [INFAST]	PLA	28	51	ASDAS	3.9	NR	2.4	NR	NR	NR
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	105	ASDAS	3.8	NR	1.4	NR	NR	v PLA p< 0.001
Song, 2011 [ESTHER]	SUL 2-3 gm/day	24	NR							
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	24	NR							
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	NR							
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	NR							
Tam, 2014	PLA	26	21	ASDAS - CRP	3.87	0.80	NR	NR	-0.38	{0.81}
Tam, 2014	GOL 50mg/mth	26	20	ASDAS - CRP	4.04	0.99	NR	NR	-1.69	{1.30}
van der Heijde, 2005 [ASSERT]	PLA	24	NR							
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	NR							
van der Heijde, 2006a [ATLAS]	PLA	12	107	BAS-G	6.9cm	1.9cm	NR	NR	-0.6cm	0.2cm
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	BAS-G	6.9cm	1.9cm	NR	NR	-2.3cm	0.2cm

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which measured	Measurement description	Baseline mean (median)	Baseline SD [IQR]	Follow-up mean	Follow-up SD	Change in score at follow-up, mean (median)	Change in score at follow-up SE {SD} (95% CI) [IQR]
van der Heijde, 2006b	PLA	12	NR							
van der Heijde, 2006b	ETN 2x25mg/1wk	12	NR							
van der Heijde, 2006b	ETN 1x50mg/1wk	12	NR							

[a] If data were reported using a 0 -100mm VAS, data was rescaled to a 0-10 cm scale
[b] reported as nocturnal and total pain combined
NB: *italicised* = data calculated from study arm follow-up scores; underlined= data read from graph; Grey cells = data not available for either arm

2.2 Adalimumab for the treatment of ankylosing spondylitis (AS)

A summary of the trial design, patient characteristics, baseline demographics and results from the randomised, double-blind, placebo-controlled phase III studies of adalimumab - ATLAS[28] and the M03-606 - have been presented in the summary tables in Section 2.1. The trials themselves have been discussed in detail in the 2006 MTA submission to NICE. However, since that submission, long-term data (5 years) confirming the efficacy and safety of adalimumab have been published, which are presented in Section 2.2.1 below.[29]

In addition, since its licence in 2006 there are a number of country specific registries that have collected real world data for adalimumab, which are discussed in Section 2.2.2. Also included in this section are any open-label studies or observational studies providing efficacy outcomes for adalimumab, including data for the use of a 2nd anti-TNF agent following failure of a first.

2.2.1 Long-term data from the adalimumab clinical trial programme

Data from the adalimumab phase III, randomised, double-blind, placebo-controlled AS trial – ATLAS – were collected from January 2004 through to July 2009.

Patients, methods and outcome measures[29]

Patients were ≥18 years of age, diagnosed with AS using the modified New York criteria, and had active disease based on the presence of at least two of the following three criteria: BASDAI score ≥4, total back pain score ≥40 mm (on a 0–100 mm visual analogue scale (VAS)) and/or morning stiffness ≥1 h. Patients must have had an inadequate response to, or intolerance of, at least one NSAID.

Of the 315 patients enrolled, 208 patients were randomised to adalimumab and 107 to placebo. This analysis included 311 patients who received at least one dose of adalimumab during the double- blind or open-label portions of the trial ('any adalimumab exposure' set). This population was representative of patients with established AS: primarily male, white, HLA-B27-positive, and with long disease duration (11.00 [9.5]).

Outcomes collected include measures discussed in Section 1.2.

Statistical analysis [29]

Univariate logistic regression was used to evaluate factors hypothesised to be predictive of ASAS PR and ASDAS ID at 1 and 5 years of adalimumab exposure. Continuous explanatory variables included age, disease duration and the following baseline disease activity measures: BASFI, BASDAI, total back pain, patient and physician global assessments of disease activity and inflammation (mean of BASDAI questions 5 and 6).

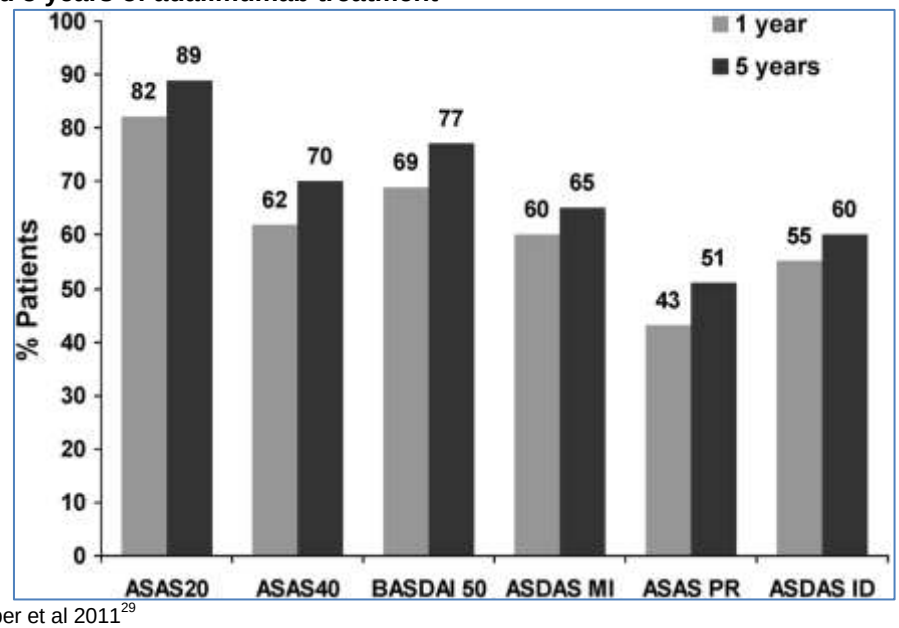
Kaplan–Meier survival curve analysis was used to determine the proportion of patients with sustained remission, defined as achieving ASAS PR or ASDAS ID on adalimumab treatment for at least three consecutive study visits spanning a period of at least 6 months at any point during the 5-year study. Patients were censored if they withdrew prematurely from the trial. All variables considered in the univariate analysis for long-term remission were included in multivariate regression for sustained remission; additionally, the original treatment assignment was added as an explanatory variable to determine if achieving sustained remission differed based on initial randomisation. The analysis was performed for all patients with data available for all independent variables.

Results [29]

Through 5 years, 113/315 (36%) randomised patients discontinued the study, including 109/311 (35%) patients who had received at least one dose of adalimumab. The most commonly listed reason for discontinuation was adverse events (38/311 (12%) patients) and withdrawal of consent (37/311 (12%) patients). The median duration of exposure to adalimumab among the 311 patients was 4.8 years (interquartile range 2.8–5.0 years).

Improvements in the signs and symptoms of AS observed after 1 year were sustained through 5 years of treatment with adalimumab among those patients originally randomised to adalimumab who completed the study (N=125) (Figure 2.2.1.1). Based on an observed analysis among patients with 1 or 5 years exposure, approximately half of the patients who had 1 year of adalimumab exposure achieved ASAS40 (143/282, 50.7%), ASDAS MI [(130/278, 46.8%) and BASDAI 50 (169/282, 59.9%) responses. At least one-third of patients experienced remission of disease activity after the first year of treatment (ASAS PR: 94/282, 33.3%; ASDAS ID: 118/282, 41.8%). The percentages of patients with good clinical responses were maintained among those originally randomised to adalimumab who completed 5 years of the study (ASAS40: 88/125, 70.4%; ASDAS MI: 79/121, 65.3%; BASDAI 50: 96/124, 77.4%). Among patients who had 5 years of adalimumab exposure, the majority exhibited disease remission based on ASAS PR (63/124, 50.8%) or ASDAS ID (75/124, 60.5%) criteria.

Figure 2.2.1.1: Percentages of patients achieving clinical response and remission states after 1 and 5 years of adalimumab treatment



Source: Sieper et al 2011[29]
Percentages based on patients originally randomised to adalimumab who completed the study and received 5 years of adalimumab (N=125). ASDAS MI: major improvement in ASDAS, decrease of ≥2.0; ASAS PR: ASAS partial remission; ASDAS ID: inactive disease, ASDAS <1.3. ASAS, Assessment in Spondyloarthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

Collinearity assessment of continuous explanatory baseline disease variables identified significant associations between all variables (p<0.001). The highest collinearity was identified between total back pain, patient global assessment of disease activity, BASFI and BASDAI (correlation coefficients, r=0.51–0.74), while physician global assessment of disease activity and morning stiffness had an intermediate level of collinearity (r=0.20–0.46). Baseline characteristics including age, patient and physician global assessments of disease activity, total back pain, inflammation and BASFI generally showed significant negative associations with long-term remission at 1 and 5 years of adalimumab exposure; however, these effects were relatively small.

The strongest predictors of ASAS PR or ASDAS ID after 1 and 5 years of adalimumab treatment were achievement of ASAS PR or ASDAS ID, respectively, at week 12. Patients who attained remission early were more than 10 times as likely to be in remission after 1 and 5 years of adalimumab treatment than those who did not achieve these disease states at week 12 (p<0.001). Other measures of treatment response (ASAS20, ASAS40, ASDAS MI and BASDAI 50) after 12 weeks were also strongly predictive of long-term remission (OR ranged from approximately 3 to 9, p≤0.01).

About half of the patients achieved a persistent state of disease remission. For ASAS PR, 141/311 (45%) patients demonstrated sustained remission at any time during the study, while 170/311 (55%) patients met the criteria for sustained ASDAS ID. For both ASAS PR and ASDAS

ID criteria, the respective achievement of these remission states at 12 weeks was the only significant positive predictor of sustained disease remission. Reaching ASAS PR at week 12 resulted in a hazard ratio (95% CI, p value) for sustained ASAS PR of 2.49 (1.40 to 4.43, p=0.002). Patients who reached ASDAS ID after 12 weeks of adalimumab had a hazard ratio (95% CI, p value) of 3.18 (1.83 to 5.53, p<0.001) for achieving sustained ASDAS ID. Additionally, decreased functional activity (higher BASFI) at baseline was significantly negatively associated with both sustained remission criteria, although the hazard ratios for both were close to 1.0 (ASAS PR: 0.98 (0.96 to 0.99), p=0.002; ASDAS ID: 0.99 (0.97 to 1.00), p=0.04)[29].

Conclusion [29]

In patients with active AS, the efficacy and safety of adalimumab were maintained through 5 years with about half of the patients experiencing sustained remission at any time during the study. Early achievement of remission was the best predictor of long-term and sustained remission.

2.2.2 Open-label studies and registry data

A formal literature search was not conducted given the inherent problems of using the known search providers to identify observational studies or cohort based analyses. Instead a free-text search of PubMed was conducted using existing knowledge of observational and cohort studies in AS patients. The inclusivity of this strategy was expanded using the “pearl growing” approach; namely by identifying additional publications of relevance from those cited as references in source publications.

The data presented in this section adds valuable information surrounding the long term efficacy of anti-TNF therapy, efficacy pre- and post-switch, and addresses some of the benefits of treatment in light of extra-articular manifestations such as uveitis.

RHAPSODY open label study - Rudwaleit M *et al* 2009[a][30] and 2009[b][31]

Study Details

This large, 12-week, open-label adalimumab cohort study recruited 1250 patients from 211 centres across 15 European countries. The mean age (SD) of the cohort was 44 (11.4) years and duration (SD) of AS was 11 (9.8) years. The proportion of female patients was 28.7% and 1098 patients (87.8%) had a history of treatment with at least two NSAIDs. Of the 1250 patients, 330 (26.9%) had advanced AS. Baseline BASDAI, BASFI, and BASMI scores (SD) were 6.3 (1.4), 5.4 (2.2), and 4.1 (2.3) respectively. In terms of treatment history, prior anti-TNF use was documented in 326 (26.1%) patients having received etanercept and/or infliximab. At baseline 929 (74.3%) patients were receiving NSAIDs, 323 (25.8%) were receiving DAMRDs, and 169 (13.5%) were receiving glucocorticoids.

Of the 1250 patients, 274 (21.9%) present with ophthalmologist-diagnosed anterior uveitis; 43 of these patients had chronic uveitis, 106 had recent history of uveitis, and 28 had symptomatic uveitis. Baseline characteristic of the 1250 patients and the various uveitis defined subgroups are reproduced from the publication[31] as Figure 2.2.2.1.

Figure 2.2.2.1: Baseline characteristics of patients in RHAPSODY trial

	All patients (n = 1250)	History of AU* (n = 274)	Recent history of AU† (n = 106)	Symptomatic AU at baseline (n = 28)	Chronic AU‡ (n = 43)
Chronic uveitis, %	3	16	25	36	100
Male, %	71	70	74	82	72
Age, years, mean (SD)	43.6 (11.4)	45.6 (10.6)	44.0 (10.0)	46.1 (13.0)	44.4 (9.9)
AS duration, years, mean (SD)	11.0 (9.8)	14.8 (10.6)	13.4 (9.3)	14.8 (8.4)	15.1 (9.2)
Advanced AS§, %	27	31	31	41	26
Time since onset of uveitis, years, mean (SD)	NA	9.9 (8.9)	6.6 (8.8)	7.4 (8.4)	9.4 (7.9)
HLA-B27 positive, %	82	91	89	82	90
BASDAI, mean (SD)	6.3 (1.4)	6.3 (1.4)	6.5 (1.4)	6.2 (1.7)	6.6 (1.5)
BASFI, mean (SD)	5.4 (2.2)	5.2 (2.3)	5.0 (2.5)	5.0 (2.8)	5.2 (2.5)
CRP, mg/dl, mean (SD)	2.0 (2.4)	2.4 (2.8)	2.8 (3.6)	4.1 (4.9)	2.6 (3.0)
Treatment with DMARDs, %	26	28	19	32	26
Treatment with sulfasalazine, %	12	13	9	25	12
Oral NSAIDs, %	74	79	78	71	84
Oral glucocorticoids, %	14	13	9	14	16
Previous etanercept and/or infliximab treatment, %	26	23	26	29	35

*History of AU, history of at least one AU flare anytime.
†Recent history of AU, history of at least one AU flare in the past year.
‡Chronic uveitis refers to persistent AU flares of at least 3-month duration and with relapse within less than 3 months according to the Standardization of Uveitis Nomenclature Working Group.
§Advanced AS, radiographically involvement of at least 50% of the spine in >2 segments.
BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

Results

At week 12, 69.9% of the 1250 patients achieved an ASAS20 response and 53.7% achieved and ASAS40 response. The BASDAI50 response rate was 57.2%. The mean change (SD) from baseline in the BASDAI score was -3.3 (2.3) and in the BASFI score the change was -2.2 (2.3). Efficacy results at week 12 are reproduced from the publication[31] as Figure 2.2.2.2.

Figure 2.2.2.2: Week 12 efficacy results from RHAPSODY trial

	All patients (n = 1250)	History of AU* (n = 274)	Recent history of AU† (n = 106)	Symptomatic AU at baseline (n = 28)	Chronic AU‡ (n = 43)
ASAS40, %	53.7	54.5	55.1	56.0	52.4
BASDAI 50, %	57.2	60.7	61.8	66.7	59.5
ASAS partial remission, %	27.7	32.5	32.7	40.0	33.3
CRP, mg/dl, mean (SD)	0.8 (1.4)	1.0 (1.8)	1.2 (2.2)	1.6 (2.6)	0.9 (0.9)
CRP absolute change, mean (SD)	−1.4 (2.5)	−1.9 (3.3)	−2.3 (4.5)	−3.8 (5.5)	−2.6 (3.2)

*History of AU, history of at least one AU flare anytime.
†Recent history of AU, history of at least one AU flare in the past year. ‡Chronic uveitis refers to persistent AU flares of at least 3-month duration and with relapse within less than 3 months according to the Standardization of Uveitis Nomenclature Working Group.[8]
ASAS, Assessments in Spondyloarthritis International Society criteria for response, partial remission (value of <2 on a 0–10-point scale in each of the four ASAS20 domains); AU, anterior uveitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein.

Of the 326 (26%) patients included in this study that had prior exposure to etanercept or infliximab 41% reached a BASDAI 50 response compared with 63% in the anti-TNF naïve

subgroup (n=924; 74%). The ASAS 40 and ASAS partial remission targets were reached by 38% vs. 59% and 13% vs.33% when comparing anti-TNF experienced vs. anti-TNF naïve subgroups.

Adalimumab was generally well tolerated by this cohort with 685 (54.8%) patients reporting at least one AE which were predominantly mild in nature. Serious AEs were documented in only 43 (3.4%) patients. Discontinuations prior to week 12 occurred in 91 patients (7.3%); of these 13 (1.0%) were due to lack of efficacy and 54 (4.3%) were due to at least one AE. Throughout the whole 20-week treatment period there were a total of 115 (9.2%) withdrawals, 66 (5.3%) due to at least one AE and 21 (1.7%) due to lack of efficacy. None of the discontinuations were due to anterior uveitis.

In terms of efficacy in the face of anterior uveitis adalimumab treatment led to a clinically relevant reduction in the incidence of anterior uveitis flares. Throughout 363 patient years of treatment with adalimumab, 27 flares of anterior uveitis were recorded in 25 out of 1250 patients (2%). The rate of uveitis flares dropped 51% in the 1250 AS patient cohort, decreased by 58% in the 274 patients with a history of anterior uveitis, by 68% in the 106 patients with recent history of uveitis, by 50% in the 28 patients with symptomatic anterior uveitis and by 45% in the 43 chronic uveitis patients. These results are summarised in the reproduction[31] below (Figure 2.2.2.3).

Figure 2.2.2.3: Improvements in uveitis among patients enrolled RHAPSODY study

Patient groups by history of AU	AU flare rate before adalimumab treatment (flares/100 PYs)	AU flare rate during adalimumab treatment (flares/100 PYs)	Reduction in AU flare rate during adalimumab treatment (%)	p Value*
All patients (n = 1250)	15	7.4	−51	<0.001
History of AU† (n = 274)	68.4	28.9	−58	<0.001
Recent history of AU‡ (n = 106)	176.9	56	−68	<0.001
Symptomatic AU at baseline (n = 28)	192.9	96.2	−50	0.001
Previous chronic uveitis§ (n = 43)	129.1	71.4	−45	0.002

*Wilcoxon signed rank test.
†History of AU, history of at least one AU flare anytime. ‡Recent history of AU, history at least one AU flare in the past year.
§Chronic uveitis refers to persistent AU flares of at least 3-month duration and with relapse within less than 3 months according to the Standardization of Uveitis Nomenclature Working Group.[8]
AU, anterior uveitis; PYs, patient years.

Conclusions

This study, although un-randomised, provides data for a large sample of patients with a clinical profile that reflects the typical patients seen by rheumatology clinics across Europe and thus enables evaluation of adalimumab use in a daily clinical practice setting. The authors also note that the baseline characteristics of these patients are comparable to those presented in randomised trials.

Efficacy estimates from this study are higher than those from randomised trials as they are based on observational data. However, conservative estimates of efficacy from this study generated using non-responder imputation (NRI), which is used in randomised trial, are similar to values reported in such randomised studies, adding value to the results presented herein.

Treatment with adalimumab has also been shown to reduce uveitis flares by at least 50% in this large cohort of AS patients; evidence that shows adalimumab to be efficacious in reducing the rate of uveitis flares in patients with active AS, including those that present with chronic uveitis and recently symptomatic uveitis.

In conclusion the authors cited four common factors that were strongly associated with achieving BASDAI50, ASAS40, and ASAS partial remission; namely younger age, higher CRP values, HLA-B27 positivity, and being naïve to anti-TNF therapy.

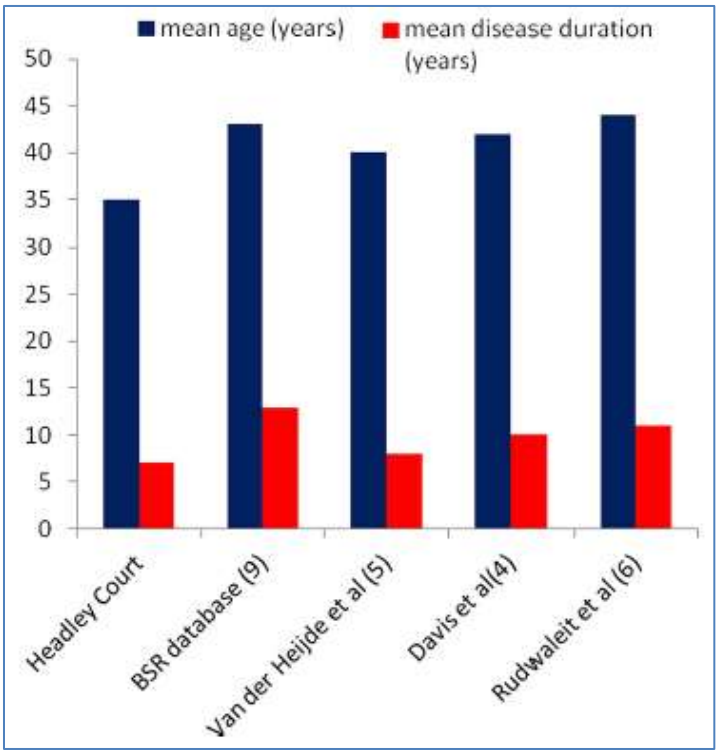
Headley Court Study - Rees JD *et al* 2014[32]

Study Details

The British Military maintains data on a cohort of service personnel diagnosed with AS which is characterised by young age and short disease duration. The majority of the most severely affected patients have been treated at the Headley Court facility with anti-TNF therapy since 2005 in accordance with NICE guidance notes.

The mean age of this 35-strong cohort is 34.7 years with mean disease duration being 6.9 years, which is much shorter than the civilian NHS comparator group. Patients were treated with etanercept or adalimumab from first anti-TNF use in 2006 up to including 2011. By comparison the mean age of the BSR cohort is 43 years with mean disease duration of 13 years and major clinical trials present mean ages between 37 and 51 years and disease durations of 7.7 to 13.7 years. This is illustrated by Figure 2.2.2.4 which is a copy from the publication.

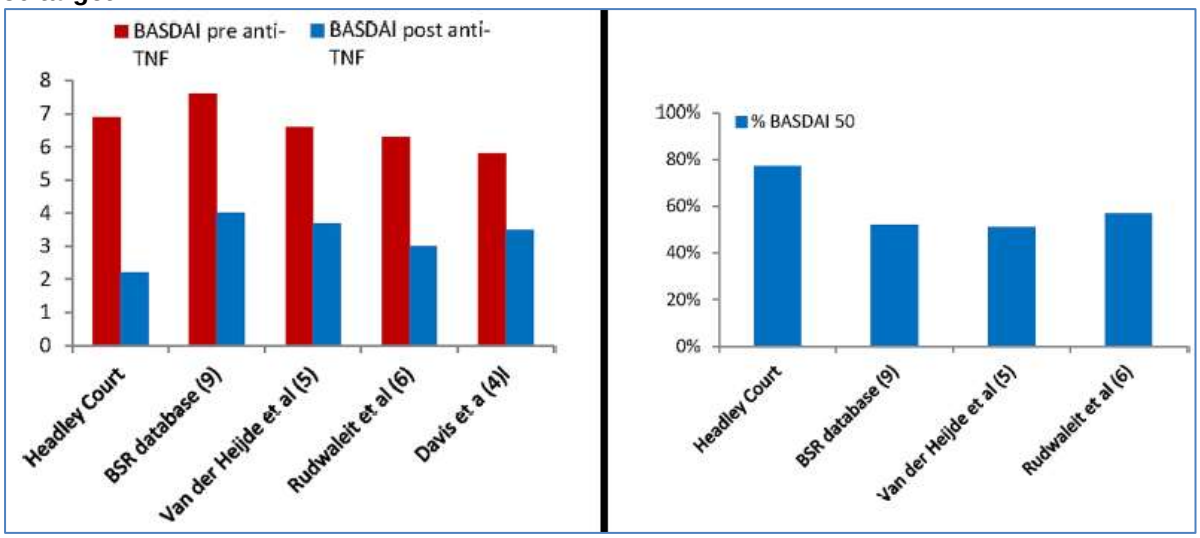
Figure 2.2.2.4: Comparison of mean age and disease duration of Headley Court patients with other studies



Results

In terms of efficacy, 77% of the 35 patients achieved a BASDAI50 response compared with 52% in the BSR cohort. An absolute mean improvement in the BASDAI score of 4.96 was also much higher than in the BSR dataset where scores improved by only 3.6 units. These results are presented graphically in reproductions from the original as Figure 2.2.2.5a below left and Figure 2.2.2.5b below right.

Figure 2.2.2.5a: BASDAI scores pre and post anti-TNF therapy form Headley Court compared with other studies; Figure 2.2.2.5b: Proportion of patients reaching the BASDAI 50 target



Conclusions

It is clear from this study that a young cohort with minimal co-morbidities has a better safety and efficacy profile than a cohort of older, less healthy patients. The results presented herein are also better than those reported in the landmark clinical trials where patients have been carefully selected.

This prospective analysis shows that early use of anti-TNF therapies is not only safe but also efficacious and is encouraging for advocates of early diagnosis and treatment.

Additionally, although not mentioned in the publication, it could be hypothesized that this cohort would also be receiving physiotherapy alongside the anti-TNF therapy and that this would have and added benefit for the patients as adherence to physiotherapy routines are likely to be high in a military setting.

BSRBR - Lord PAC *et al* 2010[33]

Study Details

This publication describes 261 AS patients recruited in the UK between 2002 and 2006 as part of the BSR biologics register (BSRBR). The cohort had a mean age of 43 years with 18% being female. Baseline median BASDAI score was 7.6 and the BASFI score was 7.9.

Baseline characteristics per anti-TNF agent administered are reproduced as Figure 2.2.2.6 below.

Figure 2.2.2.6: Baseline characteristics of study patients

Anti-TNF treatment	All	Etanercept	Infliximab	Adalimumab
No. of subjects	261	148 (57)	93 (36)	20 (7)
Age, years	43 (37–51)	43 (35–51)	43 (37–51)	44 (39–56)
Male, *n* (%)	213 (82)	124 (84)	70 (75)	19 (95)
Disease duration, years	13 (6–21)	12 (6–20)	15 (6–25)	15 (10–19)
BASDAI, U	7.6 (6.4–8.6)	7.7 (6.6–8.6)	7.5 (5.6–8.5)	7.6 (6.7–8.3)
BASFI, U	7.9 (6.2–8.9)	8.0 (6.0–8.9)	7.7 (6.0–8.9)	7.9 (6.9–8.6)
ESR, mm/h	31 (14–63)	30 (14–67)	34 (14–62)	27 (11–51)
CRP, mg/l	23 (9–55)	26 (8–57)	23 (12–49)	16 (9–26)
Smoking status, *n* (%)				
Never	85 (33)	45 (30)	32 (35)	8 (40)
Previously	81 (31)	43 (29)	34 (37)	4 (20)
Currently	94 (36)	60 (41)	26 (28)	8 (40)
DMARD at start of anti-TNF therapy, *n* (%)	116 (44)	55 (37)	50 (54)	11 (55)
MTX	90 (35)	40 (27)	40 (43)	10 (50)
SSZ	37 (14)	19 (13)	16 (17)	2 (10)
>1 DMARD	21 (8)	9 (6)	10 (11)	2 (10)
NSAID treatment, *n* (%)	189 (72)	106 (72)	69 (74)	14 (70)
Steroid treatment, *n* (%)	38 (15)	22 (15)	13 (14)	3 (15)

Values are given as median (IQR), unless otherwise specified.

Results

After six months of treatment the BASDAI and BASFI scores of the cohort had improved by 3.6 and 2.6 units respectively with 52% of patients reaching a BASDAI50 response. Patients with raised inflammatory markers at the start of therapy had a 0.9 unit (95% CI 0.2, 1.7) better improvement than those without and women had a 1.1 unit (95% CI 0.3, 2.0) greater improvement in BASFI at six months than their male counterparts; the same trend was also seen in those patients receiving concurrent DMARD therapy [0.9 units (95% CI 0.2, 1.7)].

Those patients treated with adalimumab (n=20) experienced a BASDAI and BASFI improvement of 2.5 and 3.4 units respectively. Full efficacy results are presented as Figure 2.2.2.7 in a reproduction from the publication.

Figure 2.2.2.7: Efficacy results by anti-TNF agent

Anti-TNF treatment	All	Etanercept	Infliximab	Adalimumab	*P*-value
n	261	148	93	20	
BASDAI at start of therapy, mean (s.d.)	7.3 (1.8)	7.4 (1.7)	7.0 (2.0)	7.3 (1.7)	0.31
BASDAI at 6 months, mean (s.d.)	3.7 (2.5)	3.3 (2.4)	4.0 (2.4)	4.7 (3.2)	0.01
Unadjusted change in BASDAI, mean (95% CI)	−3.6 (−3.9, −3.3)	−4.1 (−4.6, −3.8)	−2.9 (−3.4, −2.4)	−2.5 (−3.6, −1.4)	0.0002
Achieving BASDAI50 response, n (%)	136 (52)	93 (64)	36 (39)	7 (35)	$P<0.01$
BASFI at the start of therapy, mean (s.d.)	7.3 (2.2)	7.4 (2.0)	7.1 (2.4)	7.6 (1.7)	0.77
BASFI at 6 months, mean (s.d.)	4.6 (2.8)	4.4 (2.7)	5.2 (2.7)	3.8 (3.2)	0.09
Unadjusted change in BASFI, mean (95% CI)	−2.6 (−3.0, −2.2)	−3.1 (−3.6, −2.7)	−1.7 (−2.3, −1.1)	−3.4 (−4.9, −1.9)	0.0028
ESR at the start of therapy, mean (s.d.), mm/h	39.4 (29.3)	40.6 (31.2)	39.6 (27.6)	30.9 (22.6)	0.21
ESR after 6 months of therapy, mean (s.d.), mm/h	13.1 (14.8)	13.0 (14.8)	13.8 (15.9)	10.3 (5.9)	0.19
Unadjusted change in ESR, mean (95% CI), mm/h	−27.3 (−31.3, −23.4)	−27.5 (−33.1, −21.8)	−26.9 (−33.2, −20.7)	−28.3 (−37.5, −19.1)	0.48
CRP at the start of therapy, mean (s.d.), mg/l	35.3 (35.1)	36.9 (35.12)	35.5 (36.6)	24.7 (26.4)	0.36
CRP after 6 months of therapy, mean (s.d.), mg/l	11.9 (22.2)	11.4 (24.6)	12.9 (20.2)	10.7 (15.0)	0.23
Unadjusted change in CRP, mean (95% CI), mg/l	−25.3 (−32.5, −18.2)	−25.1 (−35.8, −14.4)	−29.0 (−40.0, −18.0)	−8.6 (−20.6, +3.3)	0.46

Conclusions

The authors conclude that the strongest predictors of improvement in disease activity were raised inflammatory markers at baseline and a lower initial BASFI score. These results are in line with a smaller observational study (n=99) [Rudwaleit 2004[34]] of infliximab and etanercept treated AS patients which found that raised CRP levels, raised baseline BASDAI and lower baseline BASFI were predictive of achieving a BASDAI50 response after 12 weeks of treatment. Those patients treated with adalimumab had the lowest baseline values for ESR and CRP and the highest BASFI score of the population subgroups and showed the biggest improvements in these three areas when compared with the other two therapies under scrutiny. One could argue that the efficacy of adalimumab in generating BASDAI 50 responses would be further improved should the afore mentioned baseline values be more similar to those recorded in the infliximab group, for example.

In the BSRBR, around 65% of patients had raised inflammatory markers at baseline and this was predictive of achieving a greater BASDAI score improvement at six months.

The key messages identified by the authors are that routine clinical use of anti-TNF therapy improves disease activity and functional impairment with raised inflammatory markers being a strong predictor of treatment response. Whilst concurrent DMARD therapy was seen to improve functional impairment it was not associated with improvements in disease activity.

DANBIO Danish registry - Glintborg B *et al* 2010[35] and 2013[36]

The Danish rheumatology registry DANBIO began in 2000 and covers over 90% of adults treated with biologic therapies.

Long Term data

The 2010 publication[35] describes 842 AS patients treated with anti-TNF therapy for the first time for up to 8 years after commencing treatment; patients were anti-TNF naïve prior to this. Male

patients numbered 603 (72%) with mean age and mean disease duration being 41 (IQR 32-50) and 5 (IQR 1-13) respectively. Of these 445 (53%) received infliximab, 247 (29%) received adalimumab, and 150 (18%) received etanercept. Baseline characteristics are presented below as Figure 2.2.2.8 (reproduced from publication).

Figure 2.2.2.8: Baseline Characteristics from Glintborg 2010 study[35]

Demographic variables at baseline	
Women (n (%))	239 (28)
Age (years (median (quartiles)))	41 (32–50)
Disease duration (years (median (quartiles)))	5 (1–13)
Methotrexate use (n (%))	343 (41)
TNFα inhibitor used (n (%))	
Adalimumab	247 (29)
Etanercept	150 (18)
Infliximab	445 (53)
Year of treatment initiation (n (%))	
2000	3 (0)
2001	15 (2)
2002	18 (2)
2003	48 (6)
2004	117 (14)
2005	155 (18)
2006	150 (18)
2007	188 (22)
January to November 2008	148 (18)
Reasons for drug discontinuation (n (%))	
Lack of efficacy	115 (14)
Adverse events or side effects	69 (8)
Planning pregnancy	11 (1)
Disease remission	8 (1)
Lost to follow-up	8 (1)
Other reasons	27 (3)
Not stated	72 (8)
Total	310 (37)

Numbers in brackets show quartiles or percentages of total population (n=842).

Results

Over the course of the observed period 310 (37%) patients withdrew from treatment; the most common reason for this was lack of efficacy in 115 patients (14%). In terms of treatment efficacy results are provide over a 5-year period with BASDAI and BASFI scores being maintained in the long term follow-up scenario. These results are reproduced below as Figure 2.2.2.9.

Figure 2.2.2.9: Treatment efficacy over 5-year period as seen in Glintborg 2010[35]

	Follow-up time								
	Outcome (median (IQR))								
	Baseline	2 Weeks	6 Weeks	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
CRP (mg/l)	14 (7–27)	4 (2–8)*	4 (2–10)*	5 (2–10)*	5 (2–10)*	5 (2–10)*	5 (2–10)*	6 (3–10)*	9 (3–16)*
BASDAI (mm)	59 (44–72)	36 (19– 56)*	26 (12–49)*	26 (11–45)*	21 (8–39)*	21 (8–41)*	20 (8–36)*	20 (7–32)*	20 (6–32)*
BASFI (mm)	50 (34–67)	37 (19–55)*	31 (13–50)*	28 (10–46)*	24 (9–45)*	24 (9–44)*	22 (10–43)*	22 (9–41)*	34 (17–62)
BASMI (mm)	40 (20–50)	30 (10–50)*	30 (10–50)*	30 (10–43)*	20 (10–40)*	30 (10–50)*	20 (10–40)*	40 (10–50)**	40 (20–70)
Thorax excursion (cm)	3 (2–5)	3 (2–5)*	4 (3–5)*	4 (2–5)*	4 (2–5)*	4 (2–5)**	4 (2–5)***	4 (3–5)**	3 (2–5)
VAS pain (mm)	65 (45–78)	30 (14–56)*	22 (10–46)*	20 (9–48)*	19 (7–40)*	18 (5–39)*	17 (6–26)*	15 (6–28)*	23 (7–35)*
VAS fatigue (mm)	68 (48–81)	49 (20–70)*	34 (14–62)*	33 (14–59)*	29 (9–52)*	25 (6–45)*	18 (7–41)*	41 (4–42)*	23 (10–53)
VAS global (mm)	67 (48–81)	36 (15–60)*	26 (11–51)*	24 (10–51)*	20 (8–44)*	18 (6–40)*	18 (8–37)*	18 (7–33)*	21 (11–49)*
Patients treated (n†)	842	818	794	696	504	345	213	139	61
Patients with a visit (n)	745	395	458	515	390	264	168	128	39

*p<0.001 compared with baseline, **0.001<p<0.01, ***0.01<p<0.05.
†Among patients with incomplete follow-up data (n=39), follow-up time is estimated according to the latest visit registered in DANBIO.
The baseline visit was the time point at which the patient received the first dose of TNFα inhibitor. Outcome data were reported according to the registrations in DANBIO at the following time points: 2 weeks of treatment (time interval 1–4 weeks), 6 weeks (5–9 weeks), 6 months (18–32 weeks), 1 year (46–64 weeks), 2 years (91–117 weeks), 3 years (143–182 weeks), 4 years (183–233 weeks), 5 years (234–285 weeks) and 6 years (286–338 weeks). If more DANBIO registrations occurred within a given time interval, the one closest to the given time point was selected. If a patient had no registrations within a given time interval, data were registered as missing for the given time point.
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; TNFα, tumour necrosis factor α; VAS, Visual Analogue Scale.

This data shows that responses achieved after 12 months of treatment, for example in terms of BASDAI score, are maintained up to the five year time point.

Switch Data

The 2013 publication[36] describes AS patients that initiated a treatment course before January 1st 2011 and were biologic naïve at initiation; thus 1436 patients are included in this study. Of these, 432 patients switched treatment and went on to receive at least one further biologic treatment course. Baseline demographics and disease activity are shown below in Figure 2.2.2.10 as a reproduction of table 1 from the publication with median follow up being 2.4 years (IQR 1.0-4.8 years).

Figure 2.2.2.10: Baseline patient characteristics from Glintborg 2013 study[36]

	Non-switchers N=1004	Switchers N=432	p Value
Age	41 (33–51)	41 (32–49)	0.4
Women, n (%)	218 (22)	142 (33)	0.0001
Disease duration (years)	5 (1–14)	3 (1–11)	0.01
Symptom duration (years)	14 (6–22)	11 (4–19)	0.0001
Use of methotrexate, n (%)	262 (26)	157 (36)	0.0001
CRP (mg/l)	13 (5–27)	13 (5–26)	0.4
VAS fatigue (mm)	65 (46–78)	74 (56–87)	0.0001
VAS global (mm)	66 (46–79)	72 (57–85)	0.0001
VAS pain (mm)	62 (44–77)	70 (51–81)	0.0001
BASDAI (mm)	56 (43–69)	62 (52–76)	0.0001
BASFI (mm)	47 (31–65)	54 (39–71)	0.0001
BASMI	40 (20–60)	40 (20–60)	0.9

From 2001-2008 the most prevalent first line treatment used was infliximab; from 2009-2010 this switched to adalimumab. Adalimumab was also the most frequently used drug second line (46%) and third line (31%). The frequencies of each treatment used at different points in the treatment pathway are shown below in a reproduction of table 2 from the publication as Figure 2.2.2.11.

Figure 2.2.2.11: Number of patients receiving a given treatment at different points in the treatment pathway

		Treatment course number			
Biological drug	Total (%)	1*	2*	3	4, 5, 6, 7
Adalimumab	781 (38)	532 (37)	197 (46)	42 (31)	10 (18)
Etanercept	452 (22)	231 (16)	172 (40)	40 (29)	9 (16)
Infliximab	741 (36)	653 (45)	42 (10)	37 (27)	9 (16)
Golimumab	59 (3)	20 (1)	15 (3)	9 (7)	15 (27)
Certolizumab	9 (0)	0 (0)	1 (0)	3 (2)	5 (9)
Rituximab	8 (0)	0 (0)	3 (1)	2 (1)	3 (5)
Tocilizumab	4 (0)	0 (0)	0 (0)	2 (1)	2 (4)
Abatacept	5 (0)	0 (0)	1 (0)	1 (1)	3 (5)
Anakinra	1 (0)	0 (0)	0 (0)	1 (1)	0 (0)
Not stated	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Total	2061 (100)	1436 (100)	432 (100)	137 (100)	56 (100)

Results

Of the 1436 patients that initiated anti-TNF therapy, 231 patients stopped treatment and did not restart another therapy, 432 (30%) patients switched to a second anti-TNF therapy and 773 patients continued with the same initial therapy. Of the 432 patients that switched to a second anti-TNF therapy, 217 of these remained on this therapy for the duration of the study with 137 patients switching to a third anti-TNF therapy; 78 patients withdrew form treatment at this stage and did not commence another anti-TNF agent. Of the137 patients that initiated a third anti-TNF therapy, 39 patients went on to commence at least a fourth anti-TNF option. The main reason for switching therapy or discontinuation of treatment altogether was lack of efficacy followed by adverse events.

In terms of efficacy, most scores (including CRP, BASDAI, and BASFI) decreased after three and six months' treatment during the first, second, and third treatment courses (Figure 2.2.2.11). For switch patients the baseline CRP, BASDAI, and VAS global scores were significantly lower at the start of the second treatment course when compared with the first. The delta values for the decrease in CRP, BASDAI, and VAS global scores between baseline and six months were similar in the second and third treatment courses when compared with the first.

During the first treatment course the proportion of patients reaching a BASDAI 50 response was 54% (NNT=1.9). These proportions were 37% (NNT=2.7) and 30% (NNT=3.4) in the second and third treatment courses respectively. At the two year visit, 52% of switch patients (NNT=1.9) and 63% of non-switch patients (NNT=1.6) had reached a BASADAI 50 response.

Conclusions

This registry offers up to ten years of follow-up data and overall around a third (30%) of the 1432 patients switched to a second anti-TNF therapy with 10% switching to a third anti-TNF. Patients that switched had a higher proportion of women that those that didn't switch (33% vs. 22%), they also tended to have a shorter disease duration; 3 vs 5 years, and also presented with higher BASDAI scores. The main reason for switching was lack of efficacy, explaining around half of the switch episodes observed. Although switch patients had poorer treatment response and shorter drug survival than non-switchers, around half of the switch patients achieved a clinical response and disease activity did decrease significantly with the second and third treatment courses. Two years after switching, half the switch patients maintained treatment with the second biologic

This long term follow-up data shows that efficacious responses can be reached and maintained in AS patients even where a switch to another anti-TNF therapy has occurred; as seen with half the switch patients. Thus switching to another anti-TNF therapy should be strongly considered in AS patients.

Lie E *et al* 2011 (NOR-DMARD)[37]

Study Details

This longitudinal, observational, multicentre study in Norway also draws on the NOR-DMARD registry and presents efficacy results for 514 anti-TNF naïve AS patients. Of these 514 patients, 77 patients switch to a second anti-TNF therapy during the two year follow-up period. Patient characteristics are shown in a reproduction of table 1 from the publication below (Figure 2.2.2.12).

Figure 2.2.2.12: Baseline characteristics from NOR-DMARD study population

	Non-switchers (n=437)	Switchers (n=77)	
	1st TNFi	1st TNFi	2nd TNFi
Age (years)	42 (35–50)	42 (34–50)	44 (36–52)
Male sex (n (%))	316 (72.3)	50 (64.9)	–
HLA-B27 positive (n (%))	296 (93.1)	58 (89.2)	–
Etanercept (n (%))	232 (53.1)	32 (41.6)	31 (40.3)
Infliximab (n (%))	139 (31.8)	41 (53.2)	18 (23.4)
Adalimumab (n (%))	66 (15.1)	4 (5.2)	28 (36.4)
DMARD co-medication (n (%))	104 (23.8)	16 (20.8)	17 (22.1)
Disease duration (years)	11 (4–20)	10 (5–14)	11 (6–18)
No of previous DMARDs	0 (0–1)	0 (0–1)	1 (0–2)
BASFI (0–10)*	4.5 (2.7–6.0)	5.3 (3.2–6.9)	5.4 (2.9–6.8)
BASDAI (0–10)*	5.7 (4.1–6.9)†	6.7 (5.6–7.8)†	6.0 (4.0–7.3)
ASDAS*	3.36 (2.83–4.12)	3.70 (3.13–4.32)	3.69 (2.87–4.39)
ESR (mm/h)	18 (10–35)	16 (8–31)	22 (5–39)
CRP (mg/l)	12 (5–28)	9 (5–21)	10 (5–27)
Patient global VAS (mm)	58 (38–75)	60 (37–75)	60 (36–79)
Pain VAS (mm)	53 (34–69)	59 (38–72)	58 (44–73)
Fatigue VAS (mm)	61 (35–79)	63 (44–82)	63 (38–80)
Physician global VAS (mm)	36 (25–51)	38 (27–54)	37 (25–59)
SF-36 PCS	31 (25–38)	30 (23–38)	28 (24–35)
SF-36 MCS	46 (34–54)	46 (36–52)	44 (36–54)
SF-6D	0.58 (0.52–0.65)	0.58 (0.49–0.67)	0.55 (0.48–0.64)

Results

The 77 patients that switched did so in the following manner; etanercept to infliximab (18), etanercept to adalimumab (14), infliximab to etanercept (27), infliximab to adalimumab (14), and adalimumab to etanercept (4). Response rates of both switch and non-switch patients are presented below from table 2 of the publication (Figure 2.2.2.13).

Figure 2.2.2.13: Response rates of switch and non-switch patients

	Non-switchers (n=437)	Switchers (n=77)				
	1st TNFi	1st TNFi		2nd TNFi		
	3 Months	3 Months	Last observation†	3 Months	p Value‡	p Value§
	(n=362)	(n=63)	(n=68)	(n=62)		
BASDAI 50, n (%)	105 (50.0)	6 (25.0)	2 (22.2)	13 (28.3)	0.007	1.00
	n=202	n=23	n=25	n=45		
ASAS20, n (%)	106 (52.5)	11 (47.8)	7 (28.0)	18 (40.0)	0.13	1.00
ASAS40, n (%)	76 (37.6)	7 (30.4)	4 (16.7)	14 (31.1)	0.41	1.00
	n=168	n=19	n=22	n=35		
ΔASDAS ≥1.1 (Clinically Important Improvement), n (%)	94 (56.0)	11 (57.9)	8 (36.4)	17 (48.6)	0.42	1.00
ΔASDAS ≥2.0 (Major Improvement), n (%)	51 (30.4)	2 (10.5)	2 (9.1)	11 (31.4)	0.90	0.38

A BASDAI 50 response was reached by 50% of non-switch patients after three months and by 25% of the switch patients after their first anti-TNF; this increased to 28.3% for three months after the switch to a second anti-TNF had occurred. The main reason for instigating a switch was AEs (n=44) with 30 patients reporting a lack of efficacy and 3 patients not recording a reason. Baseline and 3-month data is presented below (Figure 2.2.2.14) for the 74 patients that recorded a reason for switching as a reproduction of table 4 from the publication (IR=lack of efficacy).

Figure 2.2.2.14: Efficacy data for the 74 patients that switched treatment

	Baseline			3 Months		
	IR switchers (n=30)	AE switchers (n=44)	p Value*	IR switchers (n=23)	AE switchers (n=39)	p Value†
BASDAI 50 (n (%))‡	–	–	–	4 (21.1)	9 (33.3)	0.36
ASAS20 (n (%))‡	–	–	–	6 (31.6)	12 (46.2)	0.32
ASAS40 (n (%))‡	–	–	–	6 (31.6)	8 (30.8)	0.95
BASFI (0–10)‡	4.8 (2.7–6.7)	5.6 (2.9–7.3)	0.41	3.8 (2.0–5.8)	2.9 (1.4–5.7)	0.57
BASDAI (0–10)‡	6.1 (3.8–7.2)	5.7 (4.0–7.6)	0.42	3.9 (1.8–6.5)	4.2 (2.9–5.3)	0.37
ASDAS‡	3.65 (2.81–4.17)	3.71 (2.87–4.46)	0.97	2.62 (1.55–3.27)	1.98 (1.52–3.39)	0.16
ESR (mm/h)	14 (6–37)	23 (5–40)	0.87	8 (4–27)	10 (4–16)	0.03
CRP (mg/l)	12 (5–32)	10 (5–27)	0.81	5 (2–11)	5 (4–7)	0.10
Patient global VAS (mm)	59 (33–82)	61 (37–79)	0.85	31 (20–53)	37 (17–59)	0.98
Pain VAS (mm)	60 (47–73)	53 (39–73)	0.40	32 (21–52)	33 (11–56)	0.89
Fatigue VAS (mm)	58 (40–76)	64 (37–80)	0.67	48 (21–73)	50 (23–76)	0.92
Physician global VAS (mm)	31 (25–63)	39 (24–58)	0.89	24 (12–34)	17 (8–30)	0.48
SF-36 PCS	29 (25–36)	28 (23–35)	0.29	37 (27–43)	33 (27–42)	0.37
SF-36 MCS	43 (34–55)	44 (36–54)	0.94	49 (38–58)	49 (32–57)	0.37
SF-6D	0.55 (0.46–0.65)	0.56 (0.51–0.64)	0.67	0.68 (0.55–0.76)	0.62 (0.51–0.72)	0.54

Overall, 1-year and 2-year drug survival rates were 76% and 65% respectively for the first anti-TNF agent compared with 67% and 60% for the second anti-TNF agent.

Conclusions

This study supports the idea that switching to a second anti-TNF agent is an effective approach in treating AS first-line treatment failures with around a third of the patients showing a good clinical response and more than half the patients continuing the treatment for more than 2 years.

ATTRA Czech national registry - Pavelka K *et al* 2009[38]

Study Details

ATTRA is a Czech national registry which includes AS patients and this publication provides details for 310 of these patients that had at least one year of treatment. Patient demographic data is provided below in a reproduction from the publication as Figure 2.2.2.15.

Figure 2.2.2.15: Patient demographics of patient population from ATTRA registry

	infliximab n=153	adalimumab n=30	etanercept n=127	*p*-value
Age (mean ± SD)	37.3 ± 9.7	34.6 ± 8.9	36.9 ± 9.9	0.402
Disease duration (mean ± SD)	7.9 ± 6.2	9.8 ± 8.9	7.9 ± 7.1	0.740
Gender m/f (%)	82.4%	66.7%	71.7%	0.098
BASDAI	6.9 ± 1.5	6.2 ± 1.8	6.4 ± 1.7	0.078
ESR mm/hr	41.2 ± 21.8	39.0 ± 22.4	39.3 ± 24.3	0.672
CRP	30.4 ± 24.2	31.1 ± 22.2	31.6 ± 30.2	0.813

Results

When compared with the RA patients in the same registry, the AS patients were on average younger (36.8 vs. 45.9 years), had shorter disease duration (8.1 vs. 10.3 years), and had a smaller proportion of females (23.2 vs. 76.6%). Drug survival was also longer in AS patients (84%) when compared to RA patients (78%) after one year and 72% vs. 49% after three years of anti-THF therapy.

The efficacy results are presented for the group of AS patients as a whole and not by individual treatment option (Figure 2.2.2.16); reproduced from the publication below.

Figure 2.2.2.16: Efficacy results of all AS patients in ATTRA registry study

	Baseline (n=310)	3 months (n=286)	6 months (n=271)	9 months (n=263)	12 months (n=256)	24 months (n=148)	36 months (n=78)
BASDAI	6.4 ± 1.7	3.6 ± 2.6	3.1 ± 2.5	3.2 ± 2.6	3.1 ± 2.6	2.9 ± 2.5	3.0 ± 2.5
CRP	31.0 ± 26.5	5.2 ± 10.2	5.7 ± 10.6	6.5 ± 14.5	6.7 ± 14.0	7.5 ± 15.6	7.5 ± 16.2
ESR	40.2 ± 22.9	9.7 ± 11.0	10.7 ± 11.5	11.6 ± 12.8	11.8 ± 13.5	11.9 ± 13.1	12.1 ± 14.0
BASDAI <4 (%)	7.6	60.1	65.9	63.8	67.0	70.0	69.3

Those patients that discontinued were more likely to be female and had elevated CRP levels. Reasons for discontinuations are given below in a reproduction from the publication as Figure 2.2.2.17.

Figure 2.2.2.17: Discontinuations given by treatment type

	Infliximab (n=49/153)	Adalimumab (n=8/30)	Etanercept (n=23/127)
Incidence of discontinuation of treatment	16/100 py	19/100 py	8/100 py
Adverse events	13 (26.5%)	3 (37.5%)	7 (30.4%)
Lack of efficacy	10 (20.4%)	1 (12.5%)	7 (30.4%)
Loss of effect	3 (6.1%)	0	0
Remission	4 (8.2%)	0	2 (8.7%)
Patient's request or other reasons	10 (20.4%)	3 (37.5 %)	4 (17.4%)
Death	3 (6.1%)	0	0
Unknown	6 (12.3%)	1 (12.5%)	3 (13.1%)

Py: person-years.

Discontinuation rates for the patients receiving infliximab, adalimumab, and etanercept were 32%, 27%, and 18% respectively. Adverse events and lack of efficacy are given as the single most common reason for discontinuations across the three treatment options. Again, the authors are keen to point out that treatment adherence is more likely in AS patients that it is in RA patients; a pattern seen in other studies.

Conclusions

In terms of treatment efficacy the BASDAI scores for 12, 24, and 36 months are maintained throughout this period which is favourable for long term treatment strategies. The greatest improvement in BASADI score is observed after the first three months of treatment. Discontinuation rates are in line with those observed elsewhere. One additional comment made in this publication is that ability to maintain full-time work also improved after one-year of treatment with an increase from 48% at baseline to 63% noted in the first year of treatment with anti-TNF agents.

Haberhauer G *et al* 2010[39]

Study overview

This study reports on the treatment pathways followed by rheumatology patients in a single Austrian clinic setting, including 107 AS patients. Of these, 46 (43%) patients were analysed in this publication.

Results

Anti-TNF therapy resulted in an adequate response in 35/46 of the AS patients under investigation. The remaining 11 patients (mean age of 47 years; m/f ratio of 8/3) switched to a second anti-TNF agent citing lack of efficacy (1), loss of efficacy (8), and adverse events (2) as reasons for moving to another anti-TNF agent. Third line anti-TNF therapy was administered to five of these patients who failed to respond to second line treatments. Third line therapy induced adequate response in all of the five patients. The AS patient flow chart presented in the publication as Figure 1, is reproduced below as Figure 2.2.2.18. Specific outcome driven efficacy results are not available from this publication for the 46 patients in question.

Figure 2.2.2.18: Patient flow through different treatment lines in an Austrian clinic setting

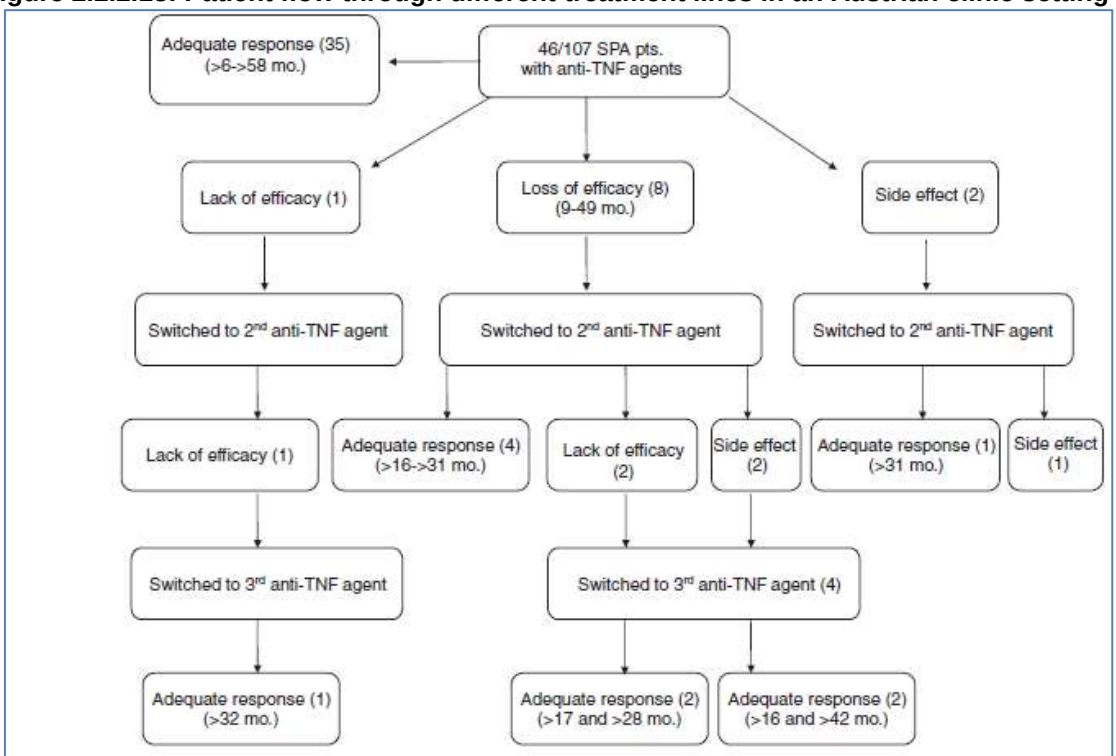


Fig. 1: Flowchart with details of anti-TNF switching in 11 patients with AS

Conclusions:

Around a quarter (24%) of patients switched to a second anti-TNF therapy and 11% switched to a third line therapy. In this study loss of efficacy is the main reason for switching to another anti-TNF therapy in the observed AS patients and 50% of these patients responded to the second line anti-TNF agent. The authors comment evidence for or against a switch due to lack of efficacy remains inconsistent amongst AS patients, perhaps because switching in AS patients tends to be less frequent than in RA patients. Either way the results presented here suggest that switching anti-TNF therapy in AS patients can be successful in generating an adequate response in second or even third line patients.

BIOBADASER Spanish national registry - Carmona L *et al* 2011[40]

BIOBASER is a Spanish Biologics registry which details 6,891 patients receiving biologic therapy in Spain. The entire cohort has a mean age (SD) of 56.3 (15.6) years with patients starting biologic therapy at a mean age (SD) of 49.6 (15.2) years. The proportion of females is 62.1%. Of these 6,891 patients, 1,120 (16.2%) are AS patients. Etanercept, infliximab, and adalimumab are the three most common first line treatments with AEs and lack of efficacy being cited as the most common reasons for discontinuation.

Study Details

To compare safety and retention rates of anti-TNF agents in approved indications, including AS. The database was analysed for patients included between February 2000 and October 2009. Of the 5150 patients for whom anti-TNF therapy was commencing *de novo*, 882 were AS patients. The baseline characteristics of these patients are presented below in Table 2.2.2.1.

Table 2.2.2.1: Baseline characteristics of Spanish patients commencing anti-TNF therapy for the first time

Number of AS patients n	882
Female, n (%)	206 (23)
Mean age in years (SD)	43.6 (12.2)
Disease Duration in years, mean (SD)	12.5 (10)
Number treated with infliximab, n (%)	522 (59)
Number treated with etanercept, n (%)	214 (24)
Number treated with adalimumab, n (%)	146 (17)

Concomitant medications were administered in 404 (46%) patients; MTX in 264 (30%), corticosteroids in 123 (14%), and leflunomide in 17 (2%) patients.

Results

Efficacy results are not forthcoming from this publication; however information surrounding adverse events is presented for all anti-TNF agents, along with their incident rates, and has been reproduced in this submission (Table 2.2.2.2).

Table 2.2.2.2: Adverse events recorded

Adverse Event Description	n	Patient years	IR (95% CI) x 1000
All AEs	714	2661	268 (249, 289)
Infections and infestations	243	2661	91 (81, 104)
General disorders and administration site reactions	64	2661	24 (19, 31)
Skin and subcutaneous tissue disorders	55	2661	21 (16, 27)
Gastrointestinal disorders	32	2661	12 (9, 17)
Other	320	2661	120 (108, 134)

Conclusion

AS efficacy estimates were not collected as part of this registry and as such are not available for comment; BIOBADASER does present AE data for the included AS cohort and this has been summarised here with infections and infestations being the single most common AE occurring in this population.

DESIR French Cohort – Molto A 2014[41]

Study Details

This is a prospective, multicentre, observational cohort study comprising 708 patients with recent-onset (< 3 years) inflammatory back pain suggestive of axial spondyloarthritis recruited from 25 French rheumatology centres. The study aims to evaluate the effectiveness of anti-TNF therapy in clinical practice in a population with early axial spondyloarthritis. The first two years of follow-up data are presented herein; a ten-year follow-up study is currently ongoing.

Of the 70 patients, 202 patients had received at least one anti-TNF therapy agent during the first two years. This population was matched with 202 patients from the other 506 patients that had not yet received any anti-TNF therapy within the first two years. Efficacy data was available for

assessment in 197 of the anti-TNF treated patients. Baseline characteristics are presented below as Figure 2.2.2.19.

Figure 2.2.2.19: Baseline characteristics of DESIR study patients

	Patients receiving TNFα blockers (n = 202)	Patients receiving usual care (n = 202)
Age, median (IQR) years	33.8 (27.1–41.44)	33.7 (27.2–39.7)
No. (%) male	88 (43.6)	80 (39.6)
Disease duration, median (IQR) months	17.2 (10.0–27.6)	16.3 (8.6–24.2)
No. (%) HLA–B27 positive	115 (56.9)	114 (56.4)
Sacroiliitis determination, no. (%)		
Radiographic (modified New York criteria)	67 (33.2)	59 (30.1)
MRI	82 (40.6)	64 (33.0)
BASDAI, median (IQR) (range 0–100)	57.0 (45.0–67.0)†	53.0 (39.0–65.0)
BASFI, median (IQR) (range 0–100)	42.0 (25.0–59.0)‡	35.0 (18.0–55.0)
CRP, median (IQR) mg/liter	5.0 (3.0–13.6)	4.4 (2.9–8.0)
ASDAS-CRP, median (IQR)	3.1 (2.4–3.7)§	2.8 (2.2–3.3)
NSAIDs		
No. (%) taking NSAIDs	174 (90.6)	168 (89.8)
ASAS NSAID score in last week, median (IQR)	55.0 (0.0–100.0)	50.0 (0.0–100.0)

Of the 197 patients for whom data was available, 127 patients presented with either radiographic sacroiliitis (67 [33.2%]), or MRI sacroiliitis (82 [40.6%]), or with abnormal CRP levels (83 [41.1%]). The remaining 72 patients presented without any objective signs of inflammation or structural damage at baseline.

Results

After at least 8 weeks of treatment 62 of 197 (31.5%) patients receiving the anti-TNF therapy achieved an ASAS 40 response; this was compared to only 26 patients (13.2%) in the control arm. Of the patients taking adalimumab (n= 78), 25 patients (32.1%) achieved the ASAS 40 response as seen in Figure 2.2.2.20 below, which is reproduced from the publication.

When looking at patient subgroups in terms of their ability to reach an ASAS 40 response those patients with diagnostic imaging confirmed axial spondyloarthritis are more likely to achieve the ASAS 40 response. Of the patients with MRI observed sacroiliitis 46% (37/80) of those receiving anti-TNF therapies vs. 15% (9/62) achieved the ASAS 40 response after at least 8 weeks of treatment. This compares with 21% (24/113) and 13% (17/127) respectively for patients without MRI sacroiliitis. Similar proportions are observed when looking at the subgroup of patients with sacroiliitis identified via X-ray imaging.

Figure 2.2.2.20: Efficacy results presented by treatment type

	ASAS improvement		Bath AS instruments		
Group	ASAS40	ASAS20	ΔBASFI	ΔBASDAI	BASDAI50
Adalimumab					
Patients	25 (32.1)	34 (43.6)	−14.1 ± 23.2	−16.7 ± 22.4	59 (75.6)
Controls	10 (13.0)	12 (15.6)	−2.6 ± 16.8	−3.6 ± 17.7	36 (46.8)
OR (95% CI)	3.07 (1.22–7.73)	4.47 (1.90–10.52)	–	–	3.46 (1.63–7.36)
P	0.017	0.001	0.027	0.001	0.001
Etanercept					
Patients	33 (32.7)	50 (50.0)	−13.0 ± 19.0	−19.4 ± 21.2	78 (78.0)
Controls	14 (14.1)	22 (22.2)	−5.0 ± 18.0	−5.5 ± 18.1	50 (49.5)
OR (95% CI)	3.42 (1.58–7.38)	3.22 (1.66–6.23)	–	–	3.02 (1.58–5.79)
P	0.002	0.001	0.027	0.002	0.001
Infliximab					
Patients	4 (22.2)	6 (35.3)	−7.3 ± 12.9	−18.2 ± 22.3	14 (77.8)
Controls	2 (11.8)	6 (35.3)	−7.8 ± 15.5	−8.4 ± 13.2	11 (61.1)
OR (95% CI)	1.80 (0.18–18.08)	0.64 (0.09–4.40)	–	–	0.64 (0.11–3.91)
P	0.619	0.649	0.864	0.838	0.700

Conclusions

Ultimately what data from the DESIR cohort shows is that early treatment of axial spondyloarthritis with anti-TNF therapy represents an effective treatment intervention, particularly in the subgroups of patients where sacroiliitis had been identified via MRI or to a lesser extent, X-ray imaging. Again the significance of this data coming from a real-world clinical setting adds weight to the arguments around the early detection and treatment of axial spondyloarthritis.

Conclusions from registry and open-label data

The inclusion of data from observational and open labels studies enables an examination of how the anti-TNF therapies perform in real-world clinical settings, including in patients that would potentially be ineligible for RCTs based on the often stringent selection criteria patients must meet to be eligible for enrolment. The advantage of this fact, from an evidence evaluation perspective, is that patients enrolled in registries for example are likely to present with sequelae that are also of interest when evaluating additional treatment benefits, for example in the amelioration of anterior uveitis associated with AS. This and other extra-articular manifestations are discussed further in section 2.6.3. The results of the RHAPSODY study show that treatment with adalimumab led to a clinically relevant reduction in the incidence of anterior uveitis flares with the rate of uveitis flares dropping 51% in the 1250 AS patient cohort over the 12-week period.

There is considerable evidence surrounding the benefits of switching between anti-TNF therapy agents in the face of lack or loss of efficacy, or due to adverse events forthcoming from open label and registry data. Data from 1436 AS patients in the DANBIO registry shows 432 patients switching to, at least, a second anti-TNF therapy, and of these 137 go onto receive a third line of anti-TNF therapy. After two years of follow up the BASDAI 50 response rates was 52% in the switch patients compared with 63% in those patients that did not switch. A significant decrease in disease activity was also recorded in those patients that switched treatment, supporting the notion that switching treatment to improve disease outcomes in patients that have failed first-line treatment is an effective treatment strategy. Similar treatment success was recorded in the open label RHAPSODY study with 41% of the 326 patients that had received prior therapy with etanercept and, or infliximab, reaching a BASDAI 50 response; this compares to 63% reaching the BASDAI 50 target in the anti-TNF naïve population (n=924, 74%).

In general terms it is also apparent that treatment adherence is much greater in the AS population when compared with RA populations from the same registries.

In addition to good evidence surrounding the benefit of treatment switch, the data in this section also shows that efficacious treatment responses can be maintained in the long-term as well as the short term, typically seen in RCTs. Evidence from a five-year follow-up period of the DANBIO data shows that efficacy responses in terms of reduction in BASDAI and BASFI scores achieved after 12-months of treatment are maintained over the five-year follow-up period.

Data from the BSRAS register is immature and not available for review at this stage but will no doubt add further value to these discussion points in the future.

Finally, the positive results from the Headley Court study suggest that younger patients with less co-morbidity are more likely to have an efficacious response and do so with a better safety profile; a notion supported by other studies in this section and suggest that early diagnosis and treatment is an important aspect for consideration when treating AS patients.

2.3 Adalimumab for the treatment of non-radiographic axial spondylitis (nr-axSpA)

2.3.0 Overview of nr-axSpA randomised controlled trials for adalimumab

A clinical programme was developed to study the safety and efficacy of adalimumab in patients with nr-axSpA. Adalimumab is the first therapy licensed for nr-axSpA that has demonstrated clinical effectiveness in a randomised phase III trial (ABILITY-1). Adalimumab demonstrated superior efficacy in the primary endpoint, all nine ranked secondary efficacy endpoints, and multiple non-ranked secondary endpoints. The clinical programme has demonstrated that:

- Adalimumab is effective in providing rapid and sustained improvement in disease response (ASAS 20/40/50/70)
- Adalimumab delivers clinically and statistically significant improvements in the signs and symptoms of nr-axSpA as measured by the BASDAI 50, reducing the high clinical burden of the disease
- Adalimumab provides significant improvements in the HRQoL and physical function of patients with nr-axSpA (as measured by the SF-36 and BASFI outcomes), reducing impairment in activities of daily living (ADL).

Adalimumab was studied in two controlled clinical studies (ABILITY-1 and an investigator-initiated study) in patients with severe nr-axSpA[8,42,10]. ABILITY-1 was a 12-week randomised, double-blind, placebo-controlled, multicentre phase III study of 185 patients with nr-axSpA. The double-blind ABILITY-1 study was extended by an additional 144 week open-label safety and efficacy study. Further details on the study design along with the results for this trial are presented in Section 2.3.1.[8,42].

It should be noted that the study population of the ABILITY-1 study was adults with active axSpA not fulfilling the modified New York criteria for AS, who had an inadequate response to or intolerance to ≥1 NSAID, or had a contraindication for NSAIDs as defined by the investigator. This is a broader population than the marketing authorisation - adalimumab is indicated for the treatment of adults with severe axSpA without radiographic evidence of AS (nr-axSpA) <u>who have objective signs of inflammation by elevated CRP and/or MRI</u>, and who have had an inadequate response to, or are intolerant to NSAIDs. The licensed indication defines a subgroup with axSpA in whom the benefit/risk balance was considered to be positive by the European Medicines Agency. Therefore, results presented in this submission are both the full analysis set (FAS) of the ABILITY-1 study (Section 2.3.1) as well as a subgroup of patients within ABILITY-1 equivalent to the licensed population, upon which the economic model is based (Section 2.3.2) [8,42].

While the pivotal study ABILITY-1 is presented in detail, a summary of the investigator initiated trial (by Haibel *et al*.) is also presented within the submission (Section 2.3.3); this was a pilot, phase II/III RCT conducted at two centres in Germany. This was the first randomised placebo-controlled trial of an anti-TNF therapy in the treatment of patients with nr-ax-SpA[10].

It should be noted that the inclusion criteria in the investigator-initiated trial differ slightly from the inclusion criteria in the ABILITY-1 study particularly around the signs of active inflammation required for study entry and how these have been defined[8,10].

2.3.1. ABILITY- 1

<u>Summary:</u> Adalimumab 40mg eow versus placebo in patients with nr-axSpA not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs. Statistically significant improvement noted in the primary endpoint of ASAS 40 at week 12, all nine ranked secondary endpoints, and in multiple non-ranked secondary endpoints.

<u>Objective</u>

To evaluate the efficacy and safety of adalimumab 40 mg given every other week (eow) subcutaneously compared to placebo for 12 weeks, followed by open-label safety and efficacy

assessments in patients with active non-radiographic axial SpA not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs, as defined by the investigator[8,42].

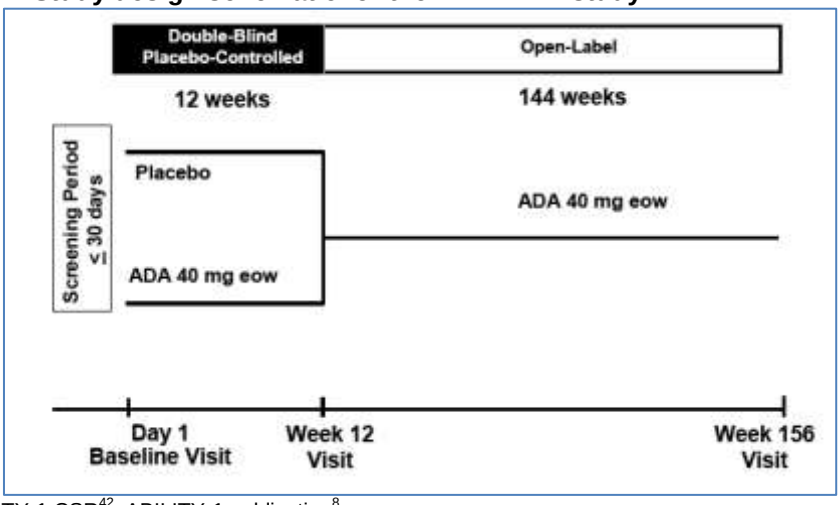
Study design

ABILITY-1 was a 12-week randomised, double-blind, placebo-controlled, multicentre Phase III study of 185 patients with nr-axSpA. The 12-week double-blind period was extended by an additional 144 weeks open-label safety and efficacy period. The study design schematic for the ABILITY-1 study is shown in Figure 2.3.1.1[8,42].

ABILITY-1 was initiated in August 2009 and was conducted at 37 centres in Australia, Belgium, Canada, the Czech Republic, France, Germany, Spain, the Netherlands, the UK, and the USA. Eligible patients were 18 years of age or older, fulfilling the ASAS classification criteria for active axial SpA without meeting the modified New York criteria for AS, who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs. The study included a 30-day screening period, following which patients were randomised in a 1:1 ratio via an interactive voice response system to receive either adalimumab 40 mg eow administered subcutaneously or matching placebo for 12 weeks. Following the initial 12-week double-blind period, patients were eligible to enter the open-label arm of the study where they received adalimumab 40 mg eow for up to an additional 144 weeks. At the Week 12 study visit, all patients on placebo were started on adalimumab 40 mg eow, and those who received active drug during the double-blind period continued on active drug[8,42].

The double-blind period began at the baseline visit (Day 1), and ended at the Week 12 visit; during this period patients were to visit the study site on Weeks 2, 4, 8 and 12, or if they terminated early from the study. The open-label period of the study began at Week 12 of study participation for each patient, and they were asked to visit the study site on Weeks 16, 20, 24, 28, 36, 44, 52, 60, 68, 80, 92, 104, 116, 128, 140, and 156 or if they terminated early from the study. No study drug was administered at the final visit[8,42].

Figure 2.3.1.1: Study design schematic for the ABILITY-1 study

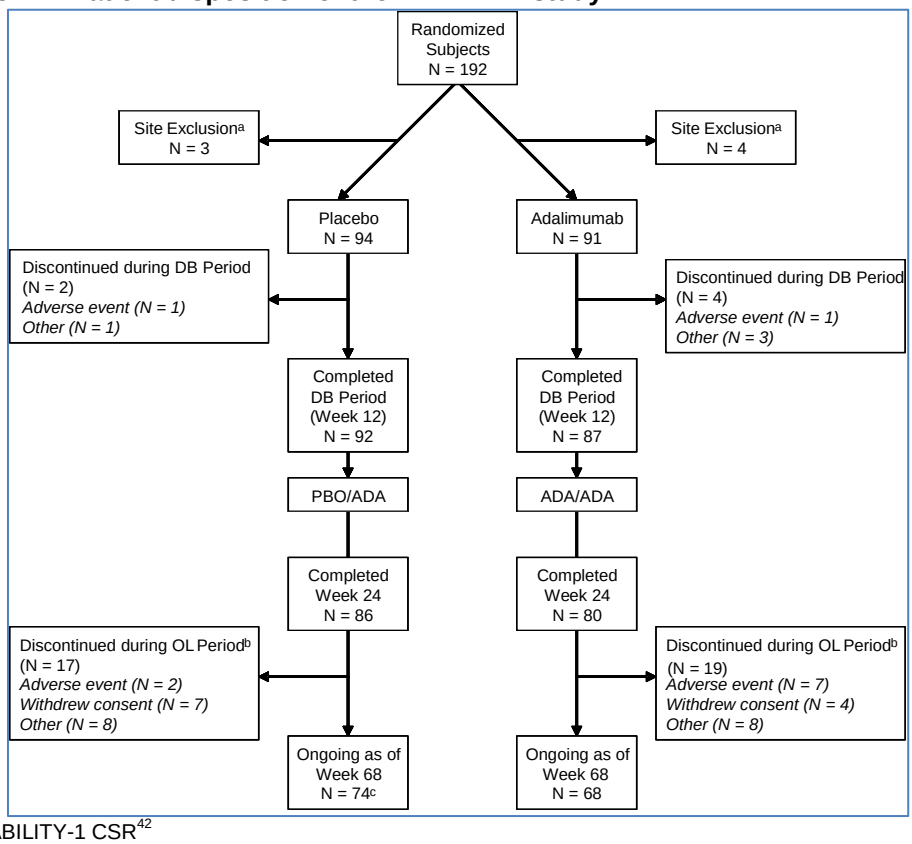


SOURCE: ABILITY-1 CSR[42], ABILITY-1 publication[8]
ADA: adalimumab

Number of patients and patient disposition

The patient disposition of the ABILITY-1 study is shown in Figure 2.3.1.2; a target sample size of 194 patients (97 to adalimumab and 97 to placebo) was planned, and 192 patients were randomised into the study. Due to investigator non-compliance identified at one of the study sites, seven patients were excluded from all the efficacy analyses (but were included in safety analyses). 179 subjects completed the 12-week double-blind period of the study, all of whom continued onto the open-label period. At Week 68, 74 patients remained in the placebo to adalimumab arm and 68 patients remained in the adalimumab treatment arm[8,42].

Figure 2.3.1.2: Patient disposition of the ABILITY-1 study



SOURCE: ABILITY-1 CSR[42]
[a] Investigator site that was excluded for non-compliance with the protocol.
[b] All discontinuations during the open-label period (before and after Week 24). Primary reason for discontinuation is shown.
[c] Does not include one placebo-treated patient who, in addition to the 74 patients, completed Week 60. This was used as the patient's last visit date. This subject is not considered to have discontinued.
ADA/ADA: adalimumab double-blind treatment followed by adalimumab open-label treatment; DB: double-blind; OL: open-label; PBO/ADA: placebo double-blind treatment followed adalimumab open-label treatment
Note: reasons for discontinuation recorded as "other" included lack of efficacy/improvement, pregnancy, investigator decision, patient moved, and inclusion/exclusion criteria violation.

Diagnosis and criteria for inclusion

Patients were included who fulfilled the following inclusion criteria.[8,42]

- Patients were ≥18 years of age
- Patients had an inadequate response to NSAIDs, intolerance to ≥1 NSAID, or had a contraindication for NSAIDs as defined by the investigator
- Patients had chronic back pain (of at least 3 months duration) with onset at age < 45 years
- Patients had MRI evidence of active inflammatory lesions of sacroiliac joints (past or present) with definite bone marrow oedema/osteitis, suggestive of sacroiliitis associated with SpA plus ≥1 of the clinical criteria listed below or positive human leukocyte antigen-B27 (HLA-B27) plus ≥2 of the clinical criteria listed below other than HLA-B27 positivity:
    - Inflammatory back pain defined as the presence at screening of at least 4 out of the following 5 parameters: 1) age at onset <40 years, 2) insidious onset, 3) improvement with exercise, 4) no improvement with rest, 5) night pain with improvement upon getting up
    - Arthritis (past or present)
    - Heel enthesitis (past or present)
    - Anterior uveitis confirmed by an ophthalmologist (past or present)
    - Dactylitis (past or present);
    - Crohn's Disease (CD) or ulcerative colitis (UC) (past or present)

  - Good prior response to an NSAID - back pain was not present anymore or much better 24 to 48 hours after a full dose of an NSAID
  - Family history of SpA
  - Positive HLA-B27
  - Elevated C-reactive protein (CRP)
- Patients had baseline disease activity as defined by having a Total Back Pain VAS score ≥40 mm and BASDAI score ≥4 at both the Screening and Baseline visits

Patients were excluded if they fulfilled the following exclusion criteria.[8,42]

- Patients fulfilling the modified New York criteria for AS were excluded.
- Patients with a diagnosis of psoriatic arthritis (PsA) and psoriasis (Ps) were also excluded from the study.
- Patients who had prior exposure to any biologic therapy with a potential therapeutic impact on SpA, including anti-TNF therapy.
- If entering the study on concomitant disease-modifying anti-rheumatic drugs (DMARDs), patients were not on stable dose of MTX (≤25 mg per week) and/or SSZ (≤3 g per day), and/or hydroxychloroquine (≤400 mg per day) for 28 days prior to the baseline visit.
- If entering the study on concomitant oral corticosteroids, patients were not on a stable dose of prednisone (≤10 mg per/day), or oral corticosteroid equivalents, for at least 14 days prior to the baseline visit.

Patient demographic/baseline characteristics

The key baseline demographics and disease characteristics of the patients in the ABILITY-1 study are summarised in Table 2.3.1.1 below. There were no significant differences between the two treatment groups[8,42]. Please note that the four people who did not receive NSAIDs prior to study entry due to investigator opinion of a contraindication for NSAID use.

Table 2.3.1.1: Key demographic and disease characteristics in ABILITY-1

	Placebo (N = 94)	Adalimumab (N = 91)
Demographic characteristic		
Age (years), Mean ± SD	38.4 (10.4)	37.6 (11.3)
Sex, n (%) Female Male	 54 (57) 40 (43)	 47 (52) 44 (48)
Body weight (kg), Mean ± SD	78.8 (16.53)	76.8 (16.56)
Disease characteristic		
Symptom duration (years), Mean ± SD	10.1 (8.8)	10.1 (9.0)
Duration since diagnosis (years), Mean ± SD	3.0 (3.8)	2.7 (4.2)
Prior NSAID use, n (%)	91 (96.8)	90 (98.9)
Prior DMARD use, n (%)	33 (35.1)	31 (34.1)
Axial spondyloarthritis-related medical history		
Inflammatory back pain, n (%)	91 (97)	88 (97)
Elevated CRP*, n (%)	36 (38)	36 (40)
Active inflammatory lesions on MRI of sacroiliac joint, n (%)**	43 (45.7)	46 (50.5)
Good prior response to NSAIDs***	70 (74)	64 (70)
Efficacy variables		
BASDAI** (0-10), Mean ± SD	6.5 (1.6)	6.4 (1.5)
ASDAS, Mean ± SD	3.4 (0.8)	3.2 (0.8)
BASFI (0-10 cm VAS), Mean ± SD	4.9 (2.3)	4.5 (1.9)
Total Back Pain VAS (0-10 cm), Mean ± SD	7.0 (1.7)	6.9 (1.8)
Patient's Global Assessment of disease activity (0-10, cm), Mean ± SD	6.8 (1.9)	6.8 (1.8)
CRP (mg/L), Mean ± SD	7.6 (10.2)	6.8 (11.8)

SOURCE: ABILITY-1 CSR[42], ABILITY-1 publication[8]

* CRP concentration above upper limit of normal in the presence of back pain; after exclusion of other causes of elevated CRP. ** MRI showing definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with SpA. *** Back pain not present or much better 24 to 48 hours after full dose of NSAID

** 6 patients in the trial had a BASDAI score at baseline <4; three patients in each arm.

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; VAS: visual analogue scale

Outcome measures

The outcomes measures used in the ABILITY-1 study were stratified into three groups, the primary endpoint, ranked secondary endpoints, and non-ranked secondary endpoints; these are summarised in Table 2.3.1.2.

Table 2.3.1.2: Outcome measures in the ABILITY-1 study

Category	Efficacy variables
Primary outcome	ASAS40 response
Ranked secondary variables at week 12	ASAS20 response
	BASDAI 50 response
	ASAS 5/6 response
	ASAS partial remission
	HAQ-S mean change from baseline
	SF-36v2 physical component score mean change from baseline
	hs-CRP mean change from baseline
	SPARCC MRI score for sacroiliac joints mean change from baseline
	SPARCC MRI score for spine mean change from baseline
Non-ranked secondary: Reduction of signs and symptoms variables – multiple time points	ASAS20/40/50/70 responses
	ASAS5/6 response
	ASAS partial remission
	Patient global assessment of pain mean change from baseline
	Total back pain mean change from baseline
	Mean change in inflammation
	BASFI mean change from baseline
	BASDAI50 response
	BASDAI mean change from baseline
	Number of patients with plantar fascia enthesitis
	Mean change in dactylitis count
	Patient global assessment of disease activity mean change from baseline
	BASMI mean change from baseline
	MASES mean change from baseline
	Nocturnal pain mean change from baseline
	Physician's global assessment of disease activity mean change from baseline
	Swollen joint count mean change from baseline
	Tender joint count mean change from baseline
	Patient global assessment of disease activity mean change from baseline
	ASDAS mean change from baseline
Non-ranked secondary: HRQoL variables – multiple time points	Mean change in HAQ-S
	Mean change in SF-36v2
	Mean change in WPAI-SHP
	PASS achievement
	MOS Sleep Scale domain scores mean change from baseline
	Mean change in EQ-5D index scores
Non-ranked secondary: Metrology variables – multiple time points	Mean change in $BASMI_{lin}$
	Mean change in $BASMI_2$
	Mean change in BASMI component scores
	Chest expansion mean change from baseline
Non-ranked secondary: Other	Biomarkers

SOURCE: ABILITY-1 CSR[42], ABILITY-1 publication[8]
ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology index; EQ-5D: EuroQoL 5-Dimension questionnaire; HAQ-S: Health Assessment Questionnaire modified for spondyloarthropathies; HCRU; health care resource utilisation; hs-CRP: high-sensitivity C-reactive protein; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MOS: Medical Outcomes Study; PASS: patient acceptable symptom state; SPARCC MRI: Spondyloarthritis Research Consortium of Canada magnetic resonance imaging; WPAI-SHP: Work Productivity and Activity Impairment – Specific Health Problem

- *Primary endpoint*

As shown in Table 2.3.1.2 (above), the primary endpoint analysed was the ASAS40 response at the Week 12 visit. The response rate observed in the group randomised to adalimumab 40 mg eow was compared to that in the placebo group. The null hypothesis associated with this comparison stated that there was no difference in response rates between the adalimumab and placebo groups; the alternative hypothesis is that the response rates were different between treatment groups. The response rates were tested using a two-sided Pearson's chi-square test with α=0.05. Patients with missing ASAS40 response at Week 12 were treated as non-responders according to non-responder imputation criterion. Analyses were conducted using a non-responder imputation, where any patients who discontinued or had missing values at Week 12 were considered to be non-responders[42].

Secondary analyses of the primary endpoint were conducted using last observation carried forward (LOCF) method and observed case (OC) analysis for the ASAS40 response. The response rates were compared using a 2-sided Pearson's chi-square test with α=0.05[42].

Note that for all efficacy endpoints, analyses were performed using the full analysis set (FAS), which includes 185 patients (94 patients in the placebo group and 91 patients in the adalimumab group, which are the 192 randomised patients minus the patients excluded at one study site due to investigator non-compliance) [8,42].

All statistical comparisons of ranked secondary efficacy variables were conducted between the adalimumab group and placebo group at Week 12 at the 2 sided α=0.05 significance level using a stepwise testing procedure[42].

Discrete variables were summarised using count and percentages and were compared between adalimumab and placebo groups using Pearson's chi-square or Fisher's exact test, if ≥25% of the cells had expected counts less than five[42].

Continuous efficacy variables were summarised by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum) at Week 12. Change from baseline at Week 12 in the continuous variables was compared between adalimumab and placebo groups using an analysis of covariance method adjusting for the baseline score. This was done for both observed and LOCF imputed values[42].

Results

Primary endpoint and ranked secondary endpoints

The primary efficacy endpoint measured was the ASAS40 response at Week 12. A statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS 40 responses at Week 12 compared with placebo, p≤0.001 (see Table 2.3.1.3)[8,42].

To assess the impact of omitting the seven patients, from the study site where there was investigator non-compliance, from the efficacy analyses, a sensitivity analysis was performed for the primary endpoint using the intention-to-treat (ITT) population, which included these seven patients. The analysis using the ITT population demonstrated the same results that were seen with the analysis using the FAS, which did not include these seven patients (34.7% who responded in the adalimumab group compared to 14.4% who responded in the placebo group, p=0.001) [8,42].

Subgroup analyses were performed to evaluate the impact of baseline conditions on the primary efficacy endpoint (ASAS40 response at Week 12). Based on subgroup interaction analyses, symptom duration, age, and baseline CRP status showed significant interactions with treatment on ASAS40 response (p=0.02, p=0.05 and p=0.03, respectively). 8 A greater treatment effect with adalimumab was observed among patients with a symptom duration of <5 years, those aged <40 years, and with patients who had elevated CRP levels at baseline. Further detail on the effect of adalimumab by CRP and MRI status at baseline are presented in Section 2.3.2 [8].

Adalimumab also showed significantly greater improvements than placebo in all nine ranked secondary efficacy endpoints at Week 12; analysis shows that there was a statistically significant difference in favour of adalimumab for all the aforementioned outcomes. These results are summarised in Table 2.3.1.3. [8,42]

Table 2.3.1.3: Summary of results for the primary endpoint and nine ranked secondary endpoints at Week 12 for the overall study population

Endpoint	Placebo N = 94		Adalimumab N = 91		P-value*
	n[a]	Result	n[a]	Result	
Primary endpoint					
ASAS 40 response (n [%])	94	14 (14.9)	91	33 (36.3)	<0.001[b]
Ranked secondary variables					
1. ASAS 20 response (n [%])	94	29 (30.9)	91	47 (51.6)	0.004[b]
2. BASDAI 50 response (n [%])	94	14 (14.9)	91	32 (35.2)	0.001[b]
3. SF-36v2 physical component score (PCS) (mean change from baseline ± SD)	93	2.0 ± 7.04	91	5.5 ± 8.98	0.001[d]
4. ASAS partial remission (n [%])	94	5 (5.3)	91	15 (16.5)	0.014[b]
5. ASAS 5/6 response (n [%])	94	6 (6.4)	91	28 (30.8)	<0.001[b]
6. HAQ-S total score (mean change from baseline ± SD)	94	–0.1 ± 0.42	91	–0.3 ± 0.49	0.027[c]
7. hs-CRP (mg/L) (mean change from baseline ± SD)	73	–0.3 ± 6.39	70	–4.7 ± 12.32	<0.001[c]
8. SPARCC MRI score for sacroiliac joints (mean change from baseline ± SD)	84	–0.6 ± 6.19	84	–3.2 ± 8.34	0.003[d]
9. SPARCC MRI score for the spine (mean change from baseline ± SD)	83	–0.2 ± 3.32	85	–1.8 ± 4.51	0.001[d]

SOURCE: ABILITY-1 CSR[42], ABILITY-1 publication[8]
[*] P-value to compare adalimumab 40 mg eow to placebo
[a] For each endpoint, n = number of subjects with non-missing value
[b] P-value for categorical variables (NRI imputation for missing values) was based on 2-sided chi-square test (or Fisher exact test).
[c] P-value for continuous variables (LOCF imputation for missing values) was based on an ANCOVA model adjusting for baseline value with treatment as a factor
[d] P-value for continuous variables (OC) was based on an ANCOVA model adjusting for Baseline value with treatment as a factor
ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ-S: Health Assessment Questionnaire modified for spondyloarthropathies; hs-CRP: high-sensitivity C-reactive protein; SPARCC MRI: Spondyloarthritis Research Consortium of Canada magnetic resonance imaging

Non-ranked secondary variables

- *Improvement of signs and symptoms*

Results of outcomes considered within the reduction of signs and symptoms outcome set are summarised in Table 2.3.1.4. In addition to the ASAS40 and ASAS20 responses evaluated for the primary and ranked secondary endpoints (Table 2.3.1.3), a statistically significantly greater proportion of subjects in the adalimumab treatment group also achieved ASAS50 and ASAS70 responses at Week 12 compared with placebo. Furthermore, subjects in the adalimumab treatment group reported a statistically significantly greater mean decrease (improvement) in patient's global assessment of disease activity and pain at week 12. Significant improvements in total back pain, inflammation/stiffness, and BASDAI were also observed in favour of adalimumab. [8,42]

Subjects in the adalimumab treatment group reported a numerically greater mean decrease (improvement) in BASFI at Week 12 compared with placebo; however, the change was not statistically significant (p=0.053). This difference was, however, observed to be statistically significant in the licensed population (see Section 2.3.2 for details). [8,42]

Table 2.3.1.4: Summary of results for the non-ranked secondary endpoints related to improvement of signs and symptoms at week 12 for overall study population

Variable	Baseline value†			Endpoint/mean change from baseline (Week 12)					Analysis Performed
	Placebo (N = 94)	Adalimumab (N = 91)	p-value*	Placebo (N = 94)		Adalimumab (N = 91)		P-value*	
				n[a]	Result	n[a]	Result		
ASAS 50 (n [%])	NA	NA	NA	94	9 (9.6)	91	28 (30.8)	<0.001	NRI
ASAS 70 (n [%])	NA	NA	NA	94	4 (4.3)	91	14 (15.4)	0.011	NRI
Patient's global assessment of disease activity (mean ± SD)	67.77 ± 18.552	67.57 ± 18.240	0.943	94	–9.3 ± 23.97	91	–21.9 ± 28.55	<0.001	LOCF
Patient's global assessment of pain (mean ± SD)	68.64 ± 17.178	67.20 ± 17.120	0.569	90	–10.1 ± 22.46	88	–22.1 ± 28.50	<0.001	OC
Total back pain (mean ± SD)	69.72 ± 17.330	69.14 ± 18.035	0.824	91	–11.5 ± 23.08	88	–23.8 ± 26.5	<0.001	LOCF
Inflammation/morning stiffness (mean ± SD)	6.71 ± 2.086	6.45 ± 1.953	0.380	94	–1.1 ± 2.20	91	–2.2 ± 2.68	<0.001	LOCF
BASDAI (mean ± SD)	6.53 ± 1.553	6.40 ± 1.483	0.566	94	–1.0 ± 1.96	91	–1.9 ± 2.50	0.004	LOCF
BASFI (mean ± SD)	48.50 ± 23.179	45.36 ± 19.406	0.322	94	–5.9 ± 19.48	90	–10.7 ± 20.75	0.053	LOCF
Plantar fascia enthesitis (n [%])	19 (20.2)	24 (26.4)	0.321	94	15 (16.0)	91	18 (19.8)	0.497	NRI
Dactylitis count (mean ± SD)	0.15 ± 0.671	0.15 ± 0.665	0.960	93	–0.054 ± 0.5588	91	–0.044 ± 0.2949	0.492	OC
$BASMII_{in}$ (mean ± SD)	2.66 ± 1.177	2.69 ± 1.268	0.862	93	–0.1 ± 0.6	90	-0.1 ± 0.67	0.828	OC
$BASMI_2$ (mean ± SD)	1.82 ± 1.481	1.80 ± 1.42	0.919	93	–0.1 ± 0.89	90	–0.0 ± 1.05	0.573	OC
BASMI component, lateral lumbar flexion in cm (mean ± SD)	14.17 ± 4.696	14.74 ± 4.981	0.421	93	0.8 ± 4.10	91	1.1 ± 3.75	0.409	OC
BASMI component, tragus to wall distance in cm (mean ± SD)	11.72 ± 2.469	11.83 ± 2.527	0.767	93	0.3 ± 2.18	89	0.2 ± 1.89	0.718	OC
BASMI component, lumbar flexion (modified Schober) in cm (mean ± SD)	6.21 ± 3.832	5.31 ± 2.835	0.073	93	0.3 ± 2.62	90	0.2 ± 2.14	0.324	OC
BASMI component, intermalleolar distance in cm (mean ± SD)	99.76 ± 22.754	101.62 ± 22.141	0.576	93	1.6 ± 15.98	91	0.9 ± 12.76	0.774	OC
BASMI component, cervical rotation in cm (mean ± SD)	65.06 ± 15.742	65.15 ± 16.889	0.968	93	0.9 ± 9.62	90	0.8 ± 11.96	0.937	OC
Chest expansion (mean ± SD)	5.26 ± 2.150	5.61 ± 2.927	0.360	93	0.3 ± 1.65	91	0.3 ± 2.54	0.585	OC
MASES (mean ± SD)	3.93 ± 3.421	3.45 ± 3.649	0.362	93	–0.8 ± 2.76	91	–0.6 ± 2.87	0.962	OC
Nocturnal pain (mean ± SD)	64.0 ± 22.62	66.0 ± 22.44	0.547	94	–7.7 ± 26.22	91	–24.3 ± 29.36	<0.001	LOCF
Physician's global assessment of disease activity (mean ± SD)	56.11 ± 15.883	58.32 ± 16.579	0.356	94	–12.5 ± 20.13	90	–21.2 ± 25.06	0.016	LOCF
Swollen joint count (mean ± SD)	1.26 ± 2.540	1.23 ± 2.895	0.951	93	–0.2 ± 2.73	91	–0.3 ± 2.59	0.754	OC
Tender joint count (mean ± SD)	6.20 ± 10.492	6.41 ± 10.680	0.896	93	–0.6 ± 7.55	91	–1.0 ± 5.85	0.730	OC
ASDAS responses: clinically important improvement (n [%])	NA	NA	NA	94	12 (12.8)	91	34 (37.4)	<0.001	NRI
ASDAS responses: major improvement (n [%])	NA	NA	NA	94	3 (3.2)	91	17 (18.7)	<0.001	NRI
ASDAS disease activity state inactive (n [%])	0	0	NA	94	4 (4.3)	91	22 (24.2)	<0.001	NRI
ASDAS disease activity state moderate (n [%])	5 (5.5)	2 (2.3)	NR	94	15 (16.0)	91	20 (22.0)	0.553	NRI
ASDAS disease activity state high (n [%])	51 (56.0)	56 (64.4)	NR	94	38 (40.4)	91	41 (45.1)	0.910	NRI
ASDAS disease activity state very high (n [%])	35 (38.5)	29 (33.3)	NR	94	31 (33.0)	91	5 (5.5)	<0.001	NRI

SOURCE: ABILITY-1 CSR[42], ABILITY-1 publication[8]

† *Data shown for the FAS population at baseline*

** P-values compare the adalimumab 40 mg eow group to the placebo group*
[a] For each endpoint, n = number of subjects with non-missing value
ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; LOCF: last observation carried forward; NA: not applicable; NRI: non-responder imputation; OC: observed case; SD: standard deviation

No statistically significant or clinically meaningful differences between the adalimumab and placebo treatment groups were observed at Week 12 for change from Baseline in $BASMI_{lin}$ total score, BASMI2 total score, or BASMI component scores. Statistically significant differences were, however, observed between patients treated with adalimumab and patients who had received placebo at Week 12 for the outcomes of nocturnal pain and physician's global assessment of disease activity. [8,42]

Clinically important and major improvements in ASDAS (defined as reductions from baseline of ≥1.10 and ≥2.00 points, respectively) were observed in a statistically significantly greater proportion of patients in the adalimumab treatment group compared with placebo at Week 12 in both populations (Table 2.3.1.4). Compared with placebo, the adalimumab treatment group had a statistically significantly greater proportion of subjects reporting an inactive disease state and a statistically significantly smaller proportion of subjects reporting a very high disease state at Week 12. [8,42]

- *HRQoL outcomes*

As previously shown (Table 2.3.1.3), subjects in the adalimumab treatment group reported a statistically significantly greater mean increase (improvement) in SF-36 PCS scores at Week 12 compared with placebo. While subjects in the adalimumab treatment group reported a numerically greater mean increase (improvement) in SF-36 MCS scores at Week 12 compared with placebo this increase was not statistically significant [8,42].

At Week 12, no statistically significant difference was observed in the number of subjects in the adalimumab and placebo treatment groups who were employed or absent from work during the previous week (as measured using the WPAI-SHP); however, subjects in the adalimumab treatment group reported statistically significantly greater mean decreases (improvements) in absenteeism and activity impairment at Week 12 compared with placebo[8,42].

A numerically greater proportion of subjects in the adalimumab treatment group than in the placebo group achieved PASS at Week 12. Subjects in the adalimumab treatment group reported a statistically significantly greater mean increase (improvement) in the sleep quantity domain of the MOS Sleep Scale at Week 12 compared with placebo. Statistically significant changes were not observed for the other domains8,[42].

Lastly, at Week 12, subjects in the adalimumab treatment group had a statistically significant increase (improvement) in the EQ-5D compared with subjects in the placebo treatment group, an improvement of 0.12 ± 0.290 vs. 0.04 ± 0.308 respectively (p=0.037) [8,42].

- *Other outcomes - biomarkers*

Subjects in the adalimumab treatment group reported a numerically greater mean decrease (improvement) in Matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor A ($VEGF_A$) at Week 12 compared with placebo; statistical significance was not observed. Further, subjects in the adalimumab treatment group reported a numerically lower mean decrease (improvement) in Type II collagen C-telopeptide (CTX-II) compared with placebo, however, this difference was not statistically significant[8,42].

Conclusion

In summary, in ABILITY-1, adalimumab therapy resulted in improvements in pain, disease activity, health-related quality of life, and work outcomes in patients with severe nr-axSpA who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs compared to placebo.[8,42]

2.3.2 Subgroup analyses; ABILITY-1 licensed population

Adalimumab is efficacious in patients with severe active nr-axSpA with objective signs of inflammation by elevated CRP and/or MRI, as demonstrated by subgroup analyses of the ABILITY-1 trial.

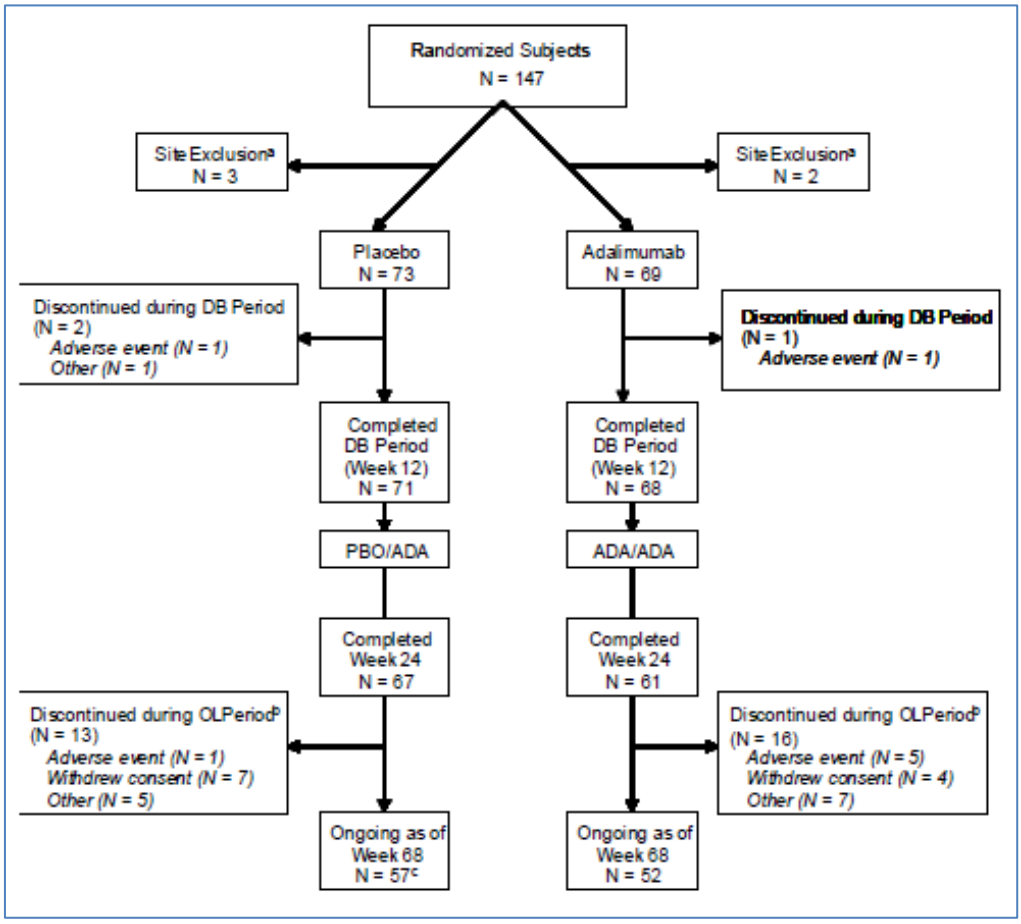
The EMA licence for adalimumab stipulates that adalimumab should be used for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (i.e. nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. This corresponds to a subgroup population within the ABILITY-1 trial; results of this subgroup analysis are presented below. All data presented herein for this population, unless specified otherwise, have not yet been published and therefore should be treated as commercial in confidence.

Diagnosis and criteria for inclusion

Diagnosis and inclusion criteria remain the same as per Section 2.3.1, but with the addition that patients have elevated CRP at baseline and/or a positive MRI result (i.e., SPARCC MRI score at baseline ≥2 either for the sacroiliac joint [SI] or for the spine).[42]

147 patients fulfilled the criteria for the nr-axSpA licensed population; 76 patients in the placebo group and 71 patients in the adalimumab group (Figure 2.3.2.1). Data presented below are for the licensed population subset (N=142) of the overall study population presented in Section 2.3.1, which is calculated as the intention-to-treat (ITT) population minus subjects from the site of Investigator 19386.[42]

Figure 2.3.2.1: Patient disposition of the licensed population (ATP) from ABILITY-1 study



Patient demographic/baseline characteristics

The key baseline demographics and disease characteristics of patients in the ABILITY-1 study are summarised in Table 2.3.2.1, stratified by patient population. No statistically significant differences were observed between the two treatment groups in either the overall study population or in the licensed (ATP) population. Furthermore, the ABILITY-1 overall study population and the licensed population characteristics were similar, with the exception of CRP levels where, as expected, the percentage of patients with elevated CRP (mg/L) was higher in the licensed population subgroup than the overall study population.[42]

Please note that three people did not receive NSAIDs prior to study entry because the investigator considered that there was a contraindication for NSAID use.

Table 2.3.2.1: Key demographic and disease characteristics in ABILITY-1, separated for the overall ABILITY-1 trial population and the licensed (ATP) population

	ABILITY-1 trial population		Licensed (ATP) population	
	Placebo (N = 94)	Adalimumab (N = 91)	Placebo (N = 73)	Adalimumab (N = 69)
Demographic Characteristic				
Age (years), Mean ± SD	38.4 (10.4)	37.6 (11.3)	38.3 ± 10.49	38.3 ± 11.70
Sex, n (%) Female Male	 54 (57.4) 40 (42.6)	 47 (51.6) 44 (48.4)	 40 (54.8) 33 (45.2)	 37 (53.6) 32 (46.4)
Body weight (kg), Mean ± SD	78.8 ± 16.53	76.8 ± 16.56	81.2 ± 17.21	78.9 ± 17.07
Disease Characteristic				
SpA symptom duration (years), Mean ± SD	10.1 ± 8.8	10.1 ± 9.0	10.50 ± 9.166	10.66 ± 9.642
Duration since diagnosis (years), Mean ± SD	3.0 ± 3.8	2.7 ± 4.2	3.10 ± 3.827	2.55 ± 3.972
Prior NSAID use, n (%)	91 (96.8)	90 (98.9)	71 (97.3)	68 (98.6)
Prior DMARD use, n (%)	33 (35.1)	31 (34.1)	26 (35.6)	22 (31.9)
Axial Spondyloarthritis-Related Medical History				
Inflammatory back pain, n (%)	91 (97)	88 (97)	71 (97.3)	66 (95.7)
Elevated CRP*, n (%)	36 (38)	36 (40)	34 (46.6)	31 (44.9)
Active inflammatory lesions on MRI of sacroiliac joint, n (%)**	43 (45.7)	46 (50.5)	32 (43.8)	40 (58.0)
Good prior response to NSAIDs***	70 (74)	64 (70)	57 (78.1)	48 (69.6)
Efficacy Variables				
BASDAI (0-10), Mean ± SD	6.5 (1.6)	6.4 (1.5)	6.38 ± 1.499	6.43 ± 1.551
ASDAS, Mean ± SD	3.4 (0.8)	3.2 (0.8)	3.43 ± 0.796	3.36 ± 0.817
BASFI (0-10 cm VAS), Mean ± SD	4.9 (2.3)	4.5 (1.9)	4.820 ± 2.3095	4.471 ± 2.0653
Total Back Pain VAS (0-10 cm), Mean ± SD	7.0 (1.7)	6.9 (1.8)	6.682 ± 1.7083	6.971 ± 1.9359
Patient's Global Assessment of disease activity (0-10, cm), Mean ± SD	6.8 (1.9)	6.8 (1.8)	6.622 ± 1.9077	6.887 ± 1.8017
CRP (mg/L), Mean ± SD	7.6 (10.2)	6.8 (11.8)	9.3 ± 10.94	8.6 ± 13.07

SOURCE: ABILITY-1 publication[8], ABILITY-1 CSR[42]
* CRP concentration above upper limit of normal in the presence of back pain; after exclusion of other causes of elevated CRP. ** MRI showing definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with SpA. *** Back pain not present or much better 24 to 48 hours after full dose of NSAID
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; DMARD: disease-modifying anti-rheumatic drug; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation; VAS: visual analogue scale

Results

Primary endpoint and ranked secondary variables

The primary efficacy endpoint measured was the ASAS40 response at Week 12. Similar to that observed in the ABILITY-1 overall study population, in the licensed (ATP) population subgroup a statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS 40 response at Week 12 compared with placebo (p<0.001) (Table 2.3.2.2). Furthermore, adalimumab demonstrated significantly greater improvements vs. placebo in all nine ranked secondary efficacy endpoints at Week 12.[42]

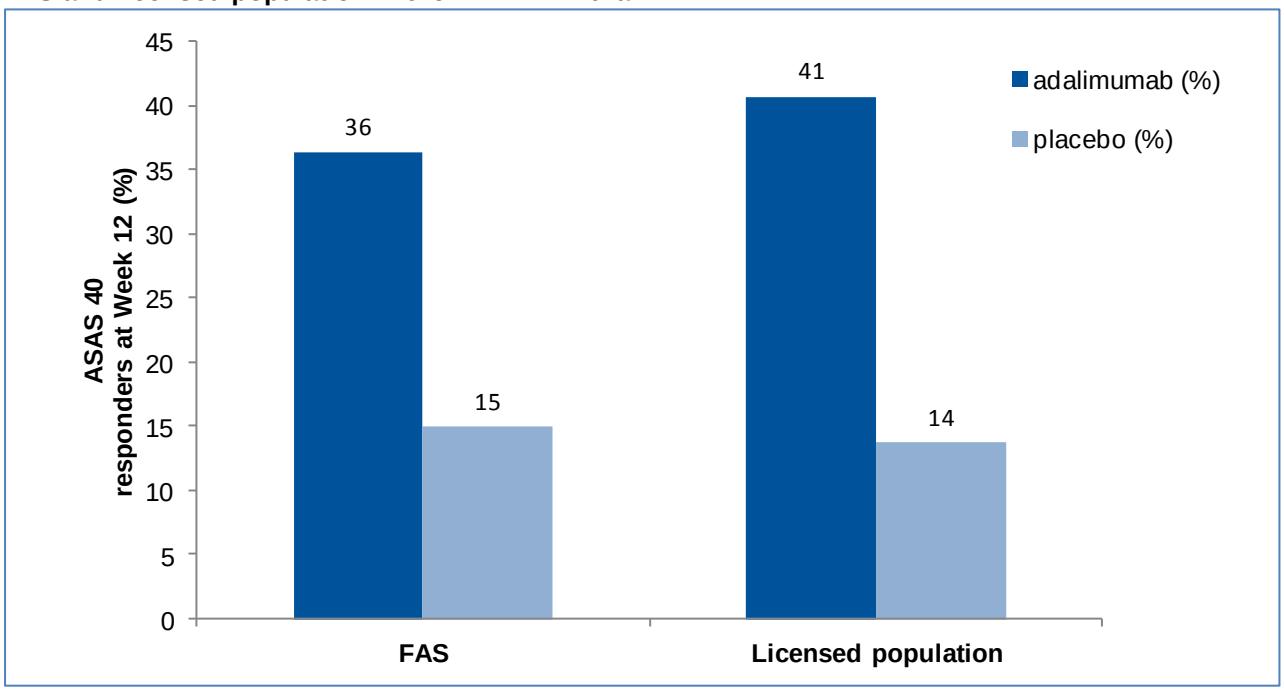
Table 2.3.2.2: Primary and ranked secondary outcomes in the licensed nr-axSpA populations in the 12-week double-blind period, stratified by treatment group

Endpoint	Placebo N = 73		Adalimumab N = 69		P-value
	n[a]	Result	n[a]	Result	
Primary endpoint					
ASAS 40 response (n [%])	73	10 (13.7)	69	28 (40.6)	<0.001[b]
Ranked secondary endpoints					
1. ASAS20 response (n [%])	73	23 (31.5)	69	41 (59.4)	<0.001[b]
2. BASDAI50 response (n [%])	73	10 (13.7)	69	27 (39.1)	<0.001[b]
3. SF-36v2 physical component score (PCS) (mean change from baseline ± SD)	72	2.3 ± 6.81	69	6.9 ± 9.32	<0.001[d]
4. ASAS partial remission (n [%])	73	4 (5.5)	69	13 (18.8)	0.014[b]
5. ASAS 5/6 response (n [%])	73	6 (8.2)	69	24 (34.8)	<0.001[b]
6. HAQ-S total score (mean change from baseline ± SD)	73	-0.1 ± 0.34	69	-0.3 ± 0.51	0.007[c]
7. hs-CRP (mg/L) (mean change from baseline ± SD)	54	-0.8 ± 7.33	50	-6.5 ± 14.18	<0.001[c]
8. SPARCC MRI score for sacroiliac joints (mean change from baseline ± SD)	64	-0.9 ± 7.09	64	-4.3 ± 9.27	0.002[d]
9. SPARCC MRI score for the spine (mean change from baseline ± SD)	63	-0.5 ± 3.66	65	-2.3 ± 5.02	0.004[c]

SOURCE: ABILITY-1 publication[8], ABILITY-1 CSR[42]
[*] P-value to compare responder numbers in the adalimumab 40 mg eow to placebo
[a] For each endpoint, n = number of subjects with non-missing value
[b] P-value for categorical variables (NRI imputation for missing values) was based on 2-sided chi-square test (or Fisher exact test).
[c] P-value for continuous variables (LOCF imputation for missing values) was based on an ANCOVA model adjusting for baseline value with treatment as a factor
[d] P-value for continuous variables (OC) was based on an ANCOVA model adjusting for Baseline value with treatment as a factor
ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ-S: Health Assessment Questionnaire modified for spondyloarthropathies; hs-CRP: high-sensitivity C-reactive protein; SPARCC MRI: Spondyloarthritis Research Consortium of Canada magnetic resonance imaging

Figure 2.3.2.2 compares ASAS 40 responses at Week 12 in the overall and licensed (ATP) populations. It should be noted that the relative benefit of adalimumab over placebo appears to be greater in the licensed population than the overall study population. This was also observed for the majority of the nine ranked secondary outcomes (Table 2.3.1.3 and 2.3.2.2)[42].

Figure 2.3.2.2: Proportion of patients achieving an ASAS 40 response at Week 12 in the FAS and licensed population in the ABILITY-1 trial



SOURCE: ABILITY-1 publication8
ASAS: Assessment of SpondyloArthritis international Society; FAS: full analysis set

Non-ranked secondary endpoints

Improvement of signs and symptoms

Results of outcomes considered within the reduction of signs and symptoms outcome set are summarised in Table 2.3.2.3. As was observed with the overall study population, in addition to the ASAS40 and ASAS20, in the licensed population, a statistically significantly greater proportion of subjects in the adalimumab treatment group also achieved ASAS50 and ASAS70 responses at Week 12 compared with placebo. Furthermore, significant improvements in favour of adalimumab for the outcomes of patient's global assessment of disease activity and pain, total back pain, inflammation/stiffness, and BASDAI observed in the overall study population were also observed in the group of patients with elevated CRP and/or positive MRI[42].

Whilst a numerical but not statistically significant benefit in favour of adalimumab was observed for BASFI at Week 12 in the overall study population, the benefit observed in the group of patients with elevated CRP and/or positive MRI did reach statistical significance (p=0.020) (Table 2.3.2.3).

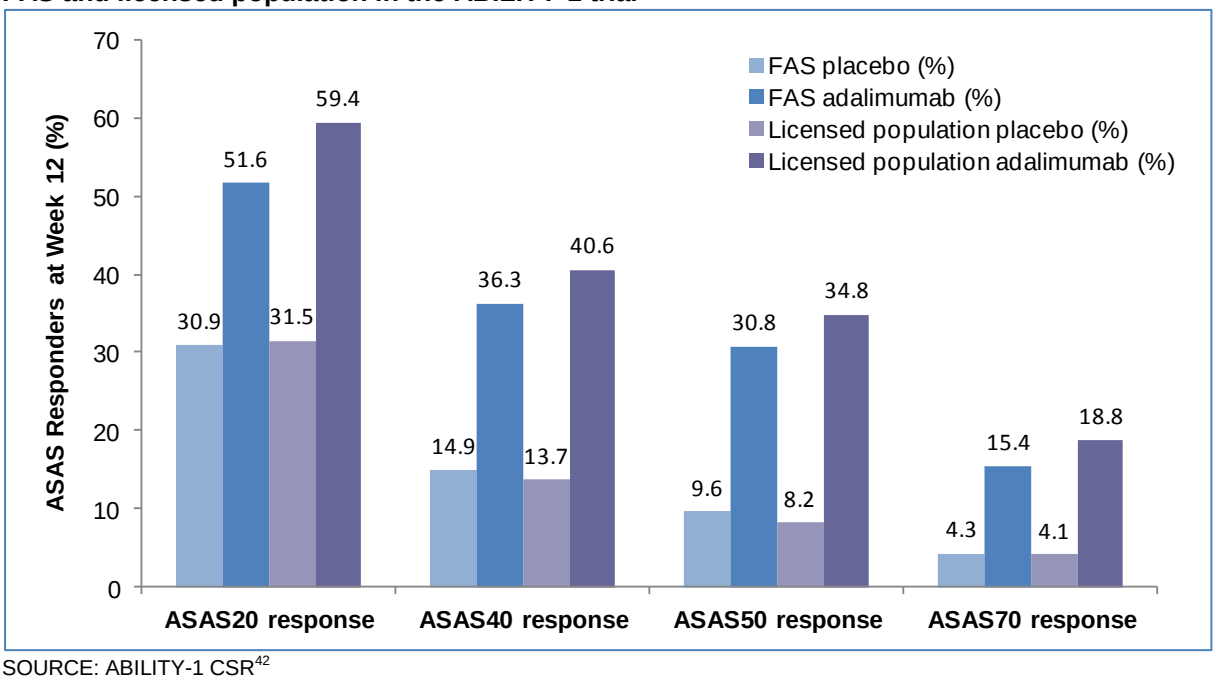
Table 2.3.2.3: Summary of results for the non-ranked secondary endpoints related to reduction of signs and symptoms

Variable	Baseline value			Endpoint/mean change from baseline (Week 12)					Result type
	Placebo (N = 73)	Adalimumab (N = 69)	P-value	Placebo (N = 73)		Adalimumab (N = 69)		P-value	
				N	Result	n	Result		
ASAS50 (n [%])	NA	NA	NA	73	6 (8.2)	69	24 (34.8)	<0.001	NRI
ASAS70 (n [%])	NA	NA	NA	73	3 (4.1)	69	13 (18.8)	0.006	NRI
Patient's global assessment of disease activity (mean ± SD)	66.22 ± 19.077	68.87 ± 18.017	0.397	73	–9.8 ± 22.60	69	–26.1 ± 27.56	<0.001	LOCF
Patient's global assessment of pain (mean ± SD)	66.47 ± 17.520	67.90 ± 17.89	0.630	73	–8.8 ± 21.21	69	–25.3 ± 28.50	<0.001	LOCF
Total back pain (mean ± SD)	66.82 ± 17.083	69.71 ± 19.36	0.347	73	–9.2 ± 21.51	69	–26.7 ± 26.73	<0.001	LOCF
Inflammation/morning stiffness (mean ± SD)	6.67 ± 2.171	6.44 ± 2.06	0.521	73	–1.2 ± 1.99	69	–2.4 ± 2.65	0.001	LOCF
BASDAI (mean ± SD)	6.38 ± 1.499	6.43 ± 1.55	0.842	73	–1.1 ± 1.96	69	–2.2 ± 2.50	0.003	LOCF
BASFI (mean ± SD)	48.20 ± 23.095	44.71 ± 20.65	0.348	73	–6.3 ± 17.92	68	–12.8 ± 20.22	0.020	LOCF
Plantar fascia enthesitis (n [%])	14 (9.2)	18 (26.1)	0.325	72	10 (13.9))	69	11 (15.9)	0.707	NRI
Dactylitis count (n [%])	0.15 ± 0.681	0.07 ± 0.312	0.385	72	-0.028 ± 0.5300	69	-0.014 ± 0.2095	0.901	OC

SOURCE: ABILITY-1 CSR[42]
** P-values compare the adalimumab 40 mg eow group to the placebo group*
[a] For each endpoint, n = number of subjects with non-missing value
ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; LOCF: last observation carried forward; NA: not applicable; NRI: non-responder imputation; OC: observed case; SD: standard deviation

Figure 2.3.2.3 compares ASAS20/40/50/70 responses at Week 12 in the FAS and sub-group of patients with elevated CRP and/or positive MRI. For all outcomes, the relative benefit of adalimumab over placebo was observed to be greater in the licensed population than the FAS.[42]

Figure 2.3.2.3: Proportion of patients achieving ASAS response targets at Week 12 in the FAS and licensed population in the ABILITY-1 trial



SOURCE: ABILITY-1 CSR[42]
ASAS: Assessment of SpondyloArthritis international Society; FAS: full analysis set

Statistically significant differences between patients treated with adalimumab and patients who had received placebo at Week 12 were observed in terms of ASDAS responses, physician's global assessment of disease activity, and nocturnal pain (see Table 2.3.2.4).

Clinically important and major improvements in ASDAS (defined as reductions from baseline of ≥1.10 and ≥2.00 points, respectively) were observed in a statistically significantly greater proportion of patients in the adalimumab treatment group compared with placebo at Week 12 (Table 2.3.2.4). Compared with placebo, the adalimumab treatment group had a statistically significantly greater proportion of subjects reporting an inactive disease state at week 12.[42]

Table 2.3.2.4: Summary of results for the non-ranked secondary endpoints related to improving signs and symptoms of disease

Variable	*Baseline value*			*Endpoint/mean change from baseline (Week 12)*					*Result type*
	Placebo (N = 73)	*Adalimumab (N = 69)*	*P-value**	*Placebo (N = 73)*		*Adalimumab (N = 69)*		*P-value**	
				N	*Result*	*N*	*Result*		
$BASMII_{in}$ (mean ± SD)	*2.7 ± NR*	*2.7 ± NR*	*NR*	*72*	*-0.2 ± 0.64*	*68*	*-0.2 ± 0.73*	*0.863*	*OC*
$BASMI_2$ (mean ± SD)	*1.8 ± NR*	*1.8 ± NR*	*NR*	*72*	*-0.1 ± 0.91*	*68*	0.0 *1.14*	*0.423*	*OC*
BASMI component, lateral lumbar flexion in cm (mean ± SD)	*14.08 ± 4.955*	*14.78 ± 5.003*	*0.404*	*72*	*1.0 ± 4.16*	*69*	*1.3 ± 4.04*	*0.454*	*OC*
BASMI component, tragus to wall distance in cm (mean ± SD)	*11.68 ± 2.364*	*11.87 ± 2.330*	*0.638*	*72*	*0.3 ± 2.07*	*67*	*0.2 ± 1.93*	*0.990*	*OC*
BASMI component, lumbar flexion (modified Schober) in cm (mean ± SD)	*6.05 ± 3.690*	*5.54 ± 2.856*	*0.366*	*72*	*0.5 ± 2.69*	*69*	*0.3 ± 2.08*	*0.433*	*OC*
BASMI component, intermalleolar distance in cm (mean ± SD)	*99.56 ± 23.331*	*101.48 ± 23.384*	*0.625*	*72*	*1.8 ± 17.39*	*69*	*1.6 ± 14.04*	*0.971*	*OC*
BASMI component, cervical rotation in cm (mean ± SD)	*64.41 ± 15.312*	*64.48 ± 16.985*	*0.978*	*72*	*1.1 ± 9.09*	*68*	*1.4 ± 12.56*	*0.862*	*OC*
Chest expansion (mean ± SD)	*5.20 ± 2.214*	*5.50 ± 2.998*	*0.501*	*72*	*0.3 ± 1.75*	*69*	*0.3 ± 2.84*	*0.658*	*OC*
MASES (mean ± SD)	*4.07 ± 3.465*	*3.45 ± 3.759*	*0.309*	*72*	*-1.0 ± 2.71*	*69*	*-0.7 ± 2.78*	*0.932*	*OC*
Nocturnal pain VAS (mean ± SD)	*61.3 ± 23.21*	*66.3 ± 22.84*	*NR*	*73*	*-6.1 ± 24.33*	*69*	*-27.1 ± 28.81*	*<0.001*	*LOCF*
Physician's global assessment of disease activity (mean ± SD)	*53.89 ± 15.820*	*58.29 ± 15.854*	*0.100*	*73*	*–12.7 ± 19.72*	*69*	*–22.3 ± 25.22*	*0.032*	*LOCF*
Swollen joint count (mean ± SD)	*1.10 ± 2.161*	*1.48 ± 3.207*	*0.404*	*72*	*–0.0 ± 2.61*	*69*	*–0.3 ± 2.96*	*0.872*	*OC*
Tender joint count (mean ± SD)	*5.42 ± 9.644*	*7.36 ± 11.815*	*0.285*	*72*	*–0.9 ± 8.19*	*69*	*–1.3 ± 6.47*	*0.812*	*OC*
ASDAS responses: clinically important improvement (n [%])	*NA*	*NA*	*NA*	*73*	*9 (12.3)*	*69*	*28 (40.6)*	*<0.001*	*NRI*
ASDAS responses: major improvement (n [%])	*NA*	*NA*	*NA*	*73*	*1 (1.4)*	*69*	*17 (24.6)*	*<0.001*	*NRI*
ASDAS disease activity state inactive (n [%])	*0*	*0*	*NA*	*73*	*3 (4.1)*	*69*	*20 (29.0)*	*<0.001*	*NRI*
ASDAS disease activity state moderate (n [%])	*3 (4.2)*	*0*	*NR*	*73*	*12 (16.4)*	*69*	*14 (20.3)*	*0.553*	*NRI*
ASDAS disease activity state very high (n [%])	*31 (43.1)*	*27 (40.9)*	*NR*	*73*	*23 (31.5)*	*69*	*6 (8.7)*	*<0.001*	*NRI*

SOURCE: ABILITY-1 CSR[42]

** P-values compare the adalimumab 40 mg eow group to the placebo group*

[a] For each endpoint, n = number of subjects with non-missing value

ASDAS: Ankylosing Spondylitis Disease Activity Score; LOCF: last observation carried forward; BASMI: Bath Ankylosing Spondylitis Metrology Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; *NA: not applicable; NRI: non-responder imputation; OC: observed case; SD: standard deviation*

HRQoL outcomes

Results of outcomes considered within the HRQoL outcome set for the licensed population are summarised in Table 2.3.2.5. Statistically significant differences between patients treated with adalimumab and patients who had received placebo at Week 12 were observed in terms of the WPAI-SHP absenteeism/activity impairment/presenteeism components, total HAQ-S score, EQ-5D index scores and MOS sleep scale sleep quantity domain[42].

Table 2.3.2.5: Summary of results for the non-ranked secondary endpoints related to HRQoL outcomes

Variable	Baseline value			Endpoint/mean change from baseline (Week 12)					Result type
	Placebo (N = 73)	Adalimumab (N = 69)	P-value*	Placebo (N = 73)		Adalimumab (N = 69)		P-value*	
				n^	Result	n^	Result		
SF-36v2 mental component score (mean ± SD)	43.69 ± 13.258	43.21 ± 9.942	0.807	72	0.7 ± 11.38	69	1.4 ± 8.63	0.729	OC
WPAI-SHP absenteeism component (mean ± SD)	8.8 ± 19.12	11.5 ± 24.92	0.568	37	1.3 ± 19.30	35	-8.9 ± 25.34	0.017	OC
WPAI-SHP presenteeism component (mean ± SD)	44.2 ± 26.48	38.5 ± 23.41	0.295	42	-7.6 ± 27.12	39	-14.4 ± 26.93	0.041	OC
WPAI-SHP overall work impairment component (mean ± SD)	48.6 ± 28.26	43.7 ± 27.36	0.418	37	-8.4 ± 28.11	35	-14.1 ± 27.60	0.128	OC
WPAI-SHP activity impairment component (mean ± SD)	55.7 ± 25.33	56.4 ± 24.13	0.870	68	-4.6 ± 26.34	69	-16.2 ± 24.02	0.005	OC
PASS (n [%])	10 (13.7)	5 (7.2)	NR	70	13 (18.6)	68	19 (27.9)	0.192	OC
MOS sleep scale sleep disturbance domain (mean ± SD)	52.4 ± 27.59	50.1 ± 22.40	0.586	72	-5.1 ± 19.75	69	-8.3 ± 18.33	0.194	OC
MOS sleep scale daytime somnolence domain (mean ± SD)	39.7 ± 23.34	42.6 ± 20.65	0.438	72	-2.6 ± 19.11	69	-5.9 ± 14.97	0.353	OC
MOS sleep scale perceived sleep adequacy domain (mean ± SD)	28.6 ± 22.57	31.4 ± 21.37	0.446	72	4.9 ± 18.91	69	5.4 ± 22.20	0.687	OC
MOS sleep scale awaken short of breath or with headache domain (mean ± SD)	20.0 ± 23.33	19.4 ± 23.51	0.883	72	-2.8 ± 24.74	68	0.6 ± 22.39	0.366	OC
MOS sleep scale snoring domain (mean ± SD)	35.3 ± 29.17	32.4 ± 31.68	0.570	70	1.1 ± 24.05	67	-0.9 ± 24.48	0.512	OC
MOS sleep scale sleep quantity domain (mean ± SD)	6.5 ± 1.82	6.4 ± 1.29	0.623	66	-0.2 ± 1.63	68	0.4 ± 1.21	0.005	OC
MOS sleep scale sleep 6 problem index 6 domain (mean ± SD)	49.3 ± 19.97	48.0 ± 15.64	0.657	72	-3.7 ± 15.04	69	-5.0 ± 13.37	0.472	OC
MOS sleep scale sleep problem index 9 domain (mean ± SD)	51.3 ± 20.35	50.3 ± 16.11	0.764	72	-4.2 ± 15.13	69	-6.2 ± 13.83	0.321	OC
EQ-5D questionnaire UK version of the index score (mean ± SD)	0.50 ± 0.290	0.47 ± 0.292	0.593	71	0.06 ± 0.276	68	0.15 ± 0.303	-	OC

** P-values compare the adalimumab 40 mg eow group to the placebo group*
^ For each endpoint, n = number of subjects with non-missing value

EQ-5D: EuroQoL-5 dimension questionnaire; HCRU: Health Care Resource Utilisation; MOS: Medical Outcomes Study; *NA: not applicable; OC: observed case; SD: standard deviation; WPAI-SHP:* Work Productivity and Activity Impairment – Specific Health Problem

Conclusion

Adalimumab therapy resulted in improvements in pain, disease activity, health-related quality of life, and work outcomes in patients with severe nr-axSpA with objective signs of inflammation by elevated CRP and/or MRI who had an inadequate response to, or intolerance to one or more NSAIDs, or had a contraindication for NSAIDs. Indeed, the relative benefit of adalimumab over placebo was observed to be greater for a number of key outcomes in this subgroup of the ABILITY-1, than in the full trial population (FAS).[42]

2.3.3 Long-term efficacy

Available evidence supports the maintenance of efficacy up to 156 weeks in patients who have responded to adalimumab.

The 12-week placebo-controlled component of the ABILITY-1 study was followed by an open-label period during which patients received adalimumab 40 mg eow sc. Patients who completed the double-blind period of the ABILITY-1 study were eligible to receive open-label adalimumab for up to an additional 144 weeks (regardless of the treatment arm they were originally randomised to) totalling 156 weeks of adalimumab data.

Results[42]

At week 156 in the overall ABILITY-1 study population, 101/122 (82.8%), 81/122 (66.4%), 72/122 (59.0%), 56/122 (45.9%) patients receiving 40mg adalimumab eow had achieved an ASAS20/40/50/70 response respectively. In the licensed population (ATP) from ABILITY-1, 83/97 (85.6), 67/97 (69.1%), 58/97 (59.8%), 47/97 (48.5%) patients receiving 40mg adalimumab eow achieved an ASAS20/40/50/70 response at week 156, respectively.

At week 156 in the overall ABILITY-1 study population, 85/122 (69.7%) patients achieved BASDAI50 response, and 70/97 (72.2%) achieved BASDAI 50 at week 156 in the licensed (ATP) population.

Conclusion[42]

The data show that the benefits of adalimumab observed in the first 12 weeks reported in Sections 2.3.1 and 2.3.2 above are sustained for up to three years in patients with nr-axSpA.

2.3.4 Investigator-initiated study (Haibel 2008)[10]

Summary: An investigator-initiated study, conducted in two centres in Germany, of adalimumab 40mg eow versus placebo in patients with nr-axSpA who have had an inadequate response to or do not tolerate NSAID therapy. Statistically significant improvement was noted in the primary endpoint of ASAS 40 at Week 12 and in multiple secondary endpoints including ASAS 20, BASDAI 50, and BASFI.

Objective

To evaluate the safety and efficacy of adalimumab in patients with severe active nr-axSpA who are refractory to conventional treatment (NSAID therapy)[10].

Study design

This study was a double-blind, placebo-controlled trial conducted at two centres in Germany of 46 patients with severe nr-axSpA. Patients were randomised to receive placebo (n=24) or adalimumab at a dosage of 40 mg subcutaneously eow (n=22) for 12 weeks. An open-label extension that continued up to week 52 was also conducted. Non-responders at the end of the initial 12-week period were eligible for dose escalation to adalimumab 40 mg per week10.

Eligible patients were adults (aged ≥18 years) with active disease (BASDAI ≥4) despite previous treatment with NSAIDs. All patients were to have a diagnosis of axSpA without radiographically defined sacroiliitis; this diagnosis was based on the presence of chronic low back pain (>3 months duration), an age at symptom onset of <50 years, and the fulfilment of at least three of six criteria (including at least two of the first three)[10].

1. Inflammatory back pain
2. HLA-B27 positivity
3. An MRI showing active inflammation of the spine or sacroiliac joints
4. A history of a good response to NSAID treatment
5. The presence (current or past) of one or more extra-spinal manifestations (anterior uveitis, peripheral arthritis, or enthesitis)
6. A family history of SpA

Patients with radiographically defined sacroiliitis as defined by the modified New York criteria were excluded.

The primary endpoint for this study was ASAS 40. Secondary outcomes included the BASDAI 50, BASFI, BASMI, ASAS 20, ASAS PR, MASES, and the mean improvement in disease activity measures. In addition, measures of physical function and HRQoL were collected including the SF-36, EQ-5D, and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire.[10]

The statistical analysis was based on the intent-to-treat (ITT) population. Fisher's exact test was applied to compare response rates and categorical variables. The Clopper and Pearson method was used to calculate 95% confidence intervals (95% CIs) of the response rates.[43] Means were compared between groups by analysis of covariance, with the baseline value as the covariate. Because all patients were switched to adalimumab after 12 weeks, combined data from both groups were analysed at 52 weeks of treatment (52 weeks of adalimumab treatment in patients randomised to receive adalimumab and 40 weeks of adalimumab treatment in those randomised to receive placebo). Non-responder imputation was used for categorical variables for those patients who withdrew from the study and LOCF was used to impute missing values for continuous variables. All statistical tests were 2-sided. P values less than 0.05 were considered significant.

Results

All 46 randomised patients completed the 12-week double-blind period. The mean age in the adalimumab and placebo groups were 38 years and 37 years respectively, with a mean disease duration of 7 years and 8 years, respectively.[10]

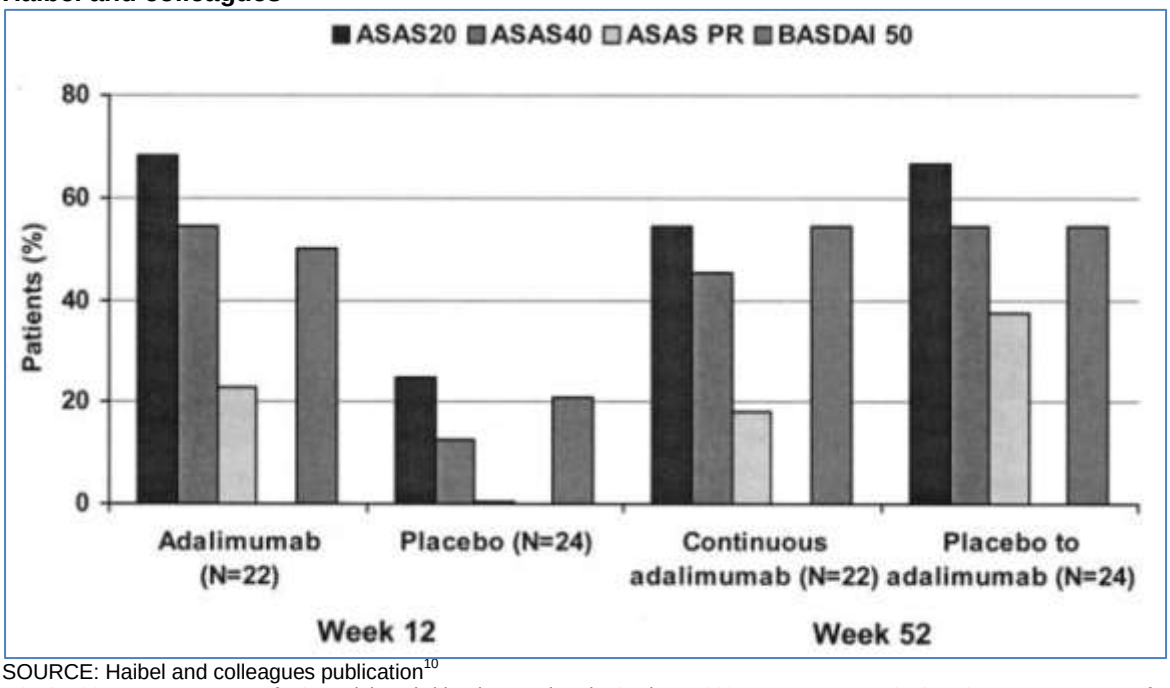
A summary of the results for the primary and key secondary outcomes for both the 12-week double-blind period and open-label extension are presented in Figure 2.3.4.1. At Week 12, a greater proportion of patients treated with adalimumab achieved an ASAS 40 (54.4%) compared with those who received placebo (12.5%); this difference was statistically significant, p=0.004. The clinical improvement achieved in patients initially treated with adalimumab was sustained through to Week 52; 45.5% of patients achieved an ASAS 40 at Week 52. Furthermore, the proportion of patients initially receiving placebo who achieved an ASAS 40 at Week 12 significantly increased at Week 52 after switching to open-label adalimumab (12.5% at week 12 to 66.7% at week 52)[10].

Similarly, statistically significant improvements in favour of adalimumab compared to placebo at Week 12 were observed for ASAS 20 response, ASAS partial remission, and BASDAI 50. The

proportion of patients who achieved ASAS 20 at Week 12 was statistically significantly greater in patients treated with adalimumab compared to patients who had received placebo (68.2% and 25% respectively, p=0.007). Approximately 23% of patients in the adalimumab group achieved an ASAS partial remission response compared to 1% in the placebo group (p=0.019). The results in terms of these key outcomes are summarised in Figure 2.3.4.1.[10]

Statistically significant improvements in favour of adalimumab over placebo were observed at Week 12 for morning stiffness, BASFI (p=0.012), CRP (p=0.049), patient's global assessment of disease (p=0.025), physician's global assessment (p=0.026), general pain (p=0.05), and nocturnal pain (p=0.019) (data not shown for all outcomes here). At Week 52, statistically significant improvements from baseline in SF-36 mental and physical component summary scores, EQ-5D scores, and ASQoL scores were reported in all patients[10].

Figure: 2.3.4.1: Proportions of patients who achieved ASAS 20, ASAS 40, ASAS PR, or BASDAI 50 response at Week 12 and 52 in the investigator initiated study conducted by Haibel and colleagues



SOURCE: Haibel and colleagues publication[10]
ASAS 20: Assessment of SpondyloArthritis international Society 20% response; ASAS 40: Assessment of SpondyloArthritis international Society 40% response; ASAS PR: Assessment of SpondyloArthritis international Society partial remission; BASDAI 50: Bath Ankylosing Spondylitis Disease Activity Index 50% response.

Conclusions

This investigator-initiated study demonstrated that the signs and symptoms of active nr-axSpA were significantly reduced in patients treated with adalimumab for 12 weeks compared to those who received placebo. Patients also experienced significant improvements in HRQoL, as measured using the SF-36 PCS, ASQoL, and EQ-5D. Importantly, the response to adalimumab was sustained for up to 52 weeks of treatment.[10]

2.4 Safety data for adalimumab

Table 2.4.1.1 presents information on treatment discontinuations where reported for the studies discussed in Section 2.1. Table 2.4.1.2 lists the number and percentage of adverse events reported including any AE, any SAE and injection site reactions from the trials of the five anti-TNFs under review.

In addition, this section presents summary results for the 2011 Cochrane review examining the potential adverse effects of tumour necrosis factor inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), interleukin (IL)-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), anti-CD28 (abatacept), and anti-B cell (rituximab) therapy in patients with any disease condition except human immunodeficiency disease (HIV/AIDS) as five of these agents are relevant to this submission.

Finally, the most recent global safety update for adalimumab including data for patients with ankylosing spondylitis and nr-axSpA is also presented here for completeness.

2.4.1 Discontinuations and Adverse events for all studies included in the NMA where reported

Table 2.4.1.1: Discontinuations during the study

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which disc. measured	Total disc, n	Disc due to lack of efficacy, n	Disc due to AEs, n
Bao, 2012 (abs)	PLA	14	NR			
Bao, 2012 (abs)	GOL 50mg/mth	14	NR			
Bao, 2012 (abs)	PLA	24	NR			
Bao, 2012 (abs)	GOL 50mg/mth	24	NR			
Barkham, 2009	PLA	16	20	1	0	0
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	20	0	0	0
Barkham, 2010	PLA	12	20	NR	NR	NR
Barkham, 2010	ETN 2x25mg/1wk	12	20	NR	NR	0
Braun, 2002	PLA	12	35	0	0	0
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	35	4	0	3
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	19	2	12
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	26	4	15
Calin, 2004	PLA	12	39	0	0	0
Calin, 2004	ETN 2x25mg/1wk	12	45	2	0	0
Davis, 2003	PLA	12	139	5	NR	NR
Davis, 2003	ETN 2x25mg/1wk	12	138	6	NR	NR
Davis, 2003	PLA	24	139	19	13	1
Davis, 2003	ETN 2x25mg/1wk	24	138	12	3	7
Dougados, 2011 [SPINE]	PLA	12	43	4	2	0
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	1	0	1
Dougados, 2013 [AS EARLY] (abs)	PLA	12	109	7[a]	NR	NR

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which disc. measured	Total disc, n	Disc due to lack of efficacy, n	Disc due to AEs, n
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	106	3	NR	NR
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	25	0	0	0
Giardina, 2010	ETN 1x50mg/1wk	12	25	0	0	0
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	25	0	0	0
Giardina, 2010	ETN 1x50mg/1wk	24	25	0	0	0
[GO-AHEAD]	PLA	NR	NR			
[GO-AHEAD]	GOL 50mg/mth	NR	NR			
Gorman, 2002	PLA	16	20	2	2	0
Gorman, 2002	ETN 2x25mg/1wk	16	20	1	0	0
Haibel, 2008	PLA	12	24	0	0	0
Haibel, 2008	ADA 40mg/2wks	12	22	0	0	0
Hu, 2012	PLA	12	NR			
Hu, 2012	ADA 40mg/2wks	12	NR			
Huang, 2014	PLA	12	115	2	0	0
Huang, 2014	ADA 40mg/2wks	12	229	5	0	4
Inman, 2008 [GO-RAISE]	PLA	14	78	2[b]	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	9[b]	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	6[b]	NR	NR
Inman, 2008 [GO-RAISE]	PLA	24	78	2	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	10	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	6	NR	NR
Landewe, 2014 [RAPID-axSpA]	PLA	12	107	10	1	2
Landewe, 2014 [RAPID-axSpA]	CTZ 200 mg/2wks	12	111	6	0	2
Landewe, 2014 [RAPID-axSpA]	CTZ 400 mg/4wks	12	107	9	3	3

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which disc. measured	Total disc, n	Disc due to lack of efficacy, n	Disc due to AEs, n
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	12	NR			
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	12	NR			
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	12	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	12	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	12	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	12	NR			
Landewe, 2014 [RAPID-axSpA]	PLA	24	107	12	2	2
Landewe, 2014 [RAPID-axSpA]	CTZ 200 mg/2wks	24	111	6	0	2
Landewe, 2014 [RAPID-axSpA]	CTZ 400 mg/4wks	24	107	9	3	3
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	PLA	24	NR			
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 200 mg/2wks	24	NR			
Landewe, 2014 [RAPID-axSpA] (AS subgroup)	CTZ 400 mg/4wks	24	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	PLA	24	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 200 mg/2wks	24	NR			
Landewe, 2014 [RAPID-axSpA] (nr-axSpA subgroup)	CTZ 400 mg/4wks	24	NR			
Maksymowych, 2008 [M03-606]	PLA	12	44	0	0	0
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	38	0	0	0
Maksymowych, 2008 [M03-606]	PLA	24	44	2	0	0
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	24	38	0	0	0
Marzo-Ortega, 2005	MTX 10mg/1wk	10	NR			
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	10	NR			
Marzo-Ortega, 2005	MTX 10mg/1wk	30	14	5	4	0
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	28	2	0	0

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which disc. measured	Total disc, n	Disc due to lack of efficacy, n	Disc due to AEs, n
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	NR			
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	NR			
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	54	5	0	2
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	54	6	0	0
Pedersen, 2013 (abs)	PLA	12	25	4	2	0
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	27	2	0	1
Sieper, 2013 [ABILITY-1]	PLA	12	94	2	0	1
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	91	4	1	1
Sieper, 2014 [INFAST]	PLA	18	NR			
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	NR			
Sieper, 2014 [INFAST]	PLA	28	52	7	0	1
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	106	10	0	5
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	36	5	1	2 [c]
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	40	5	0	0
Tam, 2014	PLA	26	21	1	0	1
Tam, 2014	GOL 50mg/mth	26	20	1	0	0
Tam, 2014	PLA	52	21	1	0	1
Tam, 2014	GOL 50mg/mth	52	20	1	0	0
van der Heijde, 2005 [ASSERT]	PLA	12	NR			
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	12	NR			
van der Heijde, 2005 [ASSERT]	PLA	24	78	4	0	1
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	201	4	1	2
van der Heijde, 2006a [ATLAS]	PLA	12	107	4	0	2
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	208	4	0	2

Author, Year [Trial name]	Study arm	Follow-up Weeks	Number in which disc. measured	Total disc, n	Disc due to lack of efficacy, n	Disc due to AEs, n
van der Heijde, 2006a [ATLAS]	PLA	24	107	6	NR	2
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	13	NR	5
van der Heijde, 2006b	PLA	12	51	7	3	0
van der Heijde, 2006b	ETN 2x25mg/1wk	12	150	14	3	8
van der Heijde, 2006b	ETN 1x50mg/1wk	12	155	14	2	6

[a] Based on the number entering the open label extension
[b] From Table 8, TA233 ERG report week 16 discontinuations
[c] One patient counted twice; *italicised*, data calculated;

Table 2.4.1.2: Adverse events

Author, Year [Trial name]	Study arm	Follow-up Weeks	Safety population, n	Any AE, n	Any AE, %	SAE (grade 3 & 4), n	SAE (grade 3 & 4), %	Injection site reactions, n	Injection site reactions, %
Bao, 2012 (abs)	PLA	24	105	*36*	34.3	*0*	0.00	NR	NR
Bao, 2012 (abs)	GOL 50mg/mth	24	108	*42*	38.9	*1*	0.90	NR	NR
Barkham, 2009	PLA	16	20	0	*0.0*	0	*0.0*	NR	NR
Barkham, 2009	IFX iv 5mg/kg/6-8wks	16	20	1	*5.0*	0	*0.0*	NR	NR
Barkham, 2010	PLA	12	20	16	*80*	NR	NR	1	*5.0*
Barkham, 2010	ETN 2x25mg/1wk	12	20	19	*95*	NR	NR	0	*0.0*
Braun, 2002	PLA	12	35	NR	NR	0	NR	0	*0.0*
Braun, 2002	IFX iv 5mg/kg/6-8wks	12	34	NR	NR	3	NR	0	*0.0*
Braun, 2011 [ASCEND]	SUL 2-3 gm/day	16	187	100	53.5	4	2.10	3	*1.6*
Braun, 2011 [ASCEND]	ETN 1x50mg/1wk	16	379	213	56.2	7	1.80	41	*10.8*
Calin, 2004	PLA	12	39	NR	NR	0	NR	6	*15.4*
Calin, 2004	ETN 2x25mg/1wk	12	45	NR	NR	1	NR	15	*33.3*
Davis, 2003	PLA	24	139	NR	NR	5	NR	13	*9.4*
Davis, 2003	ETN 2x25mg/1wk	24	138	NR	NR	9	NR	41	*29.7*

Author, Year [Trial name]	Study arm	Follow-up Weeks	Safety population, n	Any AE, n	Any AE, %	SAE (grade 3 & 4), n	SAE (grade 3 & 4), %	Injection site reactions, n	Injection site reactions, %
Dougados, 2011 [SPINE]	PLA	12	43	28	65.0	1	NR	0	*0.0*
Dougados, 2011 [SPINE]	ETN 1x50mg/1wk	12	39	24	62.0	2	NR	3	*7.7*
Dougados, 2013 [AS EARLY] (abs)	PLA	12	113	52	46.0	NR	NR	NR	NR
Dougados, 2013 [AS EARLY] (abs)	ETN 1x50mg/1wk	12	111	63	57.0	NR	NR	NR	NR
Giardina, 2010	IFX iv 5mg/kg/6-8wks	12	NR						
Giardina, 2010	ETN 1x50mg/1wk	12	NR						
Giardina, 2010	IFX iv 5mg/kg/6-8wks	24	NR						
Giardina, 2010	ETN 1x50mg/1wk	24	NR						
[GO-AHEAD]	PLA	NR	NR						
[GO-AHEAD]	GOL 50mg/mth	NR	NR						
Gorman, 2002	PLA	16	20	NR	NR	0	0.00	1	*5.0*
Gorman, 2002	ETN 2x25mg/1wk	16	20	NR	NR	0	0.00	5	*25.0*
Haibel, 2008	PLA	12	24	21	*87.5*	0	*0.0*	NR	NR
Haibel, 2008	ADA 40mg/2wks	12	22	19	*86.4*	0	*0.0*	NR	NR
Hu, 2012	PLA	12	NR						
Hu, 2012	ADA 40mg/2wks	12	NR						
Huang, 2014	PLA	12	115	16	*13.9*	1	0.44	0	*0.0*
Huang, 2014	ADA 40mg/2wks	12	229	55	*24.0*	1	0.87	NR	NR
Inman, 2008 [GO-RAISE]	PLA	14	77	*57*	74.0	4	*5.2*	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	14	138	*109*	79.0	5	*3.6*	NR	NR
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	14	140	*106*	75.7	7	*5.0*	NR	NR
Inman, 2008 [GO-RAISE]	PLA	24	77	59	76.6	5	6.50	2	2.6
Inman, 2008 [GO-RAISE]	GOL 50mg/mth	24	138	117	84.8	5	3.60	12	8.7
Inman, 2008 [GO-RAISE]	GOL 50-100mg/mth	24	140	120	85.7	9	6.40	9	6.4

Author, Year [Trial name]	Study arm	Follow-up Weeks	Safety population, n	Any AE, n	Any AE, %	SAE (grade 3 & 4), n	SAE (grade 3 & 4), %	Injection site reactions, n	Injection site reactions, %
Landewe, 2014 [RAPID-axSpA]	PLA	12	NR						
Landewe, 2014 [RAPID-axSpA]	CTZ 200 mg/2wks	12	NR						
Landewe, 2014 [RAPID-axSpA]	CTZ 400 mg/4wks	12	NR						
Landewe, 2014 [RAPID-axSpA] [a]	PLA	24	107	67	62.6	5	4.70	1	0.9
Landewe, 2014 [RAPID-axSpA] [a]	CTZ 200 mg/2wks	24	111	85	76.6	4	3.60	10	9.0
Landewe, 2014 [RAPID-axSpA] [a]	CTZ 400 mg/4wks	24	107	80	74.8	7	6.50	5	4.7
Maksymowych, 2008 [M03-606]	PLA	12	NR						
Maksymowych, 2008 [M03-606]	ADA 40mg/2wks	12	NR						
Marzo-Ortega, 2005	MTX 10mg/1wk	30	14	2	14.0	0	0.00	NR	NR
Marzo-Ortega, 2005	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	30	28	13	46.0	0	0.00	NR	NR
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks	18	NR						
Mulleman, 2011 [SPAXIM]	IFX iv 5mg/kg/6-8wks + MTX 10mg/1wk	18	NR						
Navarro, 2011 [LOADET]	ETN 1x50mg/1wk	12	54	28	*51.9*	2	*3.70*	8	14.8
Navarro, 2011 [LOADET]	ETN 2x50mg/1wk	12	54	28	*51.9*	1	*1.85*	7	13.0
Pedersen, 2013 (abs)	PLA	12	NR						
Pedersen, 2013 (abs)	ADA 40mg/2wks	12	NR						
Sieper, 2013 [ABILITY-1]	PLA	12	97	57	58.8	1	1.00	NR	NR
Sieper, 2013 [ABILITY-1]	ADA 40mg/2wks	12	95	55	57.9	3	3.20	NR	NR
Sieper, 2014 [INFAST]	PLA	18	NR						
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	18	NR						
Sieper, 2014 [INFAST]	PLA	28	52	26	50.0	3	5.80	NR	NR
Sieper, 2014 [INFAST]	IFX iv 5mg/kg/6-8wks	28	105	61	58.1	5	4.80	NR	NR
Song, 2011 [ESTHER]	SUL 2-3 gm/day	24	NR						

Author, Year [Trial name]	Study arm	Follow-up Weeks	Safety population, n	Any AE, n	Any AE, %	SAE (grade 3 & 4), n	SAE (grade 3 & 4), %	Injection site reactions, n	Injection site reactions, %
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	24	NR						
Song, 2011 [ESTHER]	SUL 2-3 gm/day	48	32	32	NR	7	NR	NR	NR
Song, 2011 [ESTHER]	ETN 2x25mg/1wk	48	39	39	NR	3	NR	NR	NR
Tam, 2014	PLA	26	NR						
Tam, 2014	GOL 50mg/mth	26	NR						
van der Heijde, 2005 [ASSERT]	PLA	24	75	54	72.0	2	2.70	NR	NR
van der Heijde, 2005 [ASSERT]	IFX iv 5mg/kg/6-8wks	24	202 [b]	166	82.2	7	3.50	NR	NR
van der Heijde, 2006a [ATLAS]	PLA	12	NR						
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	12	NR						
van der Heijde, 2006a [ATLAS]	PLA	24	107	64	59.8	3	2.80	3	*2.8*
van der Heijde, 2006a [ATLAS]	ADA 40mg/2wks	24	208	156	75.0	6	2.90	21	*10.1*
van der Heijde, 2006b	PLA	12	51	Excluding injection site reaction: 18	Excluding injection site reaction: 35.3	Non-infectious: 2; Serious infections 0	Non-infectious: 3.9; Serious infections 0	6	11.8
van der Heijde, 2006b	ETN 2x25mg/1wk	12	150	Excluding injection site reaction: 66	Excluding injection site reaction: 44.0	Non-infectious: 6; Serious infections 1	Non-infectious: 4.0; Serious infections 0.7	34	22.7
van der Heijde, 2006b	ETN 1x50mg/1wk	12	155	Excluding injection site reaction: 55	Excluding injection site reaction: 35.5	Non-infectious: 8; Serious infections 1	Non-infectious: 5.2; Serious infections 0.6	32	20.7

[a] AEs for all patients: AEs are not reported separately for the AS and nr-axSpA subgroups
[b] 202 > than the number randomised because 1 patient was assigned PLA but received infusion of IFX. This patient was included in PLA group for efficacy analysis and IFX group for safety analysis. *Italicised* = data calculated.

2.4.2 Cochrane overview of adverse effects of biologics

In February 2011, Singh *et al.*[44] published a network meta-analysis and Cochrane review of adverse effects of biologics across multiple indications, including RA and other inflammatory arthritis. Since serious risks such as tuberculosis (TB) reactivation, serious infections, and lymphomas may be common to the biologics but occur in small numbers across the various indications, the authors aimed to combine the results from all the biologics used in many conditions to obtain the risk estimates.

The biologics investigated were the anti-TNFs (etanercept, adalimumab, infliximab, golimumab, and certolizumab), the interleukin (IL)-1 antagonist (anakinra), the IL-6 antagonist (tocilizumab), the anti-CD28 (abatacept), and the anti-B cell therapy (rituximab). Randomised controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extension (OLE) studies that studied one of the nine biologics for use in any indication (with the exception of HIV/AIDS) and that reported pre-specified adverse outcomes were considered for inclusion. The authors searched The Cochrane Library, MEDLINE, and EMBASE (to January 2010). Identifying search results and data extraction were performed independently and in duplicate. For the network meta-analysis, Singh *et al.* performed mixed-effects logistic regression using an arm-based, random-effects model within an empirical Bayesian framework.[44]

The authors included 163 RCTs with 50,010 participants and 46 extension studies with 11,954 participants. The median duration of RCTs was six months and 13 months for OLEs. Data were limited for tuberculosis (TB) reactivation, lymphoma, and congestive heart failure. Adjusted for dose, biologics as a group were associated with a statistically significant higher rate of total adverse events (odds ratio (OR) 1.19, 95% CI 1.09 to 1.30; number needed to treat to harm (NNTH) = 30, 95% CI 21 to 60) and withdrawals due to adverse events (OR 1.32, 95% CI 1.06 to 1.64; NNTH = 37, 95% CI 19 to 190) and an increased risk of TB reactivation (OR 4.68, 95% CI 1.18 to 18.60; NNTH = 681, 95% CI 143 to 14706) compared to control. [44]

The rate of serious adverse events, serious infections, lymphoma, and congestive heart failure were not statistically significantly different between biologics and control treatment. Certolizumab pegol was associated with significantly higher risk of serious infections compared to control treatment (OR 3.51, 95% CI 1.59 to 7.79; NNTH = 17, 95% CI 7 to 68). Infliximab was associated with significantly higher risk of withdrawals due to adverse events compared to control (OR 2.04, 95% CI 1.43 to 2.91; NNTH = 12, 95% CI 8 to 28).

Indirect comparisons revealed that abatacept and anakinra were associated with a significantly lower risk of serious adverse events compared to other biologics. Although the overall numbers are relatively small, certolizumab pegol was associated with significantly higher odds of serious infections compared to etanercept, adalimumab, abatacept, anakinra, golimumab, infliximab, and rituximab; abatacept was significantly less likely than infliximab and tocilizumab to be associated with serious infections. Abatacept, adalimumab, etanercept and golimumab were significantly less likely than infliximab to result in withdrawals due to adverse events.

For SAEs: Certolizumab pegol was statistically significantly more likely to be associated with SAEs compared to adalimumab (OR 1.63, 95%CI 1.01 to 2.62). Abatacept was statistically significantly less likely to be associated with SAEs compared to certolizumab (OR 0.56, 95% CI 0.33 to 0.94). In sensitivity analyses in the unadjusted model, neither difference was significant. Golimumab was statistically significantly less likely to be associated with SAEs compared to adalimumab (OR 1.18, 95% CI 1.10 to 3.14). There were no other statistically significant differences between the biologics in both the unadjusted model and dose-adjusted model.

For withdrawals due to AE: In sensitivity analyses only in unadjusted model, infliximab was more likely to be associated with withdrawals due to AEs compared with abatacept (OR 1.92, 95% CI 1.01 to 3.71), adalimumab (OR 2.00, 95% CI 1.17 to 3.49), and etanercept (OR 1.72, 95% CI 1.02 to 2.91). Rituximab was also more likely to be associated with withdrawals due to AEs than adalimumab (OR 2.17, 95% CI 1.04 to 4.74)

Serious infections: Certolizumab was associated with higher odds of serious infections than abatacept, adalimumab, etanercept, golimumab and rituximab. The odds ratios were roughly 0.25-

times or lower for each of the five biologic compared with certolizumab, in the indirect comparisons. In sensitivity analyses: Anakinra was associated with a statistically significantly higher odds of serious infections compared with rituximab. [44]

The authors concluded that overall, in the short term, biologics were associated with significantly higher rates of total adverse events, withdrawals due to adverse events and TB reactivation. Some biologics had a statistically higher association with certain adverse outcomes compared to control, but there was no consistency across the outcomes so caution is needed in interpreting these results. There is a need for more research regarding the long-term safety of biologics and the comparative safety of different biologics. National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics[44].

2.4.3 Data from extensive safety databases evaluating adalimumab for multiple indications

The safety profile of adalimumab has been studied in 71 global clinical trials up to 6 November 2010, including 23,458 patients representing 36,730.5 patients years of treatment. For this analysis, published by Burmester and colleagues in 2012, data were derived from the 71 clinical trials, which included randomised controlled trials, open-label trials, and long-term extension studies conducted in Europe, North America, South America, Asia, Australia, New Zealand, and South Africa. The trials spanned multiple indications; 36 trials in RA, 3 in juvenile idiopathic arthritis, 4 in AS, 4 in PsA, 13 in psoriasis, and 11 in Crohn's disease.[45] Safety data from post-marketing surveillance for adalimumab was not included in the analysis to avoid any limitations which may be introduced with voluntary reporting.

The incidence rates of serious AEs reported during adalimumab treatment for inflammatory diseases are presented in Table 2.4.3.1, separated by indication. Serious infectious events were the most frequently reported serious adverse events across all six therapeutic indications; the greatest rates were seen in patients with RA or CD. Furthermore, the risk of serious infection rates was generally stable across time for all indications.[45]

Across all indications, the rate of active TB was 0.2/100 PYs including cases from the older RA clinical trials, which were conducted before the implementation of tuberculin test screening. No serious opportunistic infections have been reported with adalimumab in AS, PsA or psoriasis clinical trials. Twenty serious opportunistic infections, excluding TB and oral candidiasis, have been reported during adalimumab clinical trials (<0.1 events/100 PYs), 14 cases in patients with RA, four cases in patients with CD and two cases in JIA. The most common opportunistic infections were oesophageal *candidiasis* (n=3), and aspergillosis, Candida sepsis, *coccidioidomycosis*, cytomegalovirus infection, herpes zoster and nocardiosis (n=2 each).[45]

Rates of malignancies across all indications were 0.7 events/100 PYs for malignancies, excluding lymphoma and non-melanoma skin cancer (NMSC), 0.1/100 PY for lymphoma, and 0.2/100 PYs for NMSC. Compared with age- and sex-matched populations, the observed number of malignancies (all malignancies including lymphoma but excluding NMSC) in each disease population was similar to the expected number in the reference population. However, the number of lymphomas observed in the RA studies was significantly greater than expected compared with a US-based age- and sex-matched population, likely because RA itself is normally associated with a SIR of 2 irrespective of treatment, thus this increase is expected vs., a matched population that does not necessarily have RA. A greater proportion of patients with RA, psoriasis, and Crohn's disease demonstrated standardised incidence rates of NMSC of >1, indicating a higher number of observed NMSC cases than expected in the general population[45].

Lastly, for subjects treated with adalimumab in the RA, AS and psoriasis clinical studies, the observed number of deaths was lower than expected in an age- and sex-match population[45].

Table 2.4.3.1: Incidence rates of serious AEs of relevance to adalimumab treatment in patients being treated for a range of inflammatory diseases (rates are reported as E/100 PY)

	AS	RA	Juvenile idiopathic arthritis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	**1684**	14 109	212	837	3010	3606
Exposure, PYs	**1985.6**	23 942.6	604.9	997.5 5	061.8	4138.0
Serious infections	**1.4**	4.6	2.0	2.8	1.7	6.7
NMSC	**0.3**	0.2	0	0.1	0.1	<0.1
CHF	**0.1**	0.2	0	0	<0.1	0
Active tuberculosis	**0**	0.3	0	0.2	0.1	<0.1
Opportunistic infections	**0**	<0.1	0	0	0	<0.1
Demyelinating disorder	**<0.1**	<0.1	0	0	0	0.1
Lupus-like syndrome	**0.1**	<0.1	0	0	0	<0.1
New onset/worsening of psoriasis	**<0.1**	<0.1	0	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	**0.2**	0.9	0	0.2	0.6	0.5
Lymphoma	**<0.1**	0.1	0	0.2	<0.1	<0.1
Melanoma	**<0.1**	<0.1	0	0	0.2	0
Any AE leading to death	**<0.1**	0.8	0	0.3	0.2	0.1

Source: Burmester 2012[45]
AE: Adverse event, AS: Ankylosing spondylitis, CHF: Congestive heart failure, NMSC: non-melanoma skin cancer, PY: Patient year, RA: Rheumatoid arthritis

The risks of AEs associated with adalimumab and other anti-TNF agents have been extensively studied and rates are consistent with increased exposure; the results of this analysis are consistent with previous safety analyses. The increased risk of serious infections and NMSC are a well-known AE associated with anti-TNF therapy, and were no higher here for adalimumab than expected for this class of treatments. The overall rates of malignancy were similar to rates expected in the reference population, with event rates stable over time, suggesting no increased risk with prolonged exposure[45].

In summary, the analyses reported here provide additional support for the long-term safety profile of adalimumab. Important differences in events rates have been demonstrated across indications, however, the AE rates were stable over time and no new safety signals were identified.[45]

2.5 Network meta-analysis

2.5.1 Evidence Synthesis – Data Collection

A systematic review with too broad a scope will be hard to interpret in the context of decision making. In order for the estimates of treatment effects to be appropriate for cost-effectiveness analysis, the study inclusion criteria should be restricted to a specific target patient population with a specific condition, at a specific point in a disease progression pathway.[46]

Therefore this review focuses on the populations specifed in the adalimumab license, namely adults with:

- severe active ankylosing spondylitis who have had an inadequate response to conventional therapy (Sub-population 1: AS)
- severe axial spondyloarthritis without radiographic evidence of AS (nr-axSpA) but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (Sub-population 2: nr-axSpA)

Study inclusion and exclusion criteria

A study protocol was developed prior to the review to define the scope of the systematic review and meta-analysis.

The key study inclusion criteria for this systematic review are shown in Table 2.5.1.1. The criteria were developed to ensure that trials were sufficiently similar to be pooled in the meta-analysis.[46]

With regards to length of follow-up for the meta-analysis, the EMA 2009 AS guidelines (Section 6.2: Therapeutic confirmatory studies) state that for products other than NSAIDs, the main endpoint (ASAS 20 and ASAS 40) should be measured at 12 and 24 weeks. Therefore the minimum cut-off for the RCT follow-up period was 12 weeks.

Table 2.5.1.1: Inclusion and exclusion criteria for axial SpA systematic review

Inclusion Criteria	Description
Population	Sub-population 1: Adults (≥18 years) with severe, active AS For the meta-analysis this population may be sub-categorised as: • AS, TNF-α inhibitor naïve (first-line trials) • AS, previously treated with TNF-α inhibitors (second-line trials) Sub-population 2: Adults (≥18 years) with nr-axSpA
Interventions	TNF-α inhibitors used at the licensed dose (or expected dose if license pending) in AS and/or nr-axSpA
Comparators	Active: adalimumab, certolizumab, etanercept, golimumab and infliximab at EU licensed dose Controls: any active or placebo control Comparators will be used in conjunction conventional treatment with NSAIDs or conventional disease-modifying anti-rheumatic drugs (cDMARDs) e.g. methotrexate, sulfasalazine, as background therapy,
Outcomes	To be included in the main meta-analysis, studies need to report at least one of the main outcomes of interest at 12 weeks: • ASAS (Assessment in Ankylosing Spondylitis): 20%, 40% improvement in score at follow-up • BASDAI (Bath Ankylosing Spondylitis Disease Activity Index): 50% improvement in score at follow-up
Study design	Prospective, randomised, placebo or active-controlled trials, with minimum follow-up of 12 weeks If cross-over design, then results reported prior to cross-over can be used in the meta-analysis of efficacy endpoints If early escape design, then results prior to rescue or post-rescue results with suitable adjustment (e.g. last-observation carried forward for rescued patients) may be used in the meta-analysis
Publications	Full-text publications (no date restriction) Exception for recently completed trials where results have not been published in full: abstracts/posters published in 2011-2013 or results posted to clinical trial registry Full-text available in English or English translation
Exclusions	Results from uncontrolled, open-label extensions are not used in the efficacy meta-analysis but may be used in a qualitative safety summary

Treatments of interest

The treatments of interest for this review are TNF-α inhibitors licensed in the EU (see Table 2.5.1.2). In the meta-analysis the study arms are pooled by drug and dose/frequency of dose as specified in the license.

Table 1.5.1.2: Treatments of interest for this review and EU licensed dosing for axial SpA

Treatment of interest	Treatment group for meta-analysis	Brand	Current license mentions nr-axSpA?
adalimumab 40 mg every 2 weeks s/c inj [a]	ADA 40mg/2wks	Humira	Yes
certolizumab pegol 200mg every 2 weeks s/c inj, [b]	CTZ 200 mg/2wks	Cimzia	Yes
certolizumab pegol 400mg every 4 weeks s/c inj [b]	CTZ 400 mg/4wks		
etanercept 25mg twice weekly s/c inj	ETN 2x25mg/1wk	Enbrel	-*
etanercept 50mg once weekly s/c inj	ETN 1x50mg/1wk		
golimumab 50mg every month s/c inj [a, c]	GOL 50mg/mth	Simponi	-
	GOL 50-100mg/mth [c]		
infliximab 5mg/kg every 6-8 weeks iv [d]	IFX iv 5mg/kg/6-8wks	Remicade	-

s/c inj, subcutaneous injection; iv, intravenous infusion;
[a], clinical response is usually achieved within 12-14 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.
[b], The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks;
[c], In patients with a body weight of more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose.
[d], 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

* Please note that at the time the NMA was conducted, etanercept did not have a licence for nr-axSpA, although it has been included in the network.

Background therapy as a proxy to conventional therapy

Note that for all included studies, the treatments of interest listed above are given in conjunction with a background treatment.

The following background treatments were included in this review:

- +/- NSAIDs +/-
  - Oral corticosteroids (CS), e.g. prednisone
  - cDMARDs
    - methotrexate (MTX)
    - sulfasalazine (SUL)
    - hydroxychloroquine (HCQ)
  - In some studies other treatments were allowed as part of the background therapy:
    - Standard doses of analgesics (paracetamol, codeine, hydrocodone, oxycodone, tramadol)
    - Gold injections
    - Azathioprine
    - Physiotherapy

Therefore, placebo-control (i.e. placebo + background therapy) is assumed to be representative of conventional therapy.

Systematic review methodology

Search strategy and citation filtering

The following databases were searched using a structured search in OVID (31st January 2014):

- CENTRAL (Cochrane Central Register of Controlled Trials) [1991 to Current]

- MEDLINE and MEDLINE in Process [1946 to Week 4, January 2014]
- EMBASE [1980 to 2014 Week 04]

In addition, the following grey literature was searched:

- Conference proceedings:
  - European League Against Rheumatism (EULAR): 2011, London, UK; 2012 Berlin, Germany; 2013 Madrid, Spain
  - American Congress of Rheumatology (ACR): 2011, Chicago; 2012 Washington; 2013. San Diego
  - Ankylosing Spondylitis International Federation (ASIF): 2011 Turkey
- The clinical trials registries:
  - Clinicaltrials.gov
  - EU Clinical Trials Register (EU-CTR)
- Hand-searching:
  - List of studies included in the following systematic reviews
    - Shu, 2013 [10]
    - Previous NICE technology appraisal for TNF-α inhibitors in AS: TA143 and TA233 [11,12]
  - National Ankylosing Spondylitis Society: list of studies and clinical research priorities [13]
  - Post hoc: A systematic review and meta-analysis by Callhoff at al. [14] was published after our literature review was finished. For completeness, we have reviewed the Callhoff study inclusion list[68].

The search strategies are in Appendix 1.

Citations were included in the review if they matched the inclusion criteria set out in Table 2.5.1.1. All citations from the OVID search and any grey literature references were imported into EndNote X7 reference manager for filtering. The initial screening for relevant studies was based on abstract and title. The initial screening was conducted by one reviewer and verified by a second reviewer. A summary of citations excluded on the basis of the title/abstract is also provided in Appendix 1.

One reviewer re-screened all papers to ensure their eligibility for inclusion in the systematic review (AP). Disputes as to eligibility were referred to a third reviewer. A summary of citations excluded after reviewing the full-text is provided in Appendix 1. A citation flow diagram (Figure 2.5.1.2) is provided to summarise the citation filtering process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format.

Data extraction and qualitative review

Relevant data from the included studies were extracted to the template by two reviewers and verified by a third reviewer.

The pre-defined protocol specified that the extraction should cover the following:

<u>Study Design:</u>

- Unique trial identifier: Author, date [Trial name]
- Setting/Country
- Trial duration
- Summary of study enrolment criteria

- Population/sub-population identifier (e.g. nr-axSpA)
- Efficacy and safety analysis population
- Design: comment on early escape/rescue/crossover
- Description of methodology used to adjust endpoints, ANCOVA, LOCF

Patient Characteristics:

- Number of patients with baseline measurements
- Demographics (mean age, % female, ethnicity)
- Mean duration of disease
- Severity of disease:
  - Definition of severe disease
  - BASDAI score at baseline
  - BASFI score at baseline
  - BASMI score at baseline
  - Spinal pain visual analogue scale measurement
- Prior treatments: Number and duration of prior treatments[1]
- Baseline co-morbidities

Treatment Characteristics:

- Drug, dose and frequency
- Titration/run-in
- Number of patients randomised to receive treatment
- NSAIDs or other therapies used as background treatment during trial, change in background during trial
- Rescue/escape criteria and type of rescue used

Quality Assessment:

Criteria for judging risk of bias in the 'Risk of bias' assessment tool from table 8.5c of the Cochrane Handbook.

- Selection bias: Random sequence generation
- Selection bias: Allocation concealment
- Performance bias: Blinding of participants and personnel

[1] These data were not reported in most trials. Instead the minimum or maximum number of previous NSAIDS or conventional DMARDs is recorded instead.

- Detection bias: Blinding of outcome assessment
- Attrition bias: Incomplete outcome data (include assessment of early escape/rescue methodology)
- Reporting bias: Selective reporting
- Other sources of bias

Data for meta-analysis:

For each outcome of interest for the meta-analysis:

- Treatment arm identifier
- Treatment group to be used in meta-analysis
- Follow-up time point
- Patient population sub-group (if separate results are reported within one trial):
  - AS or nr-axSpA
  - Anti-TNF naïve or previous treatment with anti-TNF
- Baseline value, where applicable: mean, SD
- For continuous data: mean, standard error, number in which outcome was measured at this time point
- For binomial data: count of patients (or % of patients), number in which outcome was measured at this time point, number of ITT/mITT analysis

Priority data for meta-analysis/ economic model:

The following endpoints were identified for consideration in the economic model. The protocol specified that a network meta-analysis should be conducted for these endpoints provided there were sufficient data.

Priority endpoints were:

- % improvement in BASDAI score at 12 weeks of follow-up
  - Count of patients with 50% improvement[2]
- % improvement in ASAS score at 12 weeks of follow-up
  - Count of patients with 20% and 40% improvement
- Disease activity based on BSR criteria[3] at 12 weeks of follow-up[4]
  - Count of patients with both BASDAI<4 and spinal pain VAS <4 cm if reported or if not available

[2] One study also reported BASDAI20 and BASDAI70
[3] Active spinal disease defined as BASDAI at least 4 cm and spinal pain VAS (within last week) at least 4 cm. Both recorded on two occasions at least 4 weeks apart, without any change of treatment.
[4] No studies reported this specific outcome: Three studies reported number of patients with BASDAI<4, one study reported number of patients with BASDAI<3

        - Count of patients with BASDAI<4
        - Count of patients with spinal pain VAS <4 cm

- Discontinuations:
    - Count of patients discontinuing at week 12 (any reason)[5]

Endpoints for qualitative summary:

- Open-label phase:
    - Count of responders and non-responders entering open-label period
- Attrition during randomised and open-label phases (12, 24, and 52 weeks if reported):
    - Count of discontinuations to lack of efficacy
    - Count of discontinuations due to adverse events
    - Count of total discontinuations

Other endpoint data of interest for the review:

The following additional endpoints were extracted in anticipation of the final NICE scope.

- Adverse events:
    - Count of patients with any adverse event
    - Count of patients with serious adverse events (grade 3 and 4)
    - Count of patients with injection site reactions
- The Bath Ankylosing Spondylitis Metrology Index (BASMI): mean, SE
- The Bath Ankylosing Spondylitis Functional Index (BASFI): mean, SE
- Spinal pain VAS: mean, SE
- Night pain VAS: mean, SE
- Health related quality of life: SF-36
- Other measures of functional capacity

The OVID database search (31st January 2014) retrieved 3015 citations. Ten abstracts were added to the reference list after reviewing recent (2013 at time of the review) conference proceedings: EULAR[47,48,49,50,51,52,53] and ACR[54,55,56.] The full-text citations corresponding to two of these conference abstracts were also added: the citations were not retrieved via the OVID search as the publications were online ahead-of-print at the time of the OVID search. Five references relating to the clinical trial registry records were added to the reference list. Four citations were added as the trial registry reported additional information not covered in the full-text publication or study was published in abstract from only.[57,58,59,60,61] One trial registry record was added for the golimumab study [GO-AHEAD] which was on-going at the time of the literature search.[61] No data have been reported for this

[5] A post-extraction assessment of the discontinuations data identified possible double counting and protocol driven events. Therefore discontinuations were down prioritised and an NMA was not conducted for this outcome.

study to date (April 2014), though we anticipate that this study will be included in the golimumab manufacturer's submission using data on file.

After excluding 750 duplicates and reviewing the remaining 2282 titles/abstracts, 2208 citations were excluded (Appendix 1 for a summary of exclusion reasons). The full text was reviewed for 74 citations, from which 27 were excluded (see Appendix 1 for a list of full-text exclusions). Following the second sift, 47 citations, representing 29 distinct studies, were eligible for inclusion in the wider systematic review.

There were 22 studies covering an AS sub-population and nine studies covering an nr-axSpA population. This includes one certolizumab study reporting both AS and nr-axSpA sub-groups population and one study etanercept with a mixed SpA population: in the following sections data for the AS and nr-axSpA sub-groups have been used if reported separately.

Figure 2.5.1.1: Study flow

I1 Citations retrieved	3032	**OVID search**	3015
		MEDLINE	944
		EMBASE	1945
		Cochrane Trials Register	126
		Conference Proceedings	10
		EULAR	*7*
		ACR	*3*
		Handsearched	7
		ClinicalTrials.org	*5*
		NICE HTA ref lists	*0*
		Other	2
E1 Citations excluded at first pass *(after review of title/abstract)*	2958	*Duplicates*	750
		Other exclusions	2208
I2 Full-text reviewed	74		
E2 Citations excluded at second pass *(after review of full-text)*	27	*Child citation (no additional data)*	17
		Duration	4
		No comparators of interest	2
		Not an RCT	4
I3 Included in systematic review	47	*citations*	
representing	29	*studies*	
E3 Excluded from meta-analysis	6	*Data not reported*	1
		Comparisons not of interest	4
		Mixed SpA population	1
I4 Included in meta-analysis	23	*studies*	

Summary of studies for AS sub-population

The majority of AS studies (19 out of 22 studies) defined AS using the modified New York criteria (mNYC). The RAPID-axSpA study used ASAS criteria to identify the overall study population and then used the mNYC to subdivide into AS or nr-axSpA sub-populations. The remaining two studies did not report the criteria for defining AS.

One study did not report any criteria for defining active disease; furthermore it was unclear from text whether active disease was a study enrolment requirement. Otherwise the AS studies reported broadly similar criteria for defining active disease. The most common criteria were two or more of the following:

- BASDAI VAS on the 0 to 10 cm scale: used by 16 out of 22 studies
  - VAS 4 ≤: 15 studies
  - VAS 3 ≤: 1 study; Braun, 2011 [ASCEND]
- Back pain VAS on the 0 to 10 cm scale: used by 18 out of 22 studies
  - VAS 4 ≤: 14 studies
  - VAS 3 ≤: 4 studies, Braun, 2011 [ASCEND]; Calin, 2004; Davis, 2003; Marzo-Ortega, 2005
- Morning stiffness: Duration or composite of duration and intensity (10/22 studies)
- Global assessment of disease 4 ≤ (or 3 ≤) on a 0 to 10 scale (5/22 studies)
- BASFI VAS 3 ≤ on the 0 to 10 cm scale (3/22 studies)

The patient characteristics were broadly similar across the AS study arms:

- Age at baseline: 39.15, range 27.4 to 48
- % males: 79%, range 63% to 100%
- % white 59%, range 0% to 98%
  - Four studies had 100% Asian populations: Bao, 2012 (abs); Hu, 2012; Huang, 2014; and Tam, 2014
  - Amongst the non-Asian studies that reported ethnicity, average % of the population that were white = 87%, range 70% to 98%
- Duration of disease: 10.8 years, range 3 to 23
- BASDAI score at baseline: 6.27, range 5.46 to 7.00

Some of the AS studies had early escape or rescue therapy as part of the study design.

<u>Early escape design</u>: 6 studies switched placebo patients to active treatment if there was a lack of effect:

- at 16 weeks (Bao, 2012 (abs), Inman, 2008 [GO-RAISE], Landewe, 2014 [RAPID-axSpA])
- at 12, 16 or 20 weeks (Maksymowych, 2008 [M03-606], van der Heijde, 2006a [ATLAS])
- at 24 weeks (Tam, 2014).

The trigger for escape was similar across these studies:

- Failure to achieve ASAS20 (Landewe, 2014 [RAPID-axSpA], Maksymowych, 2008 [M03-606], van der Heijde, 2006a [ATLAS], Tam, 2014).
- Less than 20% improvement from baseline in both total back pain and morning stiffness (Bao, 2012 (abs), Inman, 2008 [GO-RAISE]).

Outcomes measured after escape may be confounded by the switch in treatment.

<u>Rescue therapy</u>: the study protocol for 6 of the AS studies allowed for rescue therapy due to:

- Intolerance or adverse events:
  - Braun, 2011 [ASCEND] - SUL dose reduced or treatment withdrawn
  - Navarro, 2011 [LOADET] - SUL suspended for up to 2 weeks
  - Song, 2011 [ESTHER] - SUL switched to MTX

- Pain or high disease activity:
    - Dougados, 2011 [SPINE] - add analgesics such as paracetamol, with or without codeine or dextropropoxyphene;
    - Marzo-Ortega, 2005 - intra-articular or intramuscular injections of corticosteroids
    - van der Heijde, 2005 [ASSERT] - Systemic corticosteroids, cytotoxic drugs, or cDMARDs added to background treatment

Dougados, 2011 [SPINE] and van der Heijde, 2005 [ASSERT] are included in the main meta-analysis. For the ASSERT study rescue therapy is unlikely to have biased the treatment effects because patients with a change in background therapy were counted as non-responders for efficacy outcomes. The number of patients requiring rescue was not reported for Dougados, 2011 [SPINE].

Other than the AS studies mentioned above changes to the main or background treatment were not allowed during the RCT phase.

Risk of Bias: Table 2.5.1.3 below summarises the risk of bias based on assessment tool in the Cochrane Handbook. The full assessment is provided below in Table 2.5.1.3.

There were concerns over the quality of the Giardina, 2010 study. This was a small (50 patients in total), open-label, head-to-head study of etanercept versus infliximab. The study does not appear to have used a robust method for randomising the patients (were allocated to study treatment alternatively), and there was no blinding of the study personnel or patients. Sufficient details were not provided in the publication such as the primary study endpoints. Overall it was felt the risk of potential study bias was high. Therefore this study would be subject to a sensitivity analysis.

The studies by Mulleman, 2011 [SPAXIM] and Song, 2011 [ESTHER] were also open-label, hence there was no blinding of the study personnel or patients. It was noted that for the study by Hu, 2012, there was a lack of detail provided regarding the number of patients included in the analysis (other bias): the efficacy or safety set was not described in the methods section and total patient numbers were not reported in the results tables. Otherwise the studies were judged to have a low risk of bias.

There were three studies where some patient characteristics were not balanced between study arms:

Calin, 2004
- On average ETN patients were older than PLA patients (45.3 v 40.7, two-sided p=0.046)
- On average the duration of disease for ETN patients was higher than PLA patients (15 v 9.7, two-sided p=0.004)
- On average CRP for ETN patients was higher than PLA patients (154 mg/L v 97mg/L, SD not reported)

Gorman, 2002:
- There were more males in the PLA arm compared to the ETN arm (90% v 75%, χ^2: p = 0.06).

GO-RAISE, 2008:
- On average the duration of disease was higher for PLA patients compared to GOL patients (16 v 11 (GOL 50mg/mth) v 9.5 (50-100mg/mth), SD not reported)

One study, RAPID-ax-SpA (Landewe 2014[69]), reported ASAS20 and ASAS40 results separately for the AS and nr-axSpA populations, but values were not reported separately for the BASDAI50 outcome. The publication states “Logistic regression analysis of the primary efficacy endpoint <ASAS20 at 12 weeks> did not reveal a difference in treatment effect between AS and nr-axSpA subpopulations (see online supplementary figure S2A).” A graph showing the absolute BASDAI score throughout the trial indicates that the AS and nr-axSpA sub-groups had similar (mean) change in scores. The evidence presented indicates that AS and nr-axSpA subgroups would have similar BASDAI50 response rates so risk of reporting bias for the BASDAI50 outcome is judged to be low.

Table 2.5.1.3: Cochrane risk of bias: summary for AS studies

Author, Year [Trial name]	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Reporting bias: Selective reporting	Other sources of bias
Bao, 2012 (abs)	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Unclear
Barkham, 2010	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
Braun, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Braun, 2011 [ASCEND]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Calin, 2004	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear
Davis, 2003	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Dougados, 2011 [SPINE]	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
Giardina, 2010	No	No	No	No	Unclear	No	Unclear
Gorman, 2002	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Hu, 2012	Unclear	Unclear	Yes	Yes	Unclear	Yes	No
Huang, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Inman, 2008 [GO-RAISE]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Landewe, 2014 [RAPID-axSpA]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Maksymowych, 2008 [M03-606]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear
Marzo-Ortega, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mulleman, 2011 [SPAXIM]	Unclear	Unclear	No	No	Unclear	Unclear	Unclear
Navarro, 2011 [LOADET]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear
Song, 2011 [ESTHER]	Unclear	Unclear	No	No	Yes	Yes	Yes
Tam, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
van der Heijde, 2005 [ASSERT]	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
van der Heijde, 2006a [ATLAS]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
van der Heijde, 2006b	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear

Judgement low risk of bias; Yes = low risk, No = high risk, Unclear = information not reported or risk is unclear

Summary of studies for nr-axSpA sub-population

Four out of the nine nr-axSpA studies used the ASAS criteria to define nr-axSpA, one study used ESSG, one used Calin criteria; one study used study specific criteria that did not match other widely used criteria and for the remaining two studies, one study is not published in full and for one study the criteria were not reported in the publication.

The eight studies that reported criteria all reported a definition of active disease as entry criteria to the trial. The most common criteria were one or more of the following:

- BASDAI VAS 4 ≤: on the 0 to 10 cm scale: 8 studies
- Back pain VAS 4 ≤: on the 0 to 10 cm scale: 5 studies

The patient characteristics were broadly similar across the nr-axSpA study arms:

- Age at baseline: 35.23, range 28.2 to 41
- % males: 59.5%, range 41% to 78%
- % whites 90.5%, range 86% to 96%
- Duration of disease: 4.48 years, range 0.7 to 13
- %HLA-B27 positive: 81.5%, range 59% to 100%
- BASDAI score at baseline: 6.30, range 5.76 to 6.70

Some of the nr-axSpA studies had early escape or rescue therapy as part of the study design.

Early escape design: one studies switched placebo patients to active treatment if there was a lack of effect:

- at 16 weeks (Landewe, 2014 [RAPID-axSpA]) if failure to achieve ASAS20

Outcomes measured after escape may be confounded by the switch in treatment.

Rescue therapy: the study protocol for two of the nr-axSpA studies allowed for rescue therapy due to:

- Intolerance or adverse events:
    - Sieper, 2013 [ABILITY-1] – Rescue could occur after the double blind period was completed; change to dose of background treatment was permitted after week 24
    - Song, 2011 [ESTHER] - SUL switched to MTX

Other than the nr-axSpA studies mentioned above changes to the main or background treatment were not allowed during the RCT phase.

2.5.2 Methodology

The main meta-analysis was conducted using network meta-analysis (NMA). In addition pairwise direct meta-analysis and indirect meta-analysis using the Bucher method[62,63] were conducted. This allows for an informal assessment of the consistency of the evidence by comparing of the pairwise direct and indirect estimates with the equivalent estimates from the NMA.[46] If the estimates are similar then a formal assessment of inconsistency would not be required.

The primary endpoints of interest for the meta-analysis are the priority data listed in the previous section. These endpoints have been selected as these will be used to support the economic model.

In the publications, the efficacy and safety endpoints were, in general, reported for those patients who started their study treatment. Therefore, the meta-analysis was conducted on an intent-to-treat (ITT) or a modified intent-to-treat (mITT) basis, where the mITT population is defined as the set of patients who were randomised and received at least one dose of study medication. For some studies the reported efficacy endpoints were restricted to those with non-missing baseline and/or ≥ 1 follow-up result.

The pooled summary measure for binomial outcomes are odds ratios (OR) since this allows for indirect comparisons to be conducted whilst avoiding framing issues.[64]

Direct meta-analysis methodology

Fixed and random-effects direct meta-analysis were conducted in Stata IC version 13.1 using the *metan* package SJ9_2: sbe24_3. The random-effects model uses the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the fixed-effect Mantel-Haenszel or inverse variance model. For binomial outcomes where a study contains a zero observation (e.g. no patients achieved BASDAI50), by default, 0.5 was added to each cell of the trial.

Bucher indirect comparisons

Simple indirect comparisons between treatment (A) and other treatments of interest (B) via a common comparator (C) were made using the Bucher method and the pooled effects produced from the direct meta-analysis. For example, the indirect OR between A and B is given by:

$$\log(OR_{AvB}) = \log(OR_{AvC}) - \log(OR_{BvC})$$

With standard error given by:

$$SE[\log(OR_{AvB})] = \sqrt{SE[\log(OR_{AvC})]^2 + SE[\log(OR_{BvC})]^2}$$

Network meta-analysis methodology

Whereas standard meta-analyses evaluate the relative efficacy of just two treatments based on head-to-head trials only, NMA comprises an extension of these methods in which treatment effects are calculated for a network of treatments.[65,66] NMA takes account of indirect comparisons, as well as head-to-head trials, thereby enabling treatment effects to be estimated for comparisons between treatments that have not been compared directly in clinical trials. These methods build on the principles of indirect comparisons and preserve the randomised comparisons within each trial.

The network meta-analysis methodology is as per the NICE Decision Support Unit recommendations for random and fixed-effect Bayesian network meta-analysis of dichotomous data.[67]

Table 2.5.2.1: NMA Model details

Endpoint	Type of NMA model	Model specification/ program code
BASDAI50; ASAS20, ASAS40, discontinuations at week 12	Binomial model with logit link	As per TSD2 section 2.1, program 1 (multi-arm)

NMA, network meta-analysis; TSD, Technical specification document

The models were fitted to the data via Bayesian Markov Chain Monte Carlo methods (specifically Gibbs sampling) using WinBUGS. This is a valid and common approach for synthesising clinical trial data, and is recommended by the NICE. The WinBUGS models were run for a minimum of 100,000 iterations to ensure model convergence with two chains of 10,000 sampled from the posterior distributions.

An estimate of how well the values predicted by the model fitted the observed dataset are provided by the mean residual deviances (total residual deviance divided by number of data points) as well as the deviance information criteria (DIC) output by WinBUGS.[46] The models that have a good fit would have a mean residual deviance is close to one. The DIC is used to compare different models for the same likelihood and data, and the model with a lower DIC best predicts a replicate dataset of the same structure to that observed. Differences in DIC of more than 10 would rule out the model with the highest DIC, whereas if differences are less than 5, then other criteria, such as average residual deviance, should be used to judge model fit.

Care should be taken in interpreting the random-effects results if the network is sparse, e.g. fewer than 10 studies, studies with small populations or contrasts with data from only one clinical trial. In a sparse network the estimates may be subject to Type II error whereby a lack of statistical significance is incorrectly interpreted as a lack of effect. Furthermore credible intervals may be unrealistically large due to a lack of data with which to estimate the between study deviation with precision, rather than significant heterogeneity.

Analysis of treatment effects

The NMAs calculate (log) odds ratio (OR) as a measure of the relative efficacy of treatments. Both random-effects models and fixed-effect models will be tested. Random-effects NMA allows the true treatment effect (e.g. OR between two treatments) to vary between studies due to heterogeneity. In these random-effects models, a uniform (uninformative) prior is used for the between-study standard deviation.

Analysis of baseline risk

The absolute risk for each treatment will be calculated using the relative effects and the baseline risk for the reference arm. [46] The reference treatment is the arm with the most data available, which in this analysis is the placebo arm.

In this indication the reference treatment is placebo plus background treatment where the background is conventional treatment with NSAIDs +/- cDMARDs or other permitted standard treatments.

Firstly, a standard direct random-effects meta-analysis was conducted using pooled data on the mean difference from baseline (or for dichotomous data, the log odds) for the reference treatment. The absolute change for the control arm is then predicted by the WinBUGS code:

$$A \sim \text{dnorm}(mA, mprecA)$$

where *mA* is the pooled mean change and *mprecA* is the precision in pooled mean change with *mA* and *mprecA* from the random-effects meta-analysis of the control arms.

The absolute change *T* for each treatment *k* is then given by:

$$T[k] = A + d[k]$$

where d[k] is the relative treatment effect (WMD or OR) calculated in the main part of the WinBUGS NMA.

Consistency of evidence

An informal assessment of consistency was performed by comparing the pairwise direct estimates and Bucher indirect estimates with the equivalent estimates from the NMA. If the estimates are similar then no formal assessment of inconsistency is required. A formal assessment of consistency may be conducted if the network contains closed loops by comparing the difference between the direct and indirect estimates within a loop using the Bucher method.

Sensitivity analysis

The following alternative analysis was conducted where studies qualify:

- An NMA including all studies
- An NMA removing all Asian studies
- An NMA removing studies where there is large unexplained uncertainty in the effect estimate.

Meta-regression

Where there were sufficient data, the following post-hoc meta-regression analyses were conducted to attempt to explain differences between treatment effects.

- A covariate analysis using the centred, average duration of disease as an explanatory factor. The analysis was conducted on the study arm-level as for some studies there was a significant difference in duration of disease across study arms (see QA section). Studies that did not report duration of disease where dropped from the analysis.

- A covariate analysis using study baseline risk for the control arm as an explanatory factor. This analysis attempts to control for differences in the background treatment across studies

There were sufficient data to conduct this analysis for the AS population, ASAS20 (~12 weeks) network. Analyses were not conducted for the nr-axSpA population or other outcomes due to insufficient data.

Limitations of meta-analysis and network meta-analysis

A limitation of meta-analysis is the underlying assumption that trials and outcomes are sufficiently similar to allow for data to be pooled. It should be noted that this assumption applies to any method of data synthesis, not just direct meta-analysis or NMA. Areas where this assumption may be challenged and other potential criticisms of the analysis include the following:

- Potentially non-comparable populations, e.g. different severity of disease, different duration of disease. We have attempted to minimise population heterogeneity by restricting the review to a specific part of the treatment pathway and splitting the analysis for early stage SpA (nr-axSpA) and severe, active AS.

- The clinical setting in which the study was conducted could restrict the generalizability of the results.

- Different follow-up times: The recommended minimum follow-up for registration of AS studies with the EMA has been used as a basis for the time point for this meta-analysis. As not all studies report endpoints at exactly 12 weeks, a small window around these time points was considered for the meta-analysis; e.g. 12 weeks to 18 weeks to cover first follow-up for most studies, pre-early escape.

- Different background treatments. We have attempted to mitigate the impact of heterogeneity in the conventional therapy background by identifying treatment arms where the background therapy is allowed to change throughout the study.

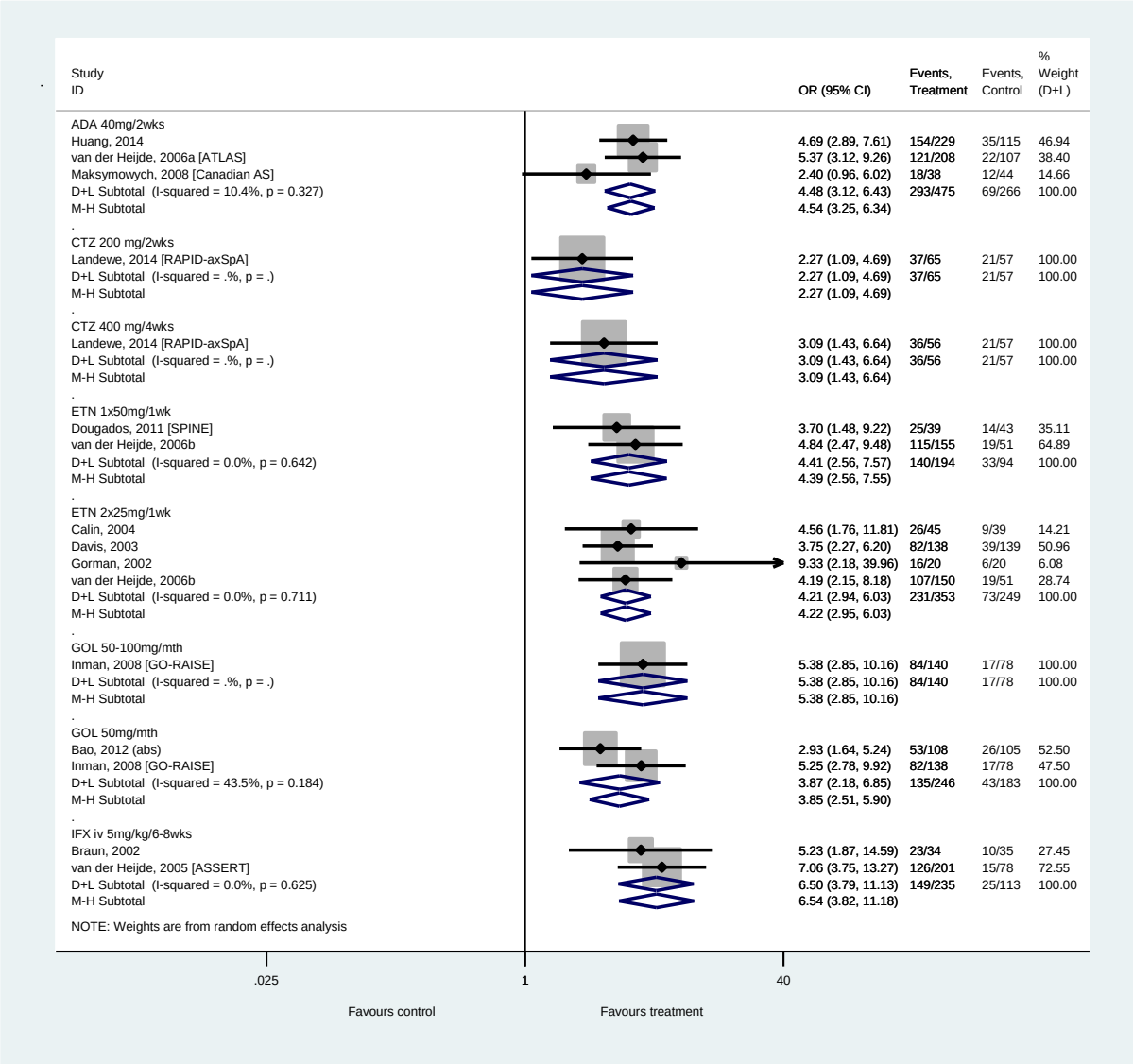
- The limited availability of data which increases the uncertainty in the treatment effect estimates and restricts the assessment of heterogeneity by limiting the scope of the sensitivity analysis.

2.5.3 Results

Forest plots for the base case analysis are presented below for the BASDAI50, ASAS20, and ASAS40 endpoints for both AS and nr-axSpA. For additional results and sensitivity analyses please refer to Appendix 1.

2.5.3.1 Ankylosing Spondylitis (AS)

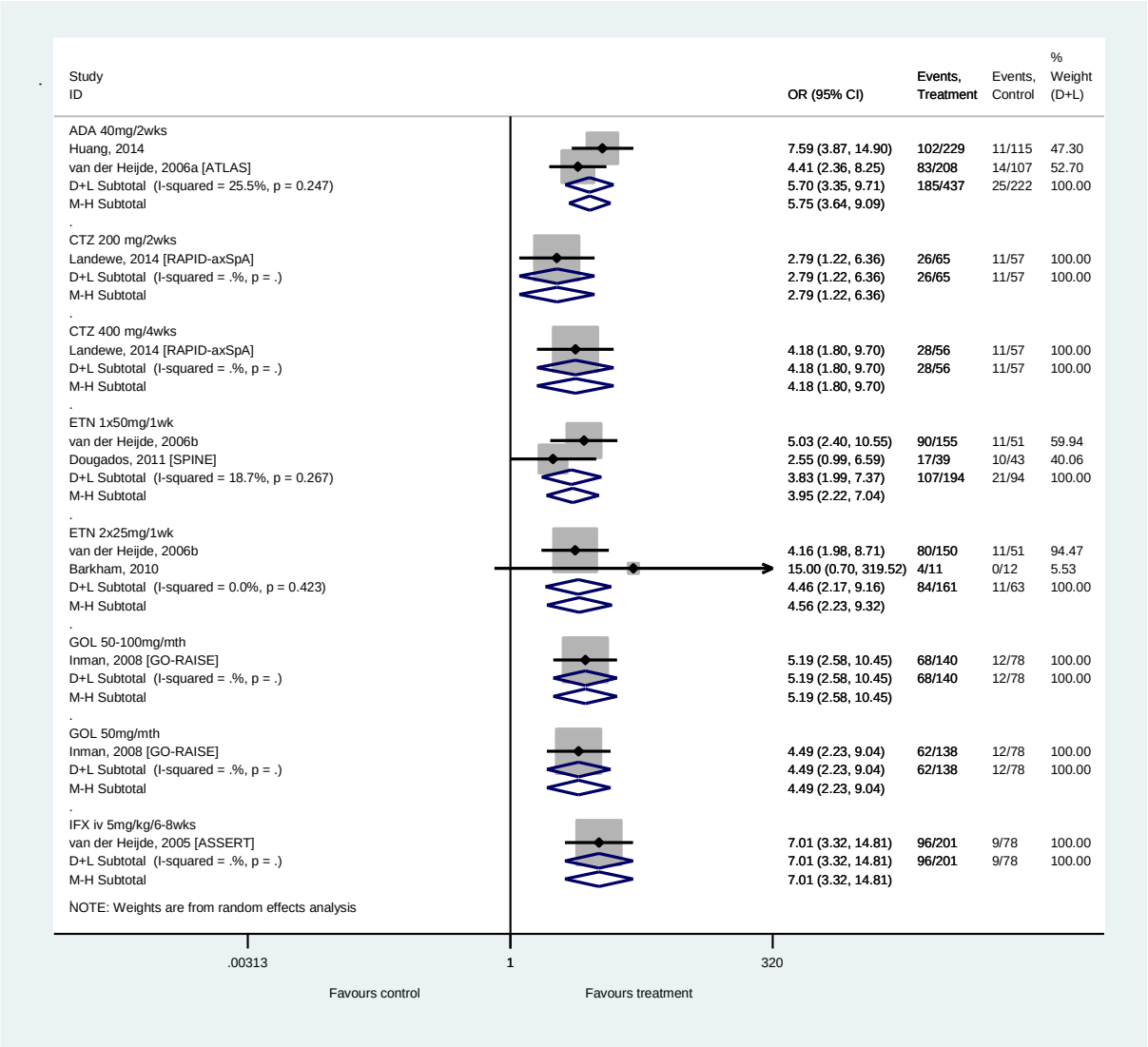
Figure 2.5.3.1.1: Forest plot for ASAS20 for AS population at 12-16 weeks v placebo



Significance test(s) of OR=1

ADA 40mg/2wks	z = 8.14	p = 0.000
CTZ 200 mg/2wks	z = 2.20	p = 0.028
CTZ 400 mg/4wks	z = 2.88	p = 0.004
ETN 1x50mg/1wk	z = 5.37	p = 0.000
ETN 2x25mg/1wk	z = 7.86	p = 0.000
GOL 50-100mg/mth	z = 5.19	p = 0.000
GOL 50mg/mth	z = 4.63	p = 0.000
IFX iv 5mg/kg/6-8wks	z = 6.82	p = 0.000

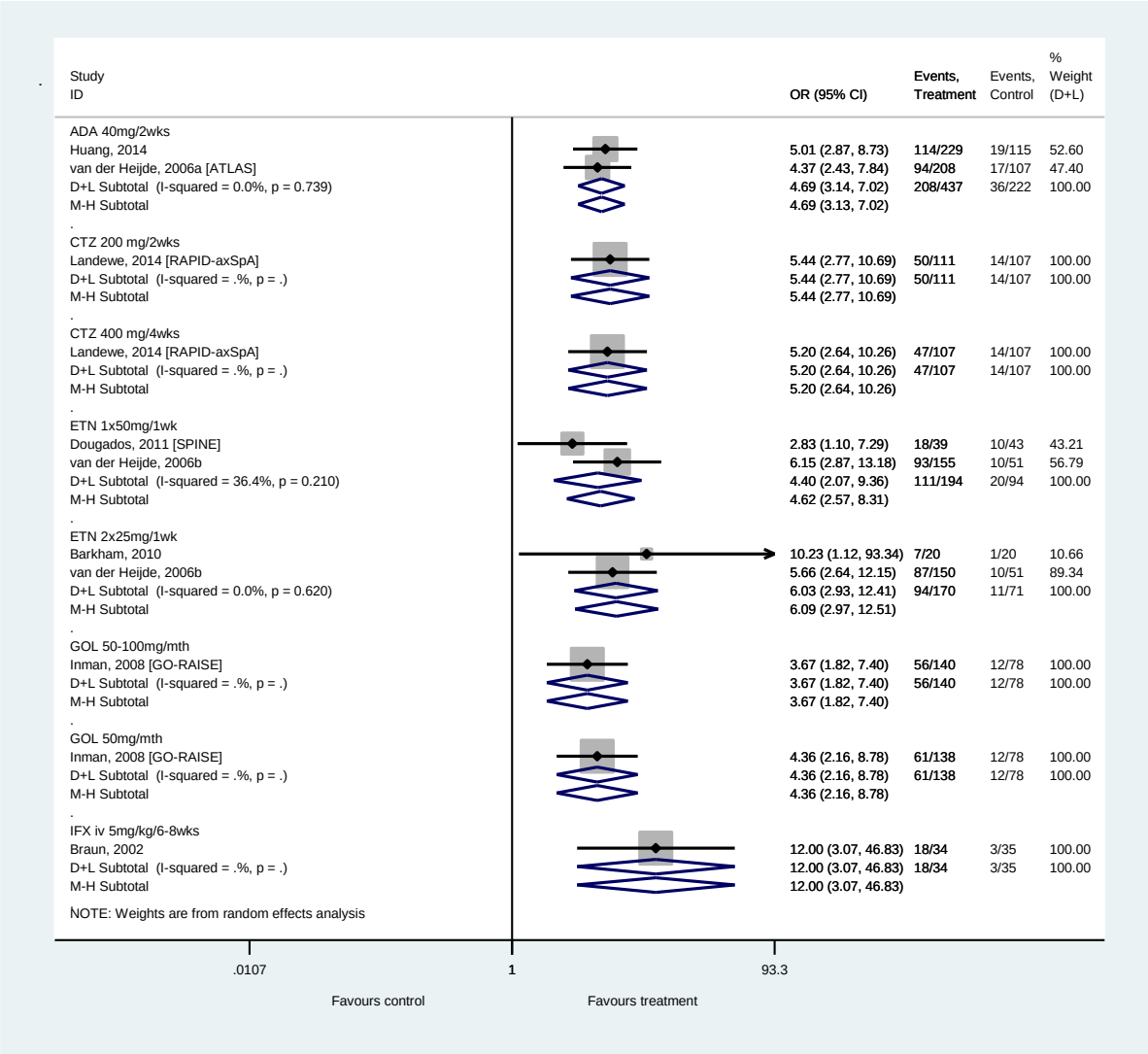
Figure 2.5.3.1.2: Forest plot for ASAS40 for AS population at 12-16 weeks v placebo



Significance test(s) of OR=1

ADA 40mg/2wks	z = 6.41	p = 0.000
CTZ 200 mg/2wks	z = 2.44	p = 0.015
CTZ 400 mg/4wks	z = 3.33	p = 0.001
ETN 1x50mg/1wk	z = 4.03	p = 0.000
ETN 2x25mg/1wk	z = 4.07	p = 0.000
GOL 50-100mg/mth	z = 4.62	p = 0.000
GOL 50mg/mth	z = 4.20	p = 0.000
IFX iv 5mg/kg/6-8wks	z = 5.10	p = 0.000

Figure 2.5.3.1.3: Forest plot for BASDAI50 for AS population at 12-14 weeks v placebo



NB: RAPID-axSpA trial publication does not report BASDAI50 separately for AS and nr-axSpA populations
Significance test(s) of OR=1

ADA 40mg/2wks	z = 7.51	p = 0.000
CTZ 200 mg/2wks	z = 4.92	p = 0.000
CTZ 400 mg/4wks	z = 4.76	p = 0.000
ETN 1x50mg/1wk	z = 3.84	p = 0.000
ETN 2x25mg/1wk	z = 4.88	p = 0.000
GOL 50-100mg/mth	z = 3.63	p = 0.000
GOL 50mg/mth	z = 4.12	p = 0.000
IFX iv 5mg/kg/6-8wks	z = 3.58	p = 0.000

Results tables for patients with AS for the following outcome measures: ASAS20, ASAS40, and BASADAI50 are presented in Tables 2.5.3.1.1 to 2.5.3.1.3 below.

Table 2.5.3.1.1: Network meta-analysis for AS population: ASAS20 at 12-16 weeks, all studies

Odds ratio		Fixed-effect NMA					Random-effects NMA				
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
ADA 40mg/2wks	PLA	4.665	4.592	3.302	6.409	*	4.634	4.562	2.827	6.887	*
CTZ 200 mg/2wks	PLA	2.471	2.298	1.111	4.827	*	2.501	2.254	0.973	5.451	
CTZ 400 mg/4wks	PLA	3.424	3.156	1.489	6.907	*	3.376	2.982	1.296	7.740	*
ETN 1x50mg/1wk	PLA	4.528	4.421	2.874	6.846	*	4.562	4.429	2.544	7.529	*
ETN 2x25mg/1wk	PLA	4.191	4.120	2.937	5.824	*	4.342	4.227	2.759	6.631	*
GOL 50mg/mth	PLA	3.994	3.901	2.552	6.028	*	4.023	3.897	2.254	6.620	*
GOL 50-100mg/mth	PLA	4.532	4.349	2.581	7.536	*	4.714	4.395	2.302	9.151	*
IFX iv 5mg/kg/6-8wks	PLA	7.285	7.022	4.321	11.790	*	7.338	6.970	3.896	12.730	*
ADA 40mg/2wks	CTZ 200 mg/2wks	2.170	1.999	0.889	4.443		2.258	2.003	0.742	5.065	
ADA 40mg/2wks	CTZ 400 mg/4wks	1.589	1.455	0.625	3.324		1.685	1.503	0.531	3.764	
ADA 40mg/2wks	ETN 1x50mg/1wk	1.083	1.040	0.601	1.796		1.098	1.020	0.502	2.077	
ADA 40mg/2wks	ETN 2x25mg/1wk	1.149	1.115	0.683	1.813		1.123	1.075	0.558	1.941	
ADA 40mg/2wks	GOL 50mg/mth	1.225	1.182	0.683	2.022		1.240	1.169	0.571	2.305	
ADA 40mg/2wks	GOL 50-100mg/mth	1.109	1.055	0.556	1.968		1.113	1.040	0.439	2.231	
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	0.683	0.654	0.355	1.190		0.693	0.651	0.305	1.355	
Absolute risk											
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
PLA		0.273	0.272	0.242	0.305		0.273	0.272	0.243	0.305	
ADA 40mg/2wks		0.631	0.632	0.545	0.714		0.627	0.630	0.509	0.726	
CTZ 200 mg/2wks		0.464	0.462	0.292	0.646		0.461	0.457	0.264	0.672	
CTZ 400 mg/4wks		0.541	0.542	0.354	0.722		0.530	0.529	0.325	0.745	
ETN 1x50mg/1wk		0.622	0.623	0.510	0.725		0.619	0.624	0.481	0.742	
ETN 2x25mg/1wk		0.606	0.607	0.516	0.693		0.611	0.612	0.502	0.718	
GOL 50mg/mth		0.592	0.593	0.483	0.699		0.590	0.593	0.452	0.716	
GOL 50-100mg/mth		0.618	0.620	0.485	0.742		0.620	0.622	0.457	0.777	
IFX iv 5mg/kg/6-8wks		0.722	0.724	0.612	0.819		0.720	0.723	0.587	0.829	

* significant difference based on 95% CrI; CrI, credible interval

Table 2.5.3.1.2: Network meta-analysis for AS population: ASAS40 at 12-16 weeks, all studies

Odds ratio		Fixed-effect NMA					Random-effects NMA				
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
ADA 40mg/2wks	PLA	6.022	5.816	3.765	9.469	*	6.854	5.804	1.916	17.870	*
CTZ 200 mg/2wks	PLA	3.150	2.880	1.274	6.626	*	4.449	2.753	0.560	14.920	
CTZ 400 mg/4wks	PLA	4.783	4.315	1.893	10.270	*	6.433	4.281	0.832	22.310	
ETN 1x50mg/1wk	PLA	4.550	4.366	2.574	7.604	*	5.180	4.409	1.650	13.330	*
ETN 2x25mg/1wk	PLA	4.109	3.917	2.186	7.181	*	7.428	4.580	1.688	30.550	*
GOL 50mg/mth	PLA	5.014	4.639	2.324	9.932	*	7.379	4.549	0.916	23.670	
GOL 50-100mg/mth	PLA	5.809	5.365	2.737	11.460	*	8.428	5.273	1.045	26.850	*
IFX iv 5mg/kg/6-8wks	PLA	7.711	7.229	3.919	14.170	*	9.200	7.180	2.060	26.920	*
ADA 40mg/2wks	CTZ 200 mg/2wks	2.293	2.044	0.770	5.245		4.254	2.085	0.278	14.890	
ADA 40mg/2wks	CTZ 400 mg/4wks	1.519	1.355	0.503	3.548		3.012	1.365	0.184	10.490	
ADA 40mg/2wks	ETN 1x50mg/1wk	1.427	1.343	0.654	2.691		1.764	1.311	0.274	5.853	
ADA 40mg/2wks	ETN 2x25mg/1wk	1.608	1.496	0.694	3.153		1.628	1.262	0.134	4.922	
ADA 40mg/2wks	GOL 50mg/mth	1.378	1.251	0.534	2.952		2.368	1.269	0.180	9.245	
ADA 40mg/2wks	GOL 50-100mg/mth	1.188	1.088	0.457	2.528		2.016	1.090	0.149	7.991	
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	0.871	0.805	0.361	1.794		1.239	0.808	0.143	4.355	
Absolute risk											
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
PLA		0.153	0.152	0.119	0.193		0.153	0.152	0.119	0.193	
ADA 40mg/2wks		0.512	0.512	0.383	0.646		0.512	0.510	0.251	0.771	
CTZ 200 mg/2wks		0.347	0.340	0.177	0.556		0.354	0.333	0.089	0.737	
CTZ 400 mg/4wks		0.441	0.437	0.243	0.662		0.442	0.434	0.126	0.805	
ETN 1x50mg/1wk		0.442	0.440	0.302	0.594		0.448	0.442	0.220	0.712	
ETN 2x25mg/1wk		0.415	0.413	0.268	0.579		0.471	0.451	0.226	0.850	
GOL 50mg/mth		0.458	0.454	0.283	0.652		0.456	0.449	0.139	0.811	
GOL 50-100mg/mth		0.493	0.490	0.316	0.684		0.490	0.487	0.155	0.832	
IFX iv 5mg/kg/6-8wks		0.565	0.566	0.397	0.730		0.560	0.563	0.266	0.834	

* significant difference based on 95% CrI; CrI, credible interval

Table 2.5.3.1.3: Network meta-analysis for AS population: BASDAI50 at 12-14 weeks, all studies

Odds ratio		Fixed-effect NMA					Random-effects NMA				
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
ADA 40mg/2wks	PLA	4.933	4.801	3.264	7.262	*	5.524	4.724	1.596	14.180	*
CTZ 200 mg/2wks	PLA	5.919	5.523	2.838	11.250	*	7.920	5.484	1.120	27.760	*
CTZ 400 mg/4wks	PLA	5.664	5.288	2.686	10.950	*	8.222	5.258	1.071	26.88	*
ETN 1x50mg/1wk	PLA	5.190	4.959	2.843	8.965	*	5.890	4.892	1.607	15.950	*
ETN 2x25mg/1wk	PLA	5.204	4.952	2.716	9.219	*	7.296	5.440	1.886	24.110	*
GOL 50mg/mth	PLA	4.878	4.529	2.290	9.416	*	6.665	4.421	0.973	22.640	
GOL 50-100mg/mth	PLA	4.103	3.803	1.954	7.956	*	5.625	3.739	0.849	20.810	
IFX iv 5mg/kg/6-8wks	PLA	18.480	13.370	3.641	65.820	*	28.020	14.620	2.077	131.300	*
ADA 40mg/2wks	CTZ 200 mg/2wks	0.942	0.874	0.388	1.901		1.632	0.865	0.125	5.821	
ADA 40mg/2wks	CTZ 400 mg/4wks	0.987	0.914	0.402	2.006		1.623	0.894	0.133	5.966	
ADA 40mg/2wks	ETN 1x50mg/1wk	1.034	0.972	0.481	1.931		1.366	0.975	0.189	4.611	
ADA 40mg/2wks	ETN 2x25mg/1wk	1.043	0.976	0.469	2.032		1.187	0.877	0.130	3.667	
ADA 40mg/2wks	GOL 50mg/mth	1.153	1.063	0.459	2.364		2.028	1.069	0.142	7.175	
ADA 40mg/2wks	GOL 50-100mg/mth	1.369	1.267	0.548	2.770		2.453	1.266	0.164	8.174	
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	0.456	0.361	0.071	1.422		0.680	0.321	0.029	2.973	
Absolute risk											
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
PLA		0.160	0.159	0.131	0.192		0.160	0.159	0.131	0.192	
ADA 40mg/2wks		0.478	0.477	0.369	0.594		0.474	0.471	0.228	0.733	
CTZ 200 mg/2wks		0.512	0.512	0.343	0.688		0.509	0.508	0.174	0.842	
CTZ 400 mg/4wks		0.501	0.500	0.330	0.681		0.501	0.498	0.166	0.836	
ETN 1x50mg/1wk		0.485	0.484	0.341	0.638		0.484	0.481	0.229	0.752	
ETN 2x25mg/1wk		0.485	0.483	0.331	0.644		0.515	0.508	0.258	0.823	
GOL 50mg/mth		0.465	0.462	0.295	0.648		0.463	0.455	0.153	0.817	
GOL 50-100mg/mth		0.423	0.419	0.262	0.608		0.426	0.415	0.137	0.796	
IFX iv 5mg/kg/6-8wks		0.703	0.717	0.403	0.928		0.705	0.734	0.279	0.962	

* significant difference based on 95% CrI; CrI, credible interval

Meta-regression was performed for the ASAS20 endpoint as sufficient data was available to facilitate this using two covariate models; disease duration and study control (placebo) baseline risk. Neither of the covariate models reached statistical significance; however there is a slight trend indicating that higher disease duration or a higher control effect (i.e. more effective background treatment) results in a lower relative treatment effect; conclusions from this analysis should be drawn with caution. The results are tabulated below (Table 2.5.3.1.4):

Table 2.5.3.1.4: Network meta-analysis for AS population: ASAS20 at 12-16 weeks, all studies, random-effects NMA with and without covariates

Odds ratio		No covariates				Covariate model 1: Disease duration[6]				Covariate model 2: Placebo-control risk[7]			
Treatment	**Control**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
ADA 40mg/2wks	PLA	4.562	2.827	6.887	*	4.217	2.495	7.077	*	4.366	2.506	6.824	*
CTZ 200 mg/2wks	PLA	2.254	0.973	5.451		2.215	0.888	5.656		2.877	1.090	6.920	*
CTZ 400 mg/4wks	PLA	2.982	1.296	7.740	*	2.997	1.121	7.888	*	3.857	1.351	10.010	*
ETN 1x50mg/1wk	PLA	4.429	2.544	7.529	*	4.475	2.545	7.714	*	5.274	2.710	9.851	*
ETN 2x25mg/1wk	PLA	4.227	2.759	6.631	*	4.290	2.780	6.887	*	4.570	2.897	7.481	*
GOL 50mg/mth	PLA	3.897	2.254	6.620	*	5.254	2.196	12.360	*	3.585	1.962	6.648	*
GOL 50-100mg/mth	PLA	4.395	2.302	9.151	*	5.511	2.348	12.650	*	4.164	1.925	8.886	*
IFX iv 5mg/kg/6-8wks	PLA	6.970	3.896	12.730	*	7.122	3.809	13.150	*	5.750	2.924	12.130	*
ADA 40mg/2wks	CTZ 200 mg/2wks	2.003	0.742	5.065		1.894	0.684	5.153		1.498	0.509	4.529	
ADA 40mg/2wks	CTZ 400 mg/4wks	1.503	0.531	3.764		1.390	0.493	3.907		1.127	0.351	3.587	
ADA 40mg/2wks	ETN 1x50mg/1wk	1.020	0.502	2.077		0.939	0.439	2.062		0.821	0.344	1.887	
ADA 40mg/2wks	ETN 2x25mg/1wk	1.075	0.558	1.941		0.969	0.475	1.948		0.947	0.445	1.819	
ADA 40mg/2wks	GOL 50mg/mth	1.169	0.571	2.305		0.802	0.302	2.078		1.217	0.542	2.360	
ADA 40mg/2wks	GOL 50-100mg/mth	1.040	0.439	2.231		0.763	0.295	2.036		1.060	0.423	2.323	
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	0.651	0.305	1.355		0.589	0.260	1.321		0.746	0.316	1.572	
Absolute risk													
Treatment		**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Median**	**Lower 95% CrI**	**Upper 95% CrI**	
PLA		0.272	0.243	0.305		0.275	0.242	0.310		0.272	0.242	0.305	
ADA 40mg/2wks		0.630	0.509	0.726		0.615	0.480	0.734		0.619	0.487	0.720	
CTZ 200 mg/2wks		0.457	0.264	0.672		0.458	0.249	0.686		0.518	0.288	0.721	
CTZ 400 mg/4wks		0.529	0.325	0.745		0.534	0.296	0.753		0.591	0.336	0.789	
ETN 1x50mg/1wk		0.624	0.481	0.742		0.630	0.485	0.750		0.664	0.502	0.787	
ETN 2x25mg/1wk		0.612	0.502	0.718		0.619	0.506	0.729		0.631	0.515	0.738	
GOL 50mg/mth		0.593	0.452	0.716		0.666	0.451	0.826		0.572	0.425	0.716	
GOL 50-100mg/mth		0.622	0.457	0.777		0.677	0.468	0.831		0.608	0.420	0.770	
IFX iv 5mg/kg/6-8wks		0.723	0.587	0.829		0.731	0.587	0.837		0.683	0.527	0.821	
Coefficient: logβ		-	-	-		-0.015	-0.083	0.052		-0.428	-1.519	0.629	

* significant difference based on 95% CrI; CrI, credible interval

[6] Bao, 2012 (abs), excluded from covariate model 1 as duration of disease not reported in the abstract
[7] Giardina, 2010 excluded from covariate model 2 as not placebo controlled

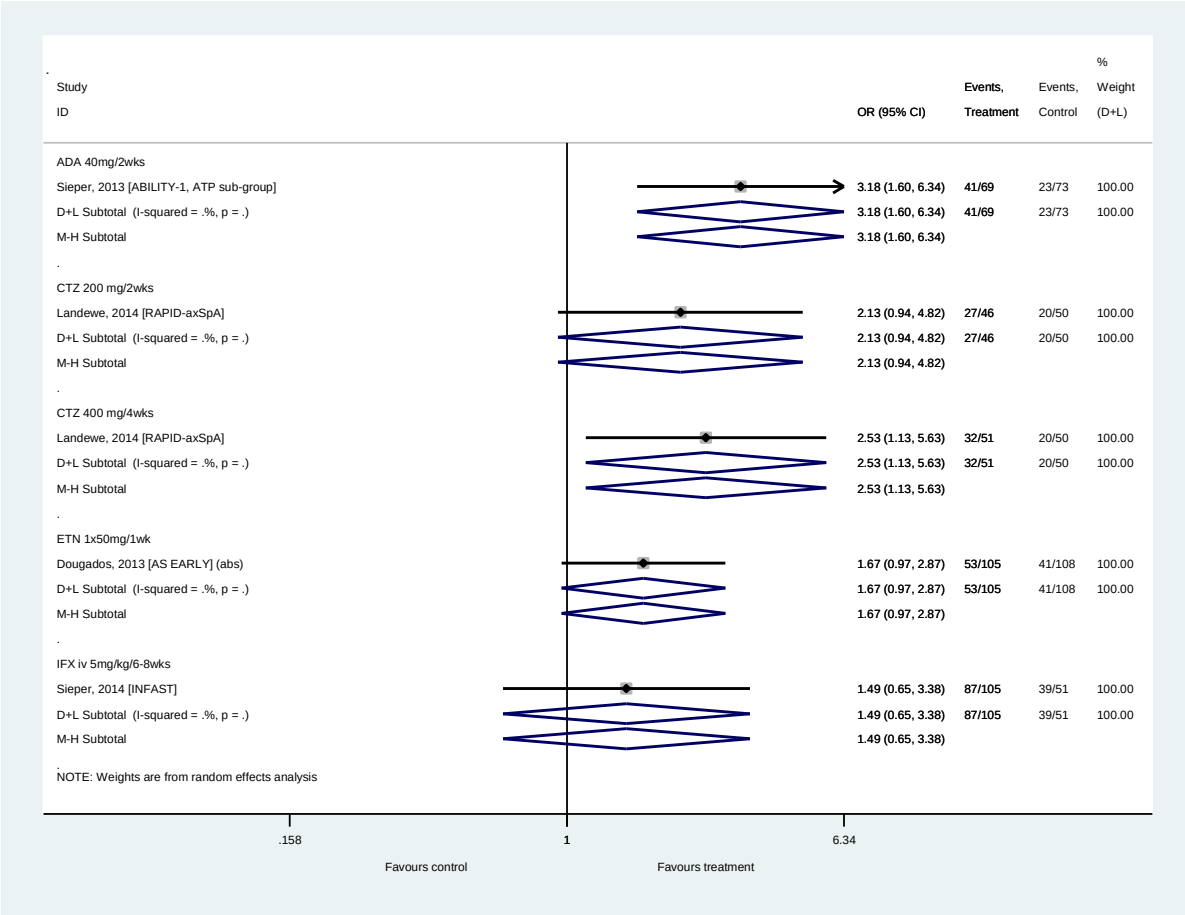
Table 2.5.3.1.5: Network meta-analysis for AS population: Summary of model parameters comparing covariate models

Model	ASAS20\AS pop \RE	ASAS20\AS pop: COV1 \RE	ASAS20\AS pop: COV2\RE
Burn in	100,000	100,000	100,000
Number of chains	2	2	2
Samples per chain	10,000	10,000	10,000
DIC	192.603	180.946	185.607
p_v + total residual deviance	51.6	50.5	53.8
Average residual deviance	0.907	0.917	0.975
Between study standard deviation	0.187	0.210	0.224

DIC, deviance information criteria; FE, fixed-effect; NA, not applicable; RE, random-effects

2.5.3.2 Non-radiographic axial spondylitis (nr-axSpA)

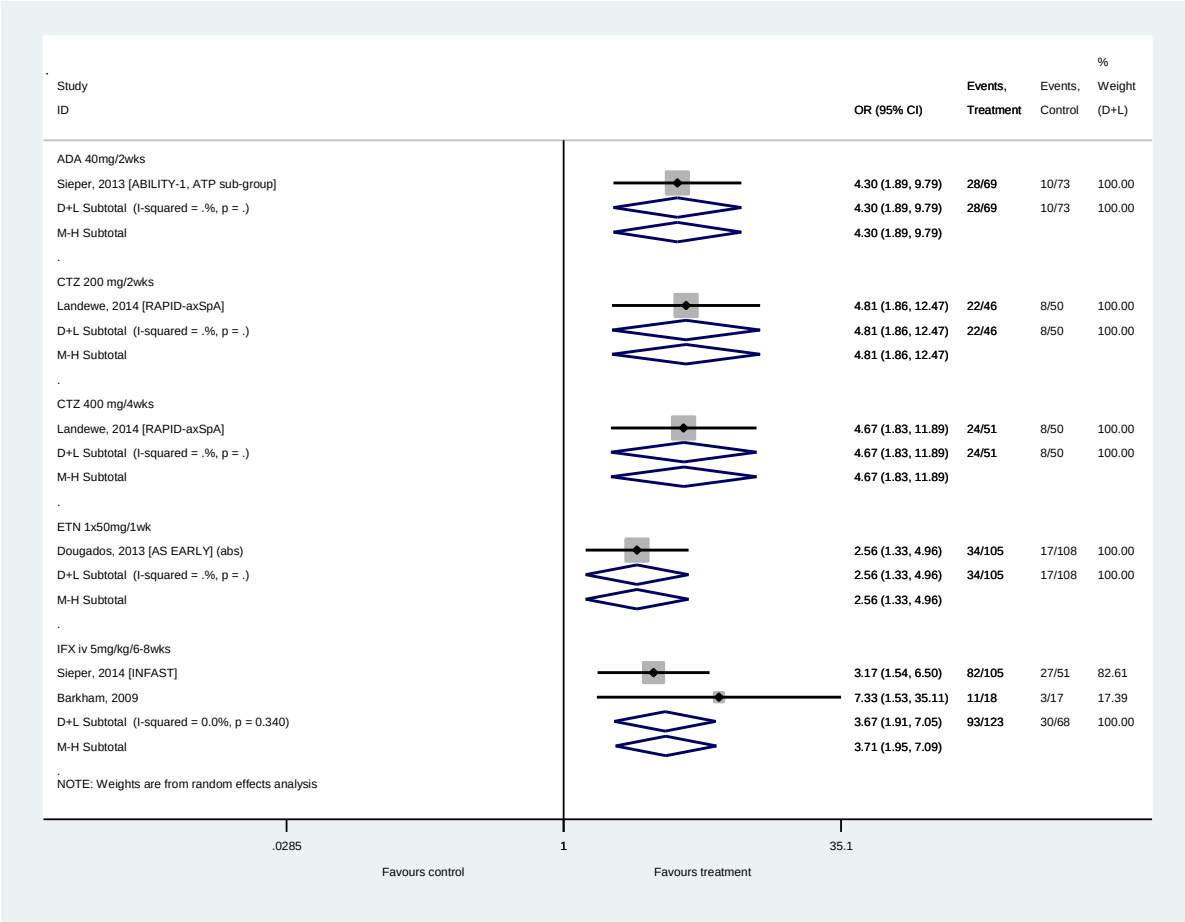
Figure 2.5.3.2.1: Forest plot for ASAS20 for nr-axSpA population at 12-18 weeks v placebo: ATP population



Significance test(s) of OR=1

ADA 40mg/2wks	z = 3.29	p = 0.001
CTZ 200 mg/2wks	z = 1.82	p = 0.069
CTZ 400 mg/4wks	z = 2.27	p = 0.023
ETN 1x50mg/1wk	z = 1.83	p = 0.067
IFX iv 5mg/kg/6-8wks	z = 0.95	p = 0.344

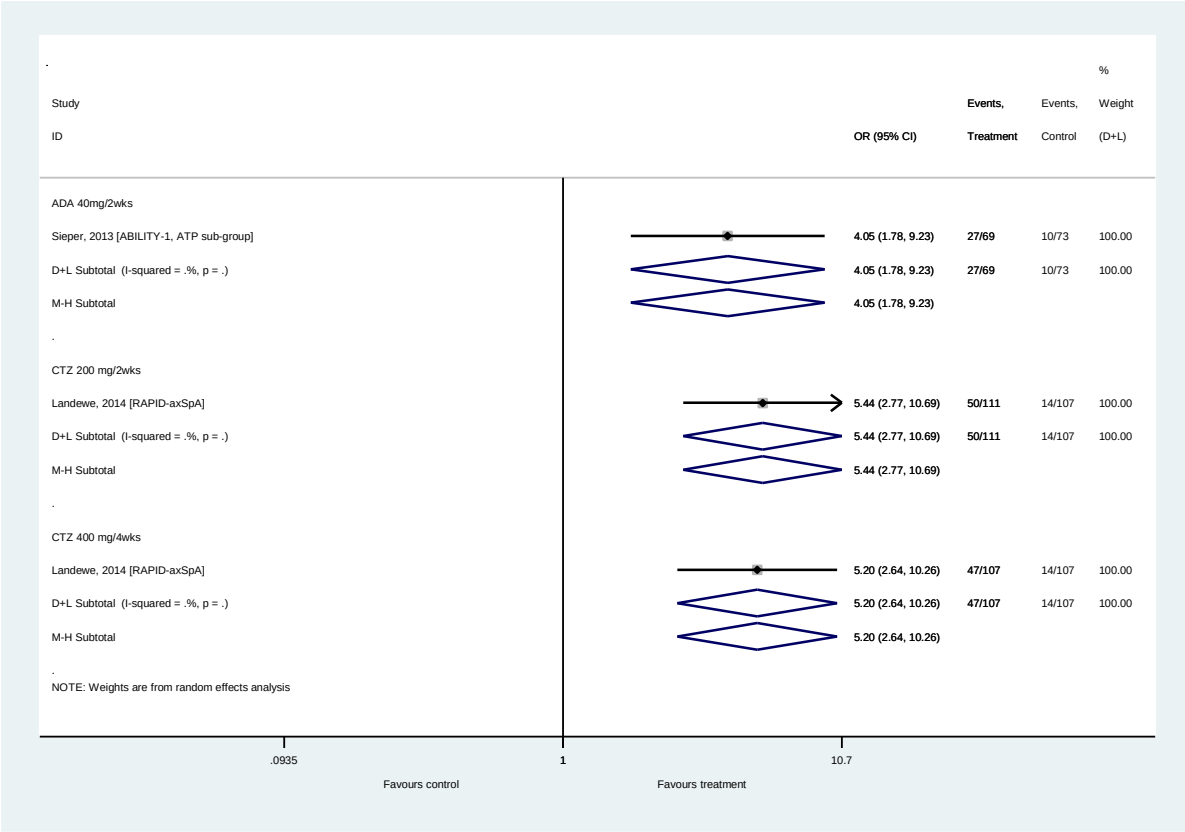
Figure 2.5.3.2.2: Forest plot for ASAS40 for nr-axSpA population at 12-18 weeks v placebo: ATP population



Significance test(s) of OR=1

ADA 40mg/2wks	z = 3.48	p = 0.001
CTZ 200 mg/2wks	z = 3.23	p = 0.001
CTZ 400 mg/4wks	z = 3.23	p = 0.001
ETN 1x50mg/1wk	z = 2.80	p = 0.005
IFX iv 5mg/kg/6-8wks	z = 3.90	p = 0.000

Figure 2.5.3.2.3: Forest plot for BASDAI50 for nr-axSpA population at 12-18 weeks v placebo: ATP population



Significance test(s) of OR=1

ADA 40mg/2wks	z = 3.33	p = 0.001
CTZ 200 mg/2wks	z = 4.92	p = 0.000
CTZ 400 mg/4wks	z = 4.76	p = 0.000

Results tables for patients with nr-axSpA for the following outcome measures: ASAS20, ASAS40, and BASADAI50 are presented in Tables 2.5.3.2.1 to 2.5.3.2.3 below.

Table 2.5.3.2.1: Network meta-analysis for nr-axSpA population: ASAS20 at 12-18 weeks, licensed population (ATP) for adalimumab

Odds ratio		Fixed-effect NMA					Random-effects NMA			
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
ADA 40mg/2wks	PLA	3.461	3.240	1.616	6.576	*	7.906	3.209	0.253	41.830
CTZ 200 mg/2wks	PLA	2.373	2.154	0.961	5.014		5.378	2.140	0.167	28.930
CTZ 400 mg/4wks	PLA	2.819	2.573	1.169	5.857	*	6.387	2.508	0.205	32.090
ETN 1x50mg/1wk	PLA	1.748	1.682	0.968	2.898		4.574	1.667	0.134	20.720
IFX iv 5mg/kg/6-8wks	PLA	1.620	1.479	0.628	3.420		3.903	1.496	0.104	20.270
ADA 40mg/2wks	CTZ 200 mg/2wks	1.744	1.499	0.507	4.404		11.210	1.498	0.043	52.380
ADA 40mg/2wks	CTZ 400 mg/4wks	1.462	1.260	0.427	3.715		8.435	1.257	0.037	42.690
ADA 40mg/2wks	ETN 1x50mg/1wk	2.142	1.924	0.811	4.697		17.200	1.948	0.054	72.180
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	2.569	2.191	0.750	6.607		19.030	2.171	0.056	86.840
Absolute risk										
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
PLA		0.459	0.457	0.291	0.638		0.462	0.460	0.290	0.640
ADA 40mg/2wks		0.722	0.733	0.498	0.883		0.691	0.732	0.168	0.974
CTZ 200 mg/2wks		0.638	0.645	0.384	0.850		0.615	0.646	0.115	0.964
CTZ 400 mg/4wks		0.675	0.685	0.423	0.869		0.648	0.683	0.136	0.967
ETN 1x50mg/1wk		0.583	0.587	0.364	0.781		0.571	0.589	0.096	0.951
IFX iv 5mg/kg/6-8wks		0.551	0.555	0.289	0.791		0.545	0.559	0.076	0.949

*significant difference based on 95% CrI; CrI, credible interval

Table 2.5.3.2.2: Network meta-analysis for nr-axSpA population: ASAS40 at 12-18 weeks, licensed population (ATP) for adalimumab

Odds ratio		Fixed-effect NMA					Random-effects NMA			
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
ADA 40mg/2wks	PLA	4.890	4.413	1.951	10.610	*	9.869	4.396	0.393	50.660
CTZ 200 mg/2wks	PLA	5.747	4.998	1.949	13.830	*	12.160	5.129	0.469	60.510
CTZ 400 mg/4wks	PLA	5.574	4.885	1.941	13.310	*	11.000	4.990	0.418	56.740
ETN 1x50mg/1wk	PLA	2.780	2.613	1.350	5.190	*	5.677	2.555	0.251	27.950
IFX iv 5mg/kg/6-8wks	PLA	3.997	3.779	1.964	7.327	*	6.860	4.331	0.825	29.200
ADA 40mg/2wks	CTZ 200 mg/2wks	1.095	0.879	0.233	3.235		7.411	0.871	0.028	25.300
ADA 40mg/2wks	CTZ 400 mg/4wks	1.117	0.903	0.248	3.257		6.196	0.902	0.028	25.620
ADA 40mg/2wks	ETN 1x50mg/1wk	1.981	1.690	0.574	5.087		12.050	1.746	0.058	45.770
ADA 40mg/2wks	IFX iv 5mg/kg/6-8wks	1.368	1.166	0.407	3.456		3.649	1.026	0.046	17.920
Absolute risk										
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
PLA		0.233	0.222	0.097	0.430		0.234	0.222	0.097	0.428
ADA 40mg/2wks		0.554	0.559	0.260	0.823		0.546	0.557	0.091	0.943
CTZ 200 mg/2wks		0.581	0.588	0.271	0.853		0.575	0.595	0.103	0.951
CTZ 400 mg/4wks		0.576	0.583	0.267	0.850		0.569	0.587	0.095	0.950
ETN 1x50mg/1wk		0.433	0.427	0.185	0.710		0.441	0.426	0.058	0.904
IFX iv 5mg/kg/6-8wks		0.517	0.519	0.248	0.780		0.551	0.556	0.160	0.911

*significant difference based on 95% CrI; CrI, credible interval

Table 2.5.3.2.3: Network meta-analysis for nr-axSpA population: BASDAI50 at 12 weeks, licensed population (ATP) for adalimumab

Odds ratio		Fixed-effect NMA					Random-effects NMA			
Treatment	**Control**	**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
ADA 40mg/2wks	PLA	4.584	4.148	1.856	9.909	*	10.780	4.087	0.305	57.270
CTZ 200 mg/2wks	PLA	5.968	5.567	2.870	11.310	*	13.200	5.496	0.414	67.990
CTZ 400 mg/4wks	PLA	5.709	5.343	2.760	10.87	*	12.130	5.214	0.378	65.000
ADA 40mg/2wks	CTZ 200 mg/2wks	0.867	0.742	0.257	2.201		8.097	0.757	0.020	32.740
ADA 40mg/2wks	CTZ 400 mg/4wks	0.908	0.780	0.267	2.326		8.373	0.785	0.021	33.020
Absolute risk										
Treatment		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**		**Mean**	**Median**	**Lower 95% CrI**	**Upper 95% CrI**
PLA		0.135	0.133	0.091	0.191		0.135	0.133	0.091	0.191
ADA 40mg/2wks		0.396	0.388	0.204	0.627		0.413	0.387	0.043	0.900
CTZ 200 mg/2wks		0.464	0.462	0.280	0.661		0.465	0.458	0.059	0.917
CTZ 400 mg/4wks		0.454	0.451	0.271	0.652		0.455	0.444	0.054	0.910

*significant difference based on 95% CrI; CrI, credible interval

2.5.4 Discussion

Given the limited numbers of trials available for synthesis in the network meta-analyses, the different populations considered, differential use of early escape arms, and relatively small populations there is uncertainty regarding the estimates of relative effectiveness obtained in the network meta-analysis conducted as part of this submission.

This will impact the strength of any conclusions surrounding the cost effectiveness of each of the anti-TNF drugs when compared to each other when these differences are generated by response rate estimates derived from the NMA.

2.6 Clinical Interpretation of the evidence

2.6.1 Comparability of the trials for nr-axSpA

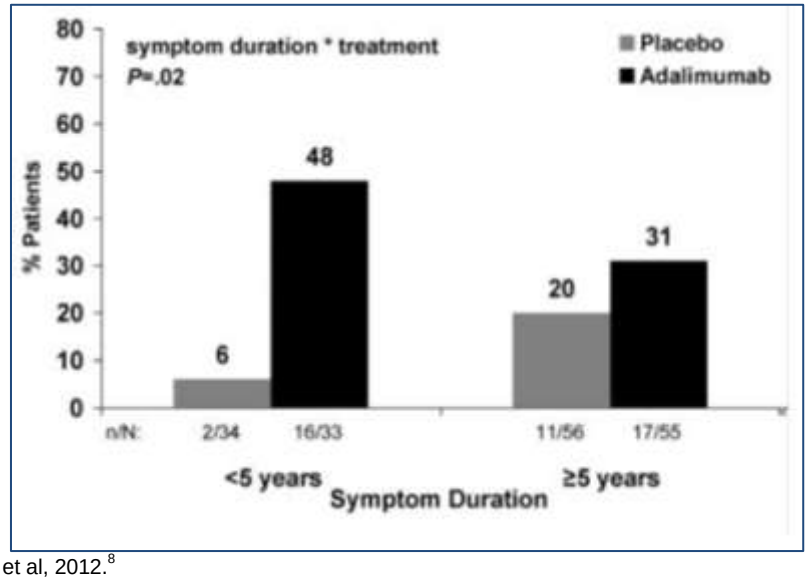
At the time of writing this submission, adalimumab and certolizumab were the only anti-TNFs licensed for use in patients with nr-axSpA. In line with the methods guide to technology appraisals, AbbVie has performed an indirect comparison to obtain estimates of the relative effectiveness of both these biological agents vs standard of care. However, the trial populations are markedly different and as discussed in Section 2.5, it was not possible to perform a meta-regression for the nr-axSpA population to test the effect different covariates had on the probability of a response as there were too few trials in the network. For example, the mean symptom duration of the adalimumab and certolizumab trials is very different, with the adalimumab arm comprising on average patients who have had symptoms of disease for more than double that of the certolizumab trial (see Table 2.6.1.1).

Table 2.6.1.1: Mean symptom duration at baseline from the adalimumab and certolizumab nr-axSpA trials

	Adalimumab – licensed population[9]		Certolizumab[68]	
Symptom duration	**ADA 40mg eow (n=68)**	**Placebo (n=72)**	**CTZ 200mg**	**Placebo**
Mean	10.71	10.37	4.8	4.5

This is important to note because Sieper *et al* showed the impact of symptom duration on achieving the primary endpoint ASAS40 (Figure 2.6.1.1 below). The percentage of patients achieving an ASAS40 response has been stratified by symptom duration <5 years vs. ≥ 5 years and the data indicate that for patients with symptom duration <5 years 48% patients achieved an ASAS40 response compared to 31% with symptoms for more than 5 years.

Figure 2.6.1.1: Percentage ASAS40 responders at week 12 from ABILITY-1 stratified by symptom duration



Source: Figure 2, Sieper et al, 2012.[8]

Figure 2.6.1.1 presents data from the full analysis set of the ABILITY-1 trial and not for the licensed population, which is the focus of this submission. Therefore, additional analysis was undertaken for ASAS40 and BASDAI50 for the licensed population stratified by symptom duration <5 years and ≥ 5 years. Table 2.6.1.2 shows the results of this analysis below:

Table 2.6.1.2 Percentage of ASAS40 and BASDAI 50 responders at week 12 stratified by symptom duration from patients in the ABILITY-1 trial fulfilling the criteria for the licensed population

	Symptom duration < 5 years N=50		Symptom duration ≥ 5 years N=89	
	ADA 40mg EOW	**Placebo**	**ADA 40mg EOW**	**Placebo**
ASAS40, %	54.2%	3.9%	34.1%	20.0%
BASDAI50, %	50.0%	0%	34.1%	22.2%

Data from Table 2.6.1.2 clearly show that for patients with <5 years symptom duration prior to initiating adalimumab, there is a much greater likelihood that they will achieve an ASAS40 and/or BASDAI50 response than if they have had disease symptoms for more than 5 years. It is also worth noting that regardless of symptom duration, both groups present a better treatment effect with adalimumab use than with placebo.

Given that the average symptom duration in the certolizumab trial was 4.8 years for patients in the CTZ 200mg eow arm with nr-axSpA, and 47.8% of these patients achieved an ASAS40;[69] the fact that 54.2% of patients with symptom duration <5 years receiving 40mg adalimumab eow achieved an ASAS40 response demonstrates the impact this particular patient characteristic has on the ability to respond. Whilst AbbVie was not able to do a covariate adjustment in the network meta-analysis, the Assessment Group might be able to do so. However, in the absence of being able to correct for these between trial differences, AbbVie suggests that caution is exercised when comparing the relative effectiveness of these two agents.

2.6.2 Placebo effects and pain

The BASDAI and BASFI measures have proved to be important measures of outcome in the assessment of AS and nr-axSpA. However, both measures may be susceptible to placebo effects as they are continuous patient-assessed outcomes, which include an assessment of pain. A Cochrane systematic review assessing the placebo effect observed that in the 10 clinical conditions investigated in three trials or more, placebo had a statistically significant pooled effect only on pain or phobia on continuous scales.[70] In the combined analyses of 156 trials, the authors did not find a statistically significant effect of placebo interventions in trials with binary outcomes, or when continuous outcomes were reported by observers, whereas a statistically significant effect was observed for trials with patient-reported continuous outcomes, especially for pain. The authors also found that in pain trials, smaller placebo effects were observed in larger trials. This review is interesting as it highlights that smaller trials using patient-assessed continuous outcomes to measure pain are most susceptible to generating placebo effects. All these conditions are present in the assessment of AS and non-radiographic trials using the BASDAI and BASFI as outcome measures. These factors may be important to consider when assessing how much more effective anti-TNF therapies are compared to placebo and when pooling trial results.

2.6.3 Extra-articular manifestations and impact on choice of treatment

Whilst this review focuses on ankylosing spondylitis and non-radiographic axial spondyloarthritis, and as such the costs and benefits are restricted to improvements in the clinical manifestations of these diseases (e.g. BASDAI and BASFI improvements mapped to EQ-5D), it is important for the Appraisal Committee to note that many patients with SpA also have extra-articular manifestations (EAMs).

EAMs associated with SpA include anterior uveitis (25–30%), psoriasis (10–25%) or inflammatory bowel disease (IBD) (5–10%) and cardiovascular manifestations[71,72]. As a result of these associated co-morbidities, the choice of treatment is particularly important as the efficacy of the biologics under review varies from agent to agent in the treatment of these EAMs. Furthermore, the 2010 ASAS/ EULAR guidelines state, “The treatment of patients with AS should be tailored according to: the current manifestation of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs).”

For example, for anterior uveitis Guignard *et al* showed that there was a clear difference between etanercept and the anti-TNF antibodies (infliximab and adalimumab); the incidence of uveitis remained unchanged with etanercept treatment (54.6 vs 58.5/100 patient-years; P=0.92), whereas it was dramatically reduced following anti-TNF antibody treatment (infliximab: 47.4 vs 9.0/100 patient-years; P=0.008, adalimumab: 60.5 vs 0/100 patient-years; P=0.04).[73] Furthermore, data from RHAPSODY (see Section 2.2.2) and an independent investigator initiated study in AS, patients with anterior uveitis (AU) showed that adalimumab significantly reduced the number of AU attacks per year. Out of 77 patients enrolled, a total of 52 AU attacks occurred in the year before baseline (68 attacks per 100 patient-yrs.), whereas during adalimumab treatment 19 attacks were seen (14 per 100 patient-yrs.; a reduction rate of 80%). Twenty-six patients with AU in the year before start of adalimumab treatment had recurrent attacks, with a median number of 2.0 AU attacks per year [interquartile range (IQR) 1.00-3.00], whereas during treatment this decreased to 10 patients with a median number of 0.56 attacks per year (IQR 0.30-0.75). Hence, the number of attacks per year decreased by 72% (p = 0.000).[74]

In a published review of the therapeutic implications of treating EAMs in SpA, Maghraoui concludes that, “Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on the course of uveitis probably inferior to the monoclonal antibodies adalimumab and infliximab.”[72]

Like Maghraoui, Van der Horst-Bruinisma et al also evaluated the management and evaluation of extra-articular manifestations in spondyloarthritis.[75] The authors found "in patients with SpA and IBD the use of NSAIDs should be minimised, except for celecoxib. Furthermore, sulfasalazine might be beneficial for both indications, but the first choice of anti-TNF is adalimumab or infliximab."

To conclude, there are sufficient published data showing differential benefits between the biologics in the treatment of EAMs associated with axial SpA. Adalimumab has been shown to be efficacious in the treatment of anterior uveitis associated with AS, IBD and psoriasis. As such, the choice of biologic treatment for patients with axial SpA should take into account not only the axial manifestations, but given the high prevalence of uveitis, IBD, psoriasis etc., also take account of any EAM and the benefit different drugs confer on these co-morbidities.

2.6.4 Long term benefits of anti-TNF therapy and rebound assumption

Available data on BASDAI from observational and registry suggest that in the absence of anti-TNF therapy this remains persistently elevated for patients with AS. For BASFI the available data indicates that for patients on conventional therapy this increases over time; whereas for patients receiving anti-TNF therapy it drops and remains constant. One of the key clinical assumptions with regard to the economic modelling is therefore what happens to the BASFI score of patients who stop anti-TNF therapy. It has been assumed in all published models that BASFI rebound on stopping therapy would be of the same magnitude as the initial gain. Therefore, given that there has been no progression whilst the patient has been on treatment, they will rebound to the same BASFI level as when therapy commenced. The implication of this assumption is that since there is a difference in progression for anti-TNF agents and conventional therapy, spending time on an anti-TNF agent results in a sustained long-term benefit compared to conventional therapy.

If we consider a patient has been on an anti-TNF agent for 5 years, the rebound to natural history assumption would conclude that the patient has an instant BASFI worsening on stopping anti TNF therapy equal to the worsening in BASFI over 5 years that would have occurred had the patient been on conventional therapy in addition to the worsening equal to the initial BASFI gain on anti-TNF therapy. If the rebound for patients on long term anti-TNF therapy were of this magnitude the phenomenon of rebound to natural history would have been noted in clinical practice by patients and rheumatologists.

2.6.5 Eligibility for an anti-TNF agent

Current NICE guidance TA143 - adalimumab, etanercept and infliximab for ankylosing spondylitis stipulates that adalimumab or etanercept is recommended in patients with severe ankylosing spondylitis who:

- have had active spinal disease (BASDAI > 4 and at least 4cm on the 0-10cm VAS for spinal pain) as assessed on two separate occasions 12 weeks apart without any change in treatment
- have tried conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks that has failed to control symptoms.

AbbVie considers that these criteria cause unnecessary delay and suffering for the patient. AbbVie agrees that patients need to have tried and failed conventional therapy prior to initiating an anti-TNF, and that their disease activity needs to be severe enough to warrant an anti-TNF in line with the licenses. However, to record a BASDAI >4 and spinal VAS >4 at the first time point, indicating severe disease, and then having to wait a further 12 weeks without any treatment changes to record another score seems to be an unnecessary amount of pain and suffering for the patient to tolerate prior to initiating an anti-TNF.

AbbVie suggests that the 2010 Update of the International ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis has more appropriate eligibility criteria, much more in line with other NICE technology appraisal guidance that don't require such a delay in treatment:

- Patients must fulfil the modified New York criteria for AS or the ASAS criteria for axial SpA
- Patients must have had active disease for $\geq$4 weeks
- BASDAI $\geq$ 4 and a positive expert opinion
- **All patients** should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a 4-week period in total at maximum recommended or tolerated anti-inflammatory dose unless contraindicated.

2.7 Summary of ongoing AbbVie sponsored clinical trials of adalimumab in axial SpA

This section summarises the ongoing AbbVie sponsored clinical trials of adalimumab in axial SpA by NCT number. Further information about these studies is available on www.clinicaltrials.gov.

1. NCT01474876 – a multi-country post marketing observational study on maintenance of effectiveness of adalimumab in patients with ankylosing spondylitis and psoriatic arthritis. This study was expected to complete in May 2014, with final data collection for the primary outcome also in May 2014. There were three primary outcome measures: 1) the percentage of patients who had BASDAI50 at the end of the observational period of 12 months as compared with baseline; 2) percentage of patients with >1.2 change in DAS28 score at 12 months from baseline; and 3) percentage of patients in ASDAS remission at 12 months.

2. NCT01808118 (M13-375) – a multicentre, randomised, double-blind, study comparing the efficacy and safety of continuing vs. withdrawing adalimumab therapy in maintaining remission in subjects with non-radiographic axial spondylitis. The primary endpoint to be collected is the proportion of participants who do not experience a flare during period 2 by Week 68 of the study where a flare is defined as having any 2 consecutive study visits with ASDAS ≥ 2.1. This study initiated in May 2013 and is expected to complete in May 2017. Recruitment is currently ongoing with target enrolment around 740 participants.

Section 3: Cost-effectiveness

3.1 Overview of economic evaluation of adalimumab for the treatment of ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

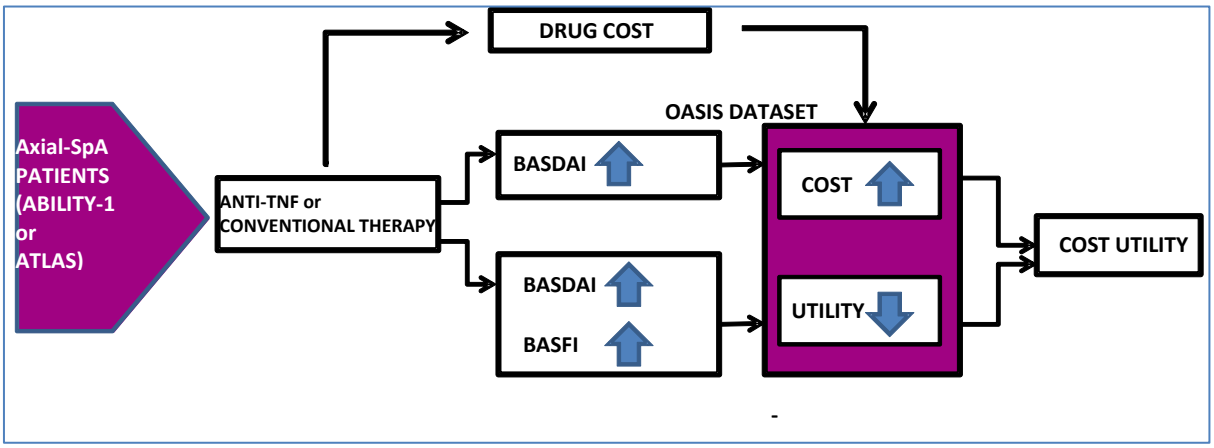
An economic model to estimate the cost effectiveness of adalimumab vs. conventional therapy and other licensed TNF antagonists for axial spondyloarthritis (both nr-axSpA and AS) patients was developed in conjunction with Pharmerit. A copy of the excel file containing the model is enclosed alongside this submission.

3.1.1 Model Structure

A state-transition model was developed based on the ASAS guidelines for the use of TNF antagonists in a population of patients with axial SpA patients to reflect real-world treatment decisions and to project long-term outcomes.[52] All patients were assumed to take conventional therapy/background therapy (e.g. NSAIDs) during the modelled horizon and also receive one of the licensed TNF-antagonists (adalimumab, certolizumab pegol, golimumab, etanercept and infliximab) or placebo (conventional therapy only). Specifically, patients were assumed to stay on therapy as long as they had an adequate therapeutic response (i.e., ASAS40 for nr-AxSpA and ASAS20 for AS), but were taken off therapy when insufficient response occurred. Discontinuations due to adverse events (AEs) or reasons other than therapeutic failures were also considered.

The model consists of two components. The short-term (first 12 weeks) component covers the impact of therapy on clinical outcomes based on the clinical trials. However, because axial SpA is a lifelong condition, it is important to assess the impact of therapy beyond the duration of the randomised controlled trials, which required assumptions on long-term disease prognosis beyond the time of switch to open label therapy. The model harnessed the available long-term trial data for adalimumab (up to 156 weeks in ABILITY-1 for nr-axSpA and 260 weeks in ATLAS for AS) as well as including assumptions beyond trial durations to demonstrate the life-time cost-effectiveness (up to 40 years). The structure of the model can be seen in figure 3.1.1.1.

Figure 3.1.1.1: Overview of Model Structure

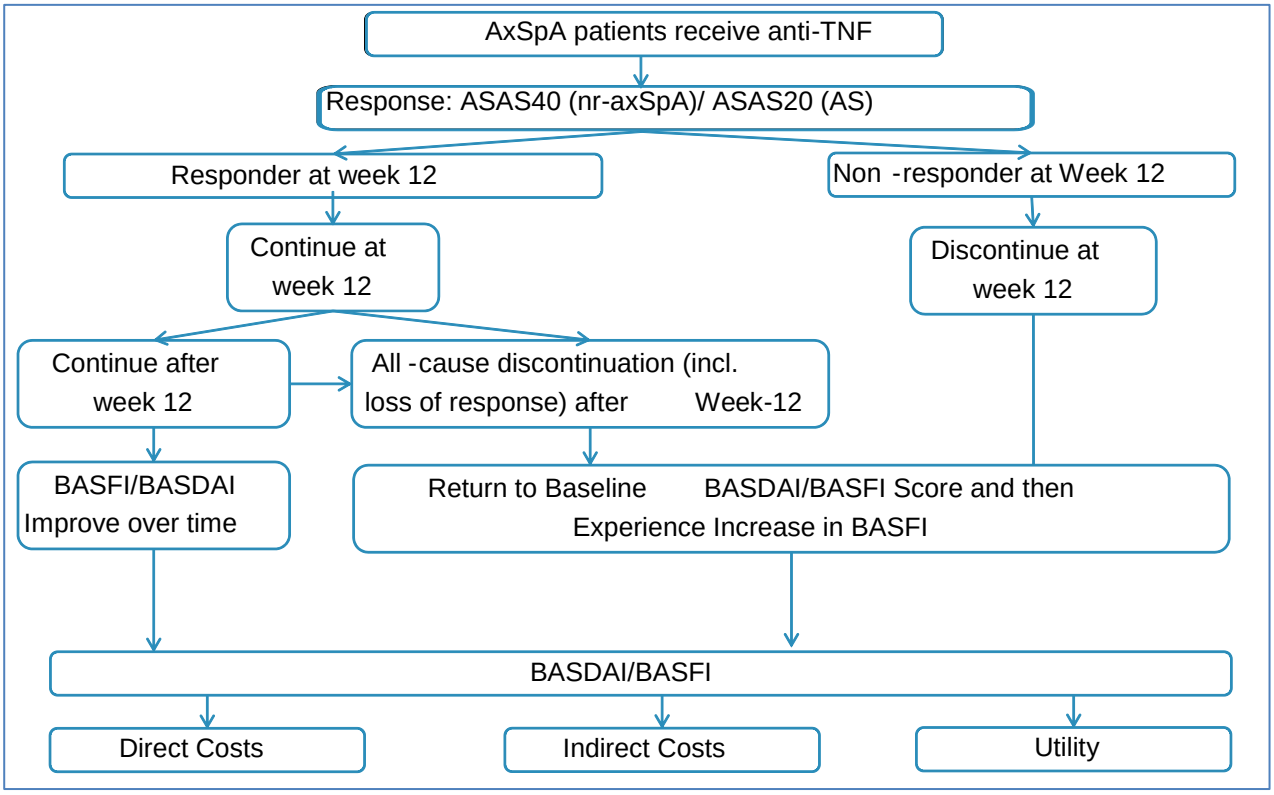


The model focuses on the progression of BASDAI and BASFI over time. The mathematical structure is that of a state-transition model, where the clinical outcomes, quality of life and costs of patients in each state are incurred over time, allowing the computation of a measure of cost-effectiveness over a given defined period.

The structure of the model is shown in Figures 3.1.1.2 (for treatment with adalimumab) and 3.1.1.3 (for treatment with conventional therapy), and reflects treatment decisions commonly followed in the UK for the treatment of AS, which many rheumatologists think are also applicable to nr-axSpA patients. The rationale is that patients are kept on treatment for as long as they can be considered to be in response and therefore, patients are categorised as responders or non-responders and whether on therapy or not. The model consists of two components. The short-term component covers the impact of therapy on clinical outcomes from the RCTs (first 12 weeks). The impact of the chronicity of axial SpA is assessed through by carrying out

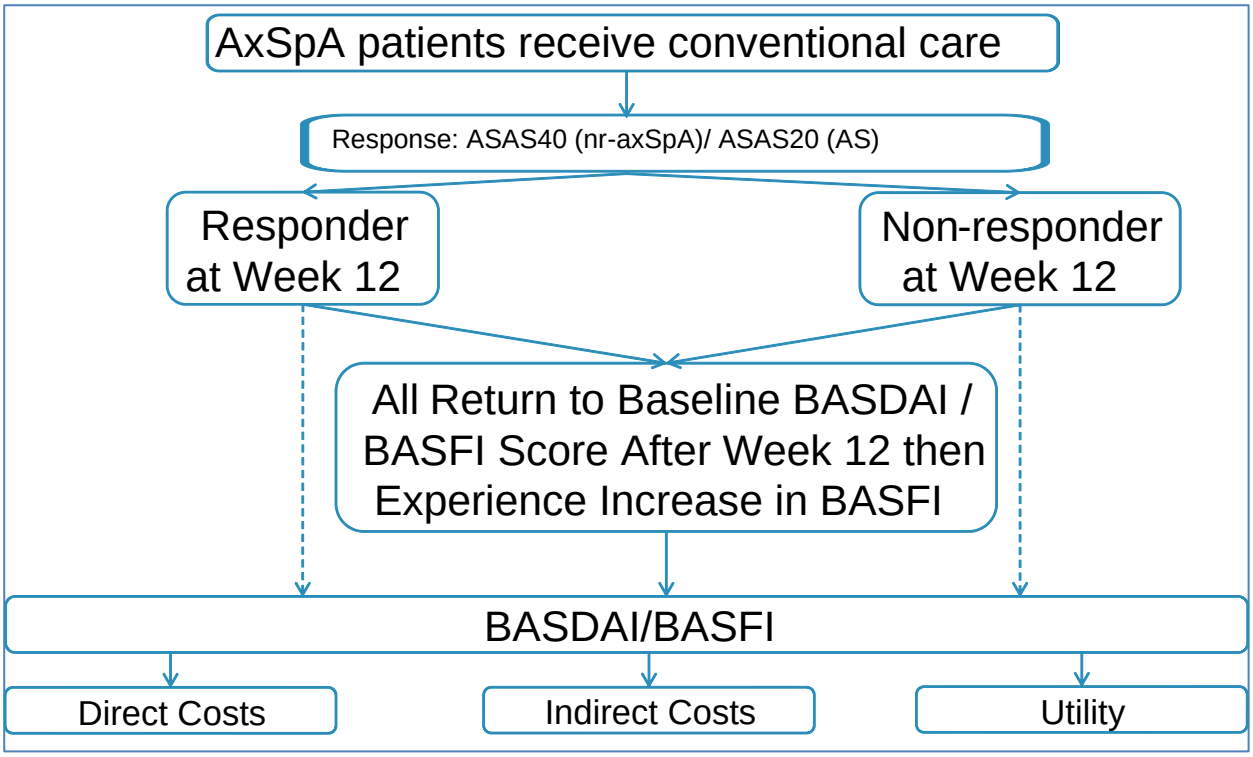
extrapolation of clinical data from the trial and observational studies over a period of 40 years. The main body of evidence is from the ABILITY-1 and ATLAS trial.

Figure 3.1.1.2: Detailed Model Structure of active anti-TNF Arm in Base Case Analysis



Legend: In the base case, ASAS40/ASAS20 response rates at week 12 were obtained from the NMA indirect comparisons of all licensed anti-TNF therapies and conventional therapy for both indications. A certain percentage (i.e., 55.90% of adalimumab in nr-AxSpA by ASAS40) of subject responded at week 12. Non-responders at week 12 are assumed to be discontinued from therapy and return to baseline BASDAI and BASFI scores. Responders are assumed to remain on therapy until subsequent discontinuation, based on observed and modelled data. Responders experience improvement in their BASDAI and BASFI scores while remaining on therapy based on observed scores in available open-label period and LOCF afterwards. However, upon discontinuation, BASDAI and BASFI scores return to baseline levels. The BASDAI scores were assumed to remain constant from that point onward. However, BASFI scores for patients who are not on anti-TNF after week 12 are expected to worsen over time. BASDAI (or BASFI) scores were used to estimate costs and BASDAI and BASFI scores were used to estimate utility.

Figure 3.1.1.3: Detailed Model Structure of Conventional Therapy Arm in Base Case Analysis



Legend: In the base case, ASAS40/ASAS20 response rates at week 12 were obtained from the NMA indirect comparisons of all licensed anti-TNF therapies and conventional therapy for both indications. A smaller percentage (i.e., 22.20% of conventional therapy in nr-AxSpA by ASAS40) of subject responded at week 12. Both responders and non-responders at week 12 were assumed to return to baseline BASDAI and BASFI scores. The BASDAI scores were assumed to remain constant from that point onward. However, BASFI scores for patients who are not on anti-TNF after week 12 are expected to worsen over time. BASDAI (or BASFI) scores were used to estimate costs and BASDAI and BASFI scores were used to estimate utility.

3.1.2 Patient populations and perspective

In nr-axSpA, the analysis was based on the pivotal placebo-controlled Phase III study (the ABILITY-1 trial) of severe nr-axSpA patients with baseline BASDAI≥4 and who had an inadequate response or were intolerant to at least one NSAID. Patients were randomised to either adalimumab 40mg every other week (n=91) or conventional therapy (n=94) for 12 weeks, followed by an open-label extension period with data to 156 weeks. It should be noted that the study population of the ABILITY-1 study was adults with active axSpA not fulfilling the modified New York criteria for AS, who had either MRI evidence of active inflammation or positive HLA-B27, and an inadequate response to or intolerance to ≥1 NSAID, or had a contraindication for NSAIDs. This is a broader population than the indication specified in the marketing authorisation and thus, the indication relevant to this submission; the licence granted was that of adults with severe axSpA without radiographic evidence of AS and with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs (adalimumab, n=69; placebo n=73). As such, data involving estimates of effectiveness presented in the economic evaluation are based on the licensed population (ATP) within the ABILITY-1 trial which had elevated CRP and/or positive MRI.

For AS, the model inputs were based on ATLAS, which is a multicentre, double-blinded, phase III, placebo-controlled randomised clinical trial. Patients were 18 years of age or older, diagnosed with definitive AS based on the modified New York criteria and fulfilling at least two of the following three criteria: (1) Bath AS Disease Activity Index (BASDAI) score 4 or greater; (2) morning stiffness for 1 h or longer and (3) visual analogue scale (VAS) score for total back pain 4 or greater on a scale of 0 to 10. Patients also had an inadequate response to at least one non-steroidal anti-inflammatory drug and may (but were not required to) have failed treatment with at least one DMARD. Patients were randomized in a 2:1 ratio to receive either adalimumab 40 mg or matching placebo subcutaneously eow for 24 weeks. Patients did not achieve ASAS 20 response at weeks 12, 16, or 20 were eligible to receive early-escape, open-label treatment with adalimumab 40 mg eow and were followed per protocol.

The model inputs of selected treatment efficacy endpoints (e.g. response rates) were obtained through a systematic review and network meta-analyses of RCTs of TNF-α inhibitors used in AS and nr-axSpA (refer to Section 2.5).

In the primary analysis, ASAS40 for nr-axSpA and ASAS20 for AS were used to define clinical response at week 12, because these were the primary outcome measures from the clinical trials of adalimumab. Placebo responders at week 12 were assumed to lose response and return to baseline disease severity. Both the BASDAI and BASFI scores were used jointly to estimate the quality of life associated with axial SpA. The relationship between BASDAI/BASFI and costs (units of resource utilisation) was derived from the OASIS observational database, which contains information on AS patients in Europe. The BASDAI and BASFI scores were used jointly to estimate quality of life associated with AS, using the relationship observed between the utility scores (measured in HUI3) and the BASDAI and BASFI scores in ATLAS trial. Since EQ-5D was not collected in ATLAS and lack of parameter uncertainties (e.g. standard errors) from the previous mapping of BASDAI/BASFI to EQ-5D from the 2006 NICE AS appraisal, we were not able to select EQ-5D as the primary utility measure. However, in secondary (scenario) analyses, EQ-5D mapping (e.g. Ara *et al*, McLeod *et al*) was examined deterministically for AS. Additionally, the BASFI score was used to substitute for the BASDAI for the relationship with costs and trial-observed utility scores were used to in place of BASDAI/BASFI as secondary analyses. Moreover, a conservative scenario where placebo responders maintain week 12 response was also examined. Due to data availability issues, it was not possible to use BASDAI and BASFI scores as joint predictors of costs.

Costs of axial SpA resource utilisation, drug, administration, initiation and monitoring, and adverse events were calculated from the healthcare perspective. Time lost due to axial SpA or seeking care was also included in a separate sensitivity analysis from a societal perspective. Standardized mortality ratio of 1 and 1.5 was assumed for nr-AxSpA and AS, respectively. Discounting was applied at 3.5% for both costs and outcomes in the base case; the discount rate was varied in sensitivity analyses. Uncertainty surrounding outcomes was addressed using probabilistic sensitivity analyses (PSA).

3.2 Model Inputs

3.2.1 Patient Characteristics

The nr-axSpA patient population in the model represented the characteristics of the licensed sub-group population from the pivotal trial (ABILITY-1) which had elevated CRP and/or positive MRI. Patients in the trial fulfilled the ASAS criteria for axial spondyloarthritis, had an inadequate response, intolerance or contraindication to NSAIDs, but did not fulfill the modified NY criteria for AS. The enrollment criteria for ABILITY-1 differed slightly from the ASAS criteria in two respects:

- Patients enrolled in the trial were required to have had an inadequate response to or intolerance to ≥1 NSAIDs as defined by the Investigator, whereas the ASAS recommendations require adequate therapeutic trials of ≥2 NSAIDs over a 4-week period in total at maximum recommended or tolerated anti-inflammatory dose unless contraindicated. However, approximately 70% of patients enrolled in ABILITY-1 had $\geq$ 2 NSAIDs prior to initiating adalimumab.

- Six patients enrolled in the trial had baseline BASDAI scores less than 4. Three in each arm.

All patients randomised in ABILITY-1 who had objective signs of inflammation (elevated CRP and/or positive MRI) were included in the economic analysis. In the modelling of health state utilities the Full Analysis Set was used, as a larger sample size (185 rather than 142 patients) allowed for an increase in the precision of the estimates. The Safety Analysis Set from the overall ABILITY-1 trial was used in the computation of the incidence of adverse events.

For AS, the ATLAS trial of adalimumab is representative of the licensed population - adults with severe active AS defined by modified New York criteria and inadequate response or intolerance to conventional therapy (e.g. NSAIDs). The model inputs were based on completed 5-year trial data with 311 randomised patients who received at least one dose of adalimumab (during the double-blinded or open-label extension).

3.2.2 Outcome measures

QALYs are used to assess the final health outcomes achieved with treatment. In ABILITY-1, EQ-5D data were collected directly from the patients in the trial; whereas in ATLAS, HUI-3 data were collected. The utility values directly collected from these trials were then modelled to account for the effect on utility of a possible increase over time in BASFI scores. Having similar utility values directly scored from the utility questionnaires in two different model specifications, drawing on different hypotheses of BASFI evolution over time, would

create an inconsistency. Furthermore, all patients on placebo stopped placebo at week 12 and had the option to receive open label adalimumab. Therefore, it was not possible to observe the utility of patients on placebo beyond 12 weeks. As such, the relationship between health state utilities, BASDAI and BASFI scores was derived from the ABILITY-1 and ATLAS trial through linear mixed regressions models[76], with random effects allowing subject-specific intercept and coefficients. The fixed-effect relationship for the base case scenario is presented below.

ABILITY-1: EQ-5D = 0.922* - 0.03924 BASDAI* - 0.04117 BASFI*
(0.01069) (0.005426) (0.006141)

ATLAS: HUI3=0.8991*-0.03109 BADSAI* -0.04146 BASFI*
(0.01155) (0.004047) (0.004802)

Value in parentheses are SE of the coefficients
*P<0.001

Besides mapping BASDAI/BASFI to HUI3 for AS, modelling using the BASDAI and BASFI scores and their relationship with EQ-5D was also adopted from the 2006 NICE appraisal as alternatives in scenario analysis, however as previously mentioned these could not be the base case because the SEs for the two EQ-5D algorithms has been redacted in the Assessment Group report.

3.2.3 Effectiveness Estimates

The effectiveness estimates for the outcomes of ASAS20/40,BASDAI50, BASDAI, BASFI and EQ-5D/HUI3 were taken from the ATP population of the nr-axSpA patients in ABILITY-1 who had elevated CRP and/or positive MRI (n=142) and for the whole analysis set for ATLAS (AS patients). Sections 2.1, 2.2 and 2.3 provide details of all the results of the primary and secondary outcome measures for these populations.

3.2.4 Disease epidemiology

- *Definition of Response*

All response rates were obtained from the network meta-analyses as specified in Section 2.5 for both indications, AS and nr-axSpA. ASAS40 and ASAS20 were the primary endpoints for the ABILITY-1 and ATLAS trial, respectively. ASAS20 has been the primary endpoint of a series of studies including RAPID, which is the major RCT for certolizumab pegol in nr-AxSpA. Although BASDAI50 had been recommended earlier by the BSR guidelines,[77] it was reported less frequently in RCTs included within the NMA and has recently been accused of being quite subjective (due to its self-reporting nature). More importantly, agreement between ASAS response criteria and expert opinion was found to be good while only moderate to good was found for BASDAI50 and expert opinion.[78] Therefore ASAS responses are preferred in this analysis and have been selected for the base case (e.g. ASAS40 for nr-AxSpA and ASAS20 for AS). Nevertheless, all response criteria including BASDAI50 were also tested under scenario analyses for both indications.

- *Timing of Assessments of Response*

Assessment timing varied from week 12 to 16 from the RCTs included in the analysis. We applied the meta-analysed response rates to week 12 in the model for simplicity in analysing the ABILITY-1 and ATLAS trial data for BASDAI/BASFI scores and subsequent responder discontinuation rates. In ABILITY-1, response to adalimumab or placebo was assessed at week 12 - the end of the double-blind, randomised period, consistent with the ASAS guidelines recommendation of assessment of response between week 6 and 12. No patients were taken off therapy until week 12 due to lack of efficacy in line with the recommendation in the summary of product characteristics for adalimumab. Patients with missing ASAS40 responses at week 12 were treated as non-responders according to "non-responder imputation" criterion. Any patients who discontinued or had missing values at week 12 were counted as non-responders in the analysis. In ATLAS, patients without ASAS20 response from week 12 to 24 were entitled to switch to open-label or discontinue the study, which may bring unnecessary complexities for the model structure (mostly because this affects the placebo estimates where many more patients did not achieve an ASAS20 response at week 12, and escaped to open-label therapy). Therefore, only the first 12 weeks of the 24-week double-blinded period was used for BASDAI/BASFI scores and adalimumab discontinuation rates after week 12.

- *Relationship of BASDAI, BASFI, and EQ-5D/HUI3 to costs and quality of life*

In the primary analysis, the BASDAI score was used to estimate the costs of resource use based on the OASIS observational database. Both the BASDAI and BASFI scores were used jointly to estimate the quality of life associated with axial SpA. Observed EQ-5D scores were mapped to BASDAI and BASFI for the relationship in the base case for nr-axSpA. However, only HUI3 was collected in ATLAS for AS patients and it states in the NICE DSU report (Brazier et al, 2011) that HUI3 is acceptable in absence of EQ-5D generic measure, although the preference should be given to the more consistent and universal measure of EQ-5D. Therefore, we modelled the quality of life of AS patients using HUI3 as the primary analysis and tested other algorithms using EQ-5D from previous AS appraisals (i.e., Ara et al, McLeod et al) in secondary (scenario) analyses. The BASFI score was also used to substitute for the BASDAI for the relationship with costs, and the observed EQ-5D scores in ABILITY-1 and HUI3 in ATLAS for the relationship with utilities. As previously highlighted observed utility scores were only available for placebo for the first 12 weeks, after which all patients continuing in the study were switched to open-label adalimumab.

- *BASDAI and BASFI and EQ-5D scores over time*

In the model, it is assumed that BASDAI scores for patients not on adalimumab (i.e., conventional therapy patients, and patients who discontinued adalimumab) remain at the common baseline scores from week 12 onward. The assumption of constant BASDAI score while not on adalimumab is supported by baseline data from the ABILITY-1 trial. Specifically, baseline BASDAI scores can be predicted via linear regression analysis using time since symptom onset as a predictor. Each additional year of symptom duration was associated with a non-significant coefficient (+0.02 per year).

In the base case model, the BASFI score for all patients not on anti-TNF treatment increases in a linear fashion by 0.084 per year, in line with the evidence from the ABILITY-1 trial, where each additional year of baseline symptom duration was associated with a significant (+0.084, p=0.0005) increase in baseline BASFI score adjusting for the age of onset (age at first reported axial SpA symptom) to control for the age effect on functional damage. This worsening of BASFI over time has also been observed in studies in AS patients: firstly in the ATLAS trial where a significant annual BASFI increase of 0.056 adjusting for age at disease diagnosis was reported, and also in Taylor *et al.*[79] and Kobelt *et al* (in a subgroup of patients with BASDAI≥4 at baseline).[80] Further, an increase in BASFI score is consistent with a study by Heikkila *et al.* (+0.300 per year)[81], and the OASIS study (personal written communication: van der Heijde and Boonen 2005) (+0.075 in a subgroup of AS patients with BASDAI≥4 at baseline). These observations may also be consistent with the observation that patients with nr-axSpA have lower but possibly a faster functional damage than patients with AS, suggesting that these BASFI scores are subject to change and that time and/or disease progression impact BASFI scores. However, given the lack of sufficient follow-up data on disease progression of most literature, this model does not attempt to link nr-axSpA progression to AS by BASFI score.

Responder BASFI/ BASDAI scores were divided into three subgroups according to the timing of the assessment and adalimumab treatment discontinuation status:

- All responders at Week 12;
- All responders post-week 12 who continue on therapy; and
- All responders post-week 12 who discontinue on therapy

In the base case analysis, it was assumed that placebo response at week 12 would be lost immediately after week 12 and the BASDAI and BASFI scores of the placebo responders in conventional therapy would return to baseline. The ASAS40 endpoint in ABILITY-1 comprises a number of subjective visual analogue scales and is therefore quite prone to reporting of subjective placebo effects. However, if we examine the difference in the objective secondary point of change in CRP (measured in mg/l) from baseline to 12 weeks, the response in the placebo arm is approximately seven times <u>less</u> than in the adalimumab arm (-0.8 for placebo vs. -6.5 for adalimumab), compared to an approximately threefold difference for the ASAS40 response (see Table 2.3.2.2 in Section 2.3.2). AbbVie believes that the placebo effect present in the primary outcome (ASAS40) may be due to a large extent as a result of the disease flare-up at baseline (more likely to participate in clinical trials at flare-ups) and regression to the mean at week 12. Subjectivity of the measure could also explain the placebo response and that this effect would be much less relevant in real world clinical practice. The mean BASDAI and BASFI scores at 12 weeks were low in the 10 placebo patients who were ASAS40 responders, however further analysis of the mean changes in scores is hampered by the small sample of only 10 responders in the placebo arm. Nevertheless, alternatively a more conservative assumption was examined in scenario analysis where placebo effect was not lost but maintained through the lifetime horizon.

The BASDAI and BASFI scores of adalimumab responders in the licensed population showed consistent improvement in ABILITY-1 (week 12 to 140) and ATLAS (week 12 to week 260), as illustrated in the observed mean values presented in Figures 3.2.4.1 and 3.2.4.2. It is therefore reasonable to assume that patients benefit from the therapies as long as they continue on adalimumab treatment over time. To avoid extrapolating life-time improvement by subjective functional forms from only the first 2 to 5 years data, we applied the mean observed BASDAI and BASFI scores until the last available data point and carried forward the last observed values to the end of horizon. As a result, the life time benefit of being treated is not subjective to bold statistical assumption that may overestimate the effect of adalimumab. The same BASDAI/BASFI scores by response status from ABILITY-1/ATLAS trial were applied to all active anti-TNF comparators due to the limitation that scores by week-12 response from other RCTs were not accessible at the time of analysis.

Figure 3.2.4.1: Observed mean BASDAI and BASFI scores for adalimumab ASAS40 responders in the licensed population from ABILITY-1 (ATP population)

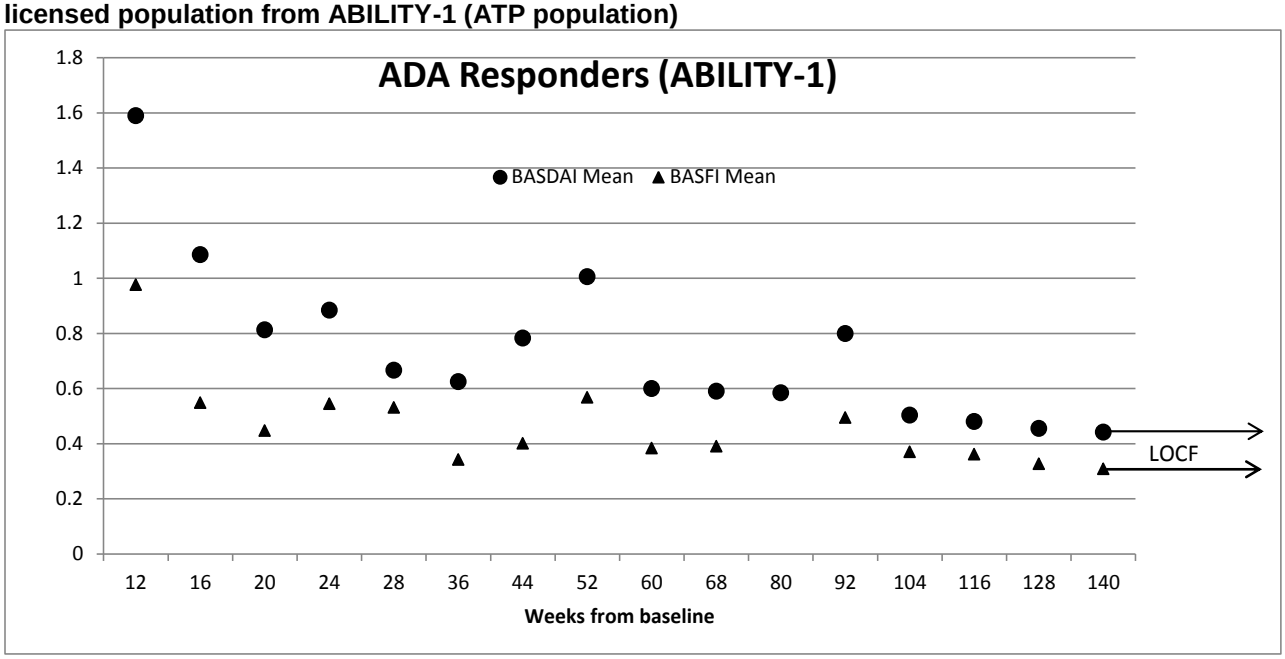
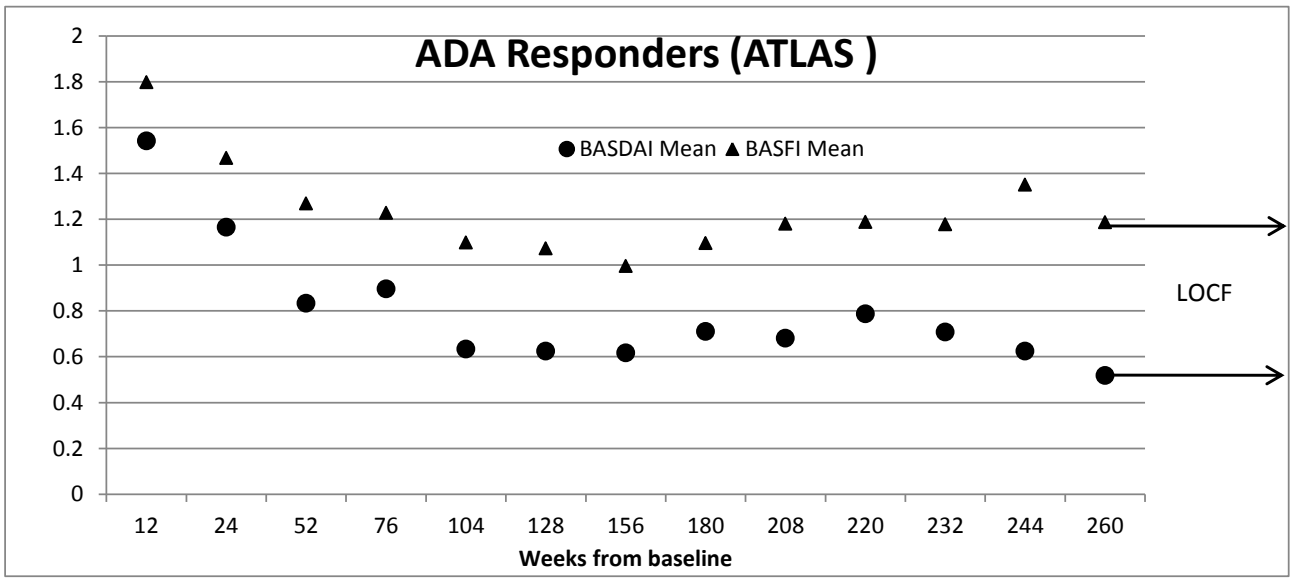


Figure 3.2.4.2: Observed mean BASDAI/BASFI scores for adalimumab ASAS20 responders from ATLAS



Although no statistically different baseline characteristics and scores were found between treatment arms (i.e. between ADA and placebo) in the two RCTs, slight differences do exist due to statistical noise and imperfect randomisation. The difference, although miniscule, may accumulate over the time horizon and create considerable bias in cost-effectiveness estimation in the deterministic setting. As such, to ensure patients from anti-TNFα and conventional therapy arm start at the same level of BASDAI/BASFI, which drive

the estimation of cost and benefit; we weighted the trial-observed mean baseline scores from the two arms by the number of patients and created a uniform baseline scores as shown in Table 3.2.4.1.

The uniform baselines are numerically equal to the mean baseline scores of all patients regardless of arm. The scores by responder/non-responder and treatment arm can be predicted by certain regression analyses controlling for baseline axial SpA features and baseline scores as covariates. However, given that baseline characteristics between the adalimumab and placebo arms from ABILITY-1 and ATLAS are not significantly different; the estimated coefficients were not significant as expected. Thus, it would not add much information to the prediction. To avoid unnecessary complexities, we adopted a simplified method to derive scores which does not involve multivariate analysis: the difference between trial-observed and the uniform baseline was retained and added to all observed mean scores (both responders and non-responders) from week 12 onward. As such, the information from trial-observed values is preserved in a logical and simple way with minimum data manipulation. The standard errors of the derived scores were also calculated based on pooled variance estimation. Similarly, the trial-observed utility (EQ-5D or HUI3) inputs (for scenario analysis) were derived.

The following data set were generated:

- Uniform baseline scores for both treatment arms (adalimumab/other anti-TNFα and placebo)
- Adjusted scores for responders and non-responders at week 12 for each treatment arm separately.

Table 3.2.4.1: BASDAI/BASFI Scores Inputs by Group, Time Points, and Treatment at Week 12 (Base case scenario)

Outcome	Group	Time of Assessment	Nr-AxSpA: ASAS40 Response (ABILITY-1 ATP)		AS: ASAS20 Response (ATLAS)	
			Adalimumab	Conventional therapy	Adalimumab	Conventional therapy
BASDAI	All	Uniform Baseline	6.432	6.432	6.297	6.297
	Responders	At 12 Weeks	1.589	2.150	2.329	2.663
	Responder-Continuers	>12 Weeks	Mean Observed then LOCF	6.432	Mean Observed then LOCF	6.297
	Responder-Discontinuers	>12 Weeks	6.432	6.432	6.297	6.297
	Non-Responders	At 12 Week	6.432	6.432	6.297	6.297
	Non-Responders	>12 Week	6.432	6.432	6.297	6.297
BASFI	All	Uniform Baseline	4.629	4.629	5.372	5.372
	Responders	At 12 Weeks	0.976	1.484	2.477	2.178
	Responder-Continuers	>12 Weeks	Mean Observed + LOCF	4.629	Mean Observed + LOCF	5.372
	Responder-Discontinuers	>12 Weeks	4.629	4.629	5.372	5.372
	Non-Responders	At 12 Weeks	4.629	4.629	5.372	5.372
	Non-Responders	>12 Weeks	4.629	4.629	5.372	5.372

Patients who did not respond at week 12 were assumed to discontinue therapy at that time. In addition, week-12 responders from anti-TNF arms could discontinue over time due to a series of reasons.

In both cases, when anti-TNF responders were discontinuing, it was assumed that their BASDAI and BASFI scores would immediately rebound to baseline. From that point onward, it was assumed that patients who had discontinued would experience a worsening of BASFI over time (+0.084/year for Nr-AxSpA and +0.056 for AS). This rate was based on the observed change in BASFI per year of since axSpA symptom/diagnosis duration among ABILITY-1/ATLAS patients at baseline, as discussed above.

Baseline BASDAI scores modelled via linear regression yielded non-significant coefficients for time since symptom onset/diagnosis and age at onset used as the explanatory variables. This fact and the body of literature that supports the assumption of independence of disease duration and BASDAI scores - e.g.

Taylor et al (1998)[79] - led to assuming that BASDAI scores for patients on conventional therapy, and patients who discontinued adalimumab would remain at the common baseline scores from Week 12 onward.

3.2.5 Treatment discontinuations

The base case response rates obtained from NMA median estimates at week 12 (when randomisation ended) for nr-axSpA were 55.9%, 58.8% and 22.2% (ASAS40) of the ATP (licensed population) for the adalimumab, certolizumab pegol and conventional therapy group, respectively. It was therefore assumed in the model that 44.1% and 41.2% of patients in the adalimumab and certolizumab pegol group would discontinue at week 12, due to lack of response. Response for AS patients and assumptions on non-responder discontinuation at week 12 follow the same method.

From week 12 to the last available trial follow-up date (week 156 in ABILITY-1 and 260 in ATLAS), adalimumab responders were observed to discontinue over time due to adverse events, loss of follow-up or other reasons. For instance in nr-AxSpA, 7.1% (2/28) of adalimumab week-12 responders (ASAS40) in ABILITY-1 were observed to have discontinued the treatment by week 156. In addition, it was found that for adalimumab responders remaining on therapy, 50.0% (14/28) lost the initial week-12 ASAS40 response at certain time point throughout the period of week 12 to 156. For consistency with treatment guidelines, we imposed an additional rate (from ABILITY-1 data for the licensed population by checking ASAS40 response for each observed time point) on top of the observed 7.1% as the new discontinuation rate due to any reason. At any time point after week 12, a patient would be discontinued due to loss of response if the ASAS40 response was observed to be lost even if the patient regained ASAS40 afterwards. Thus, the total proportion of patients discontinuing due to any reason (i.e., observed discontinuations plus discontinuation imposed due to loss of response) from week 12 to week 156 was 57.1% (i.e., 7.1% observed plus 50.0% loss of response). Similarly, discontinuation of AS responders was derived from the ATALS trial following the same assumption.

Since the discontinuation rate varied across the open-label period, it was in effect assumed that the discontinuation rate would also be time-dependent across 40 years. For example in ABILITY-1, a time-dependent discontinuation rate over 40 years was projected from the data for adalimumab responders in the licensed population. The long-term discontinuation rate was extrapolated using parametric survival functions with its flexibility of non-constant or non-monotonic hazard rate over time The choice of parametric distribution was based on the model fit statistics (e.g. AIC, BIC) as well as visual inspection of the hazard plot. As shown in Figure 3.2.5.1, the hazard of discontinuing adalimumab was not constant and non-monotonic, particularly for AS where rebound was observed at week 150. It follows that exponential, Weibull and Gompertz distributions would not be ideal candidates since they assume that the instant hazard is either constant or monotonic. In testing out exponential, Weibull, Gompertz, lognormal and log-logistic distributions, the model fit favoured lognormal as the optimal fit, which also supported the evidence from the hazard plots. The function for this projection was as follows:

Nr-AxSpA (ASAS40): $S(w) = 1-\Phi[(Ln(w)-4.4392^{*})/2.1479^{*}]$
(0.4665) (0.4218)

AS (ASAS20): $S(w) = 1-\Phi[(Ln(w)-5.6037^{*})/1.7965^{*}]$
(0.2060) (0.1875)

Value in parentheses are SE of the coefficients
*P<0.001

,where $\Phi[x]$ is the cumulative density function of standard normal distribution and $S(w)$ is the proportion remaining on therapy at week “w”.

The observed Kaplan-Meier curve juxtaposed with projection for responders over 40 years is shown in Figure 3.2.5.2, in which the left graph is for nr-axSpA with the blue projection curve appearing somewhat lower than the K-M curve particularly in tail. The reason could be due the shape of hazard in nr-axSpA (left of Figure 3.2.5.1), in which the hazard is decreasing at a non-constant rate. Although the log-normal projected curve accounts for the long flat tail, it would be challenging to fully capture the hazard. More importantly, a lower projected discontinuation curve would only underestimate the true benefit of adalimumab in the base case as shown below in the one-way sensitivity analyses that more discontinuation was associated with worse ICER. The reason was that in the base case, conventional therapy responders lost efficacy after week 12 while adalimumab responders maintained and improved the response, thus creating a large relative benefit, outweighing the cost of study drug. Therefore, the less adalimumab responders stay on treatment, the more conservative the results compare to conventional therapy. The long-term extrapolated curves

(lognormal) used as model inputs are shown in Figure 3.2.5.3, where less than 10% and 15% of week-12 responders were projected to stay on treatment at year 40 for nr-axSpA and AS, respectively.

Due to the lack of access to patient level data on RCTs and conflicting data sources of other anti-TNFα comparators, we had to assume that other anti-TNFα followed the same discontinuation rate as in adalimumab.

Figure 3.2.5.1: Plot of Discontinuation Hazard Rate over 40 years for Nr-AxSpA and AS Populations

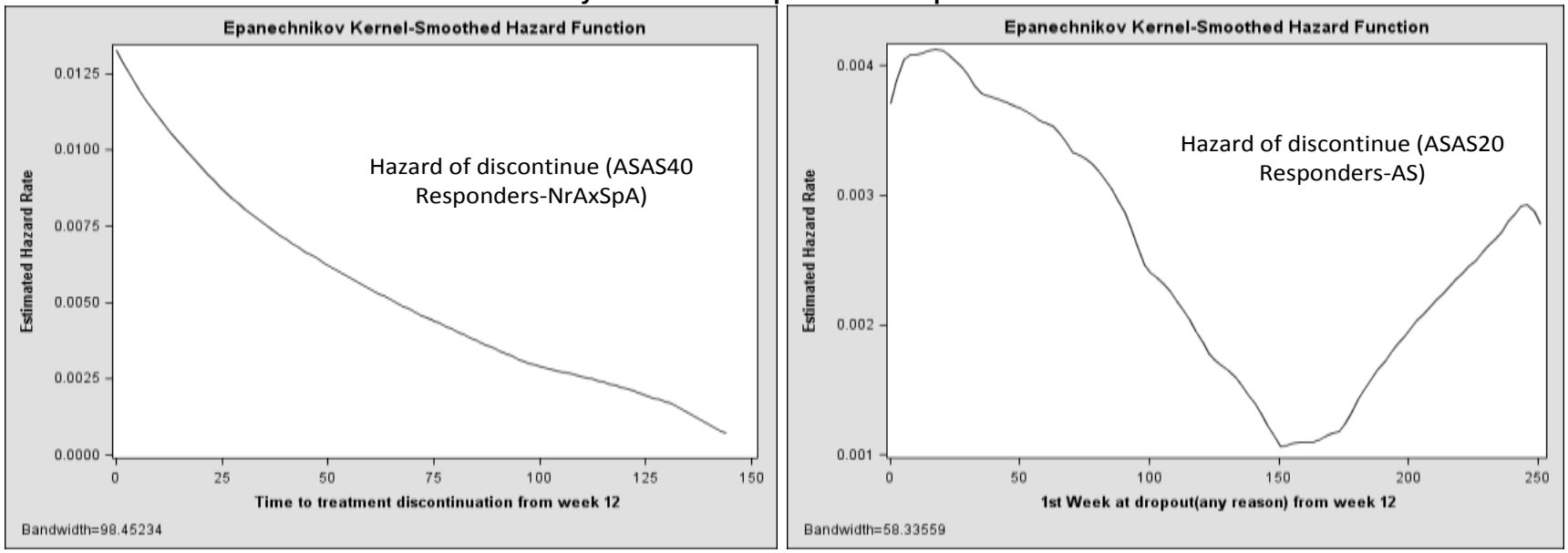
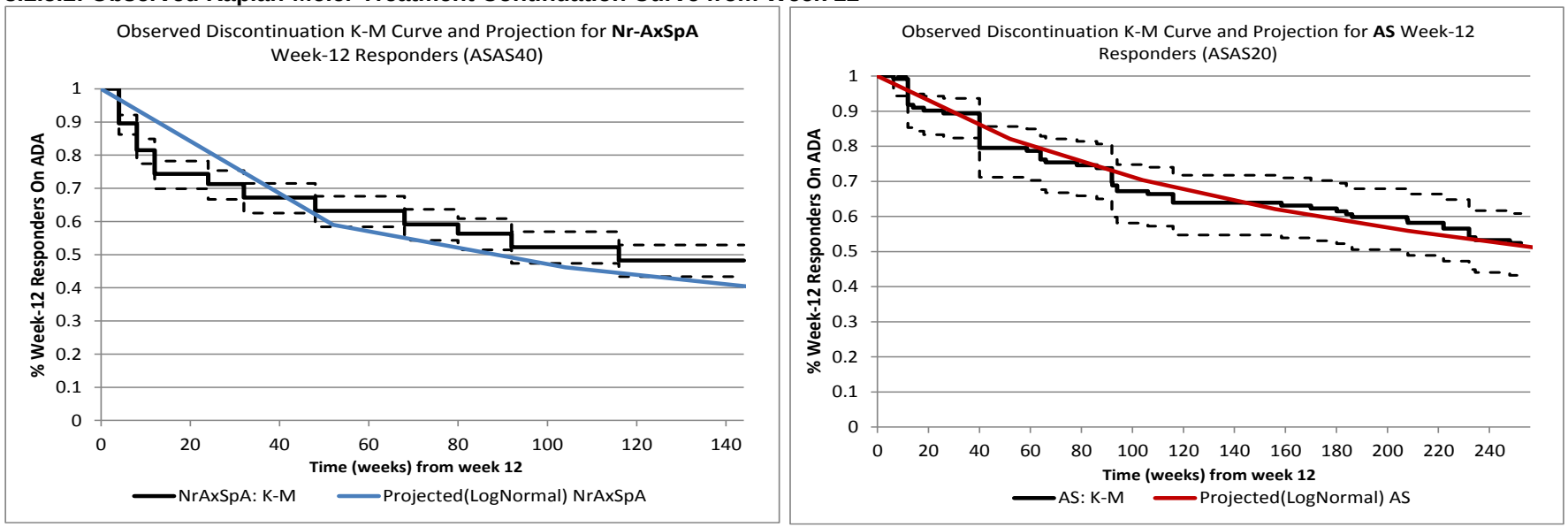
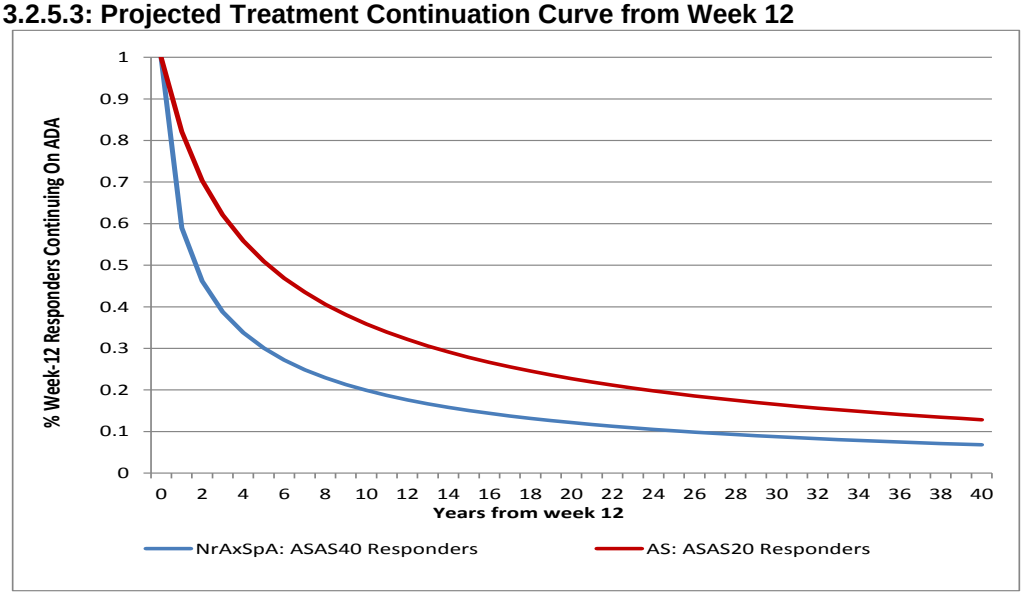


Figure 3.2.5.2: Observed Kaplan-Meier Treatment Continuation Curve from Week 12



Note: K-M curves start from week 12 (e.g., time=0 in graph) treating all **adalimumab responders as 100%** and demonstrated the time to discontinue to the last available observed data point

Figure 3.2.5.3: Projected Treatment Continuation Curve from Week 12



3.2.6 Safety

AS

During the double-blinded period of the ATLAS trial, the safety analysis set for all randomised patients showed comparable results for adalimumab and conventional therapy in terms of the percentage of patients with any AE (%): all AEs (75.0/59.8), serious AEs (2.9/2.8), severe AEs (2.9/3.7) and infectious AEs (31.7/21.5), respectively. One (1) serious infectious AE and 1 AE of drug hypersensitivity reaction were reported for placebo. No serious infections, TB, malignancies, demyelinating disease or death were reported for adalimumab in the double-blinded period.

In the long-term open-label analysis (5 years), there were 1201.1 PY of adalimumab exposure. Number of infectious AE was reported as 1,120 events (93.2 events per 100PY). No TB was reported. One (1) subject died after the follow-up period due to adenocarcinoma at the gastro-oesophageal junction with liver metastases 450 days after the last dose of adalimumab.

Given that during the double-blinded period, the incidence of serious AEs was similar between adalimumab and placebo and that placebo patients had more serious AEs than adalimumab, these costs would not affect the computation of incremental cost and we excluded them from analysis. However, there was a higher incidence in infectious AEs (ratio of 31.7/21.5=1.47) in adalimumab. Therefore, it follows that the conventional therapy patients would have an estimated 63.4 infectious events/100 PY (93.2/1.47) and the excess rate for adalimumab would be 29.8 events per 100 PY (93.2-63.4), which is equivalent to 7.45 events per 100 patient-quarters (29.8/4).

nr-axSpA

During the double-blind portion of ABILITY-1, safety analyses for all randomised patients revealed comparable results for adalimumab and conventional therapy (%): AEs (57.9/58.8), serious AEs (3.2/1.0), and infectious AEs (29.5/28.9); there were no serious infections, TB, malignancies, or demyelinating disease. For the open-label portion as of week 156, there were 412.2 patient-years (PY) of adalimumab exposure. Forty five (45) serious AEs (10.9 events/100 PY) were reported, which included one case of TB. There were two deaths, one due to suicide and second due to opiate toxicity. No malignancies or demyelinating diseases have been reported.

The assumption used in modelling was that the rate of non-serious AE was identical between treatment and placebo groups, so they were excluded from the analysis, given that they would not affect the computation of incremental costs. It was assumed that the excess incidence rate of non-TB serious AEs associated with adalimumab therapy was 7.33 events per 100 PY and the excess incidence of TB AEs associated with adalimumab therapy was 0.16 events per 100 PY (see computations in Table 3.2.6.1). These excess rates were divided by 4 to obtain incidence rates on a quarterly basis (i.e. 1.83 events per 100 patient-quarters for non TB serious AEs and 0.04 events per patient-quarter for TB AEs).

Table 3.2.6.1: Estimated Incidence of Excess Serious (TB and Non TB) AEs with adalimumab per 100 PY (nr-AxSpA in ABILITY-1 Trial)

AE type	Observed adalimumab	Estimated conventional therapy	Estimated excess of adalimumab over conventional therapy
Serious non-TB AEs	10.67 (44 per 412.2 PY)	3.34	7.33
Serious TB AEs	0.24 (1 per 412.2 PY)	0.08	0.16
All serious AEs	10.92 (45 per 412.2 PY)	3.41	7.51

‡Calculated as the incidence of adalimumab divided by 3.2 (ratio of serious AEs in double-blinded period)

It was assumed that all non-TB serious AEs would require a specialist visit (£133.00) plus an inpatient stay at a cost of £4,083[85] (for a total of £4,216). The cost of an active TB case (£6,559.76) was based on Botteman et al (£5,100) adjusted to 2013 from 2004 (using an index derived from the HCHS Pay and Prices Index[84]) Hence, every quarter, a cost of AE of £79.78 was added for each patient on adalimumab (i.e., £4,216 x 1.83/100 + £6,559.76 x 0.04/100).

For AS patients, it was assumed that infectious AEs would only require a visit to general physicians (£45 per visit). Since they were non-serious infections, no inpatient stay was assumed. Hence, the cost of AE per quarter of £3.35 (i.e., £45×7.45/100) was added for patients on adalimumab.

3.2.7 Mortality

UK age and gender specific mortality rates were used to simulate the mortality in the cohort of patients in the model. While there is evidence for reduction of life expectancy for AS patients, with one study reporting a standardised mortality ratio (SMR) of 1.5[82], AbbVie is unaware of evidence that applies specifically to nr-axSpA. For this analysis, it was assumed that the risk of mortality did not differ from that of the general population (SMR of 1) for nr-AxSpA. In a sensitivity analysis it was assumed that the risk of mortality would be increased by 50%, reflecting the mortality risk of AS patients. For AS patients, base case SMR 1.5 was varied at 1.0 and 2.0 in sensitivity analyses.

3.2.8 Cost of study drugs

The cost of anti-TNF agents are listed by first year (with loading doses) in Table 3.2.8.1 and subsequent years in Table 3.2.8.2, both on the following page. Subcutaneous injections are assumed to incur no administration cost.

Table 3.2.8.1: Cost of anti-TNF agents in the first year

Treatment	Cost per pack	Doses per pack	Cost per dose	1st year doses	1st year cost	Administration Cost	Total 1st year Cost
ADA	£704.28	2 x 40mg	£352.14	26	£9,155.64	£0	**£9,155.64**
ETN	£357.50	4 x 25mg	£178.75	52	£9,295.00	£0	**£9,295.00**
IFL every 6 weeks (BASE CASE) †	£419.62	1 x 100mg	£2,098.10±	10	20,981.00	£990.00§	**£21,971.00**
IFL every 8 weeks†	£419.62	1 x 100mg	£2,098.10±	8	£16,784.80	£792.00§	**£17,576.80**
CTZ with PAS ¥	£715.00	2 x 200mg	£357.50	19	£6,792.50	£0	**£6,792.50**
CTZ without PAS (BASE CASE)	£715.00	2 x 200mg	£357.50	29	£10,367.50	£0	**£10,367.50**
GOL	£762.97	1 x 50mg	£762.97	12	£9,155.64	£0	**£9,155.64**

*Assuming no VAT added to drug cost
†First year dosing with infliximab occurs at week 0,2,6,12,18,24,30,36,42 and 48 in the every 6-week base case cycle (10 doses); and weeks 0,2,6,14,22,30,38,46 in the every 8-weeks cycle (8 doses)
± Body weight of 81.09 kg (mean from ATLAS) is assumed; Infliximab SPC - Ankylosing spondylitis: 5 mg/kg given as an intravenous infusion. Therefore a total of 405.45 mg (5×81.09) is needed and due to wastage five packs (500 mg) is assumed for each infusion. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given
§ Assuming infusion cost £99.00 per session (insert ref.)
¥First 12 weeks of certolizumab provided free of charge [ref]. The only doses for which a cost is incurred are the doses given between the end of week 14 and the first dose given at the beginning of year 2. The total number of doses that incur a charge is 19, corresponding to doses administered at weeks 14, 16, then every other week until week 50.

Table 3.2.8.2: Cost of subsequent years anti-TNF agents*

Treatment	Cost per pack	Doses per pack	Cost per dose	Annual doses	Annual cost	Administration Cost	Total 1st year Cost
ADA	£704.28	2 x 40mg	£352.14	26	£9,155.64	£0	**£9,155.64**
ETN	£357.50	4 x 25mg	£178.75	52	£9,295.00	£0	**£9,295.00**
IFL every 6 weeks (BASE CASE)	£419.62	1 x 100mg	£2,098.10±	10†	20,981.00	£990.00§	**£21,971.00**
IFL every 8 weeks	£419.62	1 x 100mg	£2,098.10±	8†	£16,784.80	£792.00§	**£17,576.80**
CTZ with PAS	£715.00	2 x 200mg	£357.50	19	£6,792.50	£0	**£6,792.50**
CTZ without PAS (BASE CASE)	£715.00	2 x 200mg	£357.50	29	£10,367.50	£0	**£10,367.50**
GOL	£762.97	1 x 50mg	£762.97	12	£9,155.64	£0	**£9,155.64**

*Assuming no VAT.
± Body weight of 81.09 kg (mean from ATLAS) is assumed; Infliximab SPC - Ankylosing spondylitis: 5 mg/kg given as an intravenous infusion. Therefore a total of 405.45 mg (5×81.09) is needed and due to wastage five packs (500 mg) is assumed for each infusion. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given
† The default number of doses per year of infliximab after the first year results from averaging 7 doses per year in every even year (in weeks 2, 10, 18, 26, 34, 42, 50) and 6 doses per year in every odd year (in weeks 6, 14, 22, 30, 38, 46)
§ Assuming infusion cost £99.00 per session (insert ref.)

3.2.9 Monitoring and administration

It was assumed that, at treatment initiation, patients initiating adalimumab require 2 full blood count (FBC) tests, 2 erythrocyte sedimentation rate (ESR) tests, 2 liver function test (LFT) tests, 2 urea and electrolytes (U&E) tests, 1 chest X-ray, 1 tuberculosis (TB) heaf test, 1 anti-nuclear antibody (ANA)

test and 1 double-stranded (ds) DNA test. All of the resource use assumptions are comparable to those used in other economic analyses of the use of anti-TNF therapy, and were validated by an expert consultant rheumatologist working in the NHS. Hence, the monitoring cost was generalized to other active anti-TNFα comparators. These costs (Table 3.2.9.1) were taken from the York Model [83] and inflated to 2013 prices using the Hospital and Community Health Services (HCHS) Pay and Price Index.[84, 8] In addition, it was assumed that all patients will require two initial specialist visits (£133) (one when therapy starts and the other when therapy is evaluated). It was further assumed that one MRI would be performed at baseline, at a cost of £144[85, 9]. The total cost at therapy initiation was £470.95.

Additional monitoring visits were included to account for the follow up of assessment of response to anti-TNF therapy after initiation of treatment and at regular intervals, in the form of 4 quarterly monitoring specialist visits per year. The model considered only the incremental visits that nr-axSpA adalimumab patients would require with respect to nr-axSpA patients that would not be on anti-TNFα, assumed to be 2[80, 32]. The incremental cost of consulting a specialist for adalimumab patients is therefore, based on a unit cost of £133[10], £66.5 per quarter. It was assumed, as validated by an expert clinician working in the NHS, that the routine lab tests would be performed 2 times a year. It was also assumed that 1 MRI test would also be performed annually. Total quarterly costs sum to £110.98.

Table 3.2.9.1: Cost of anti-TNF initiation and monitoring

Item	Initiation	Quarterly Monitoring
Full blood count (FBC)	£5.90	£1.47
Erythrocyte sedimentation rate (ESR)	£5.83	£5.83
Liver function test (LFT)	£1.49	£0.37
Urea and Electrolytes (U&E)	£2.73	£0.68
Chest X-ray	£25.87	£0.00
Tuberculosis (TB) Heaf test	£8.62	£0.00
Antinuclear antibody (ANA)	£4.60	£0.00
Double-stranded (ds) DNA test	£4.60	£0.00
Specialist visit	£266.00	£66.50
MRI cost	£144.45	£36.11
Total	**£470.09**	**£110.98**

3.2.10 Costs associated with nr-axSpA and AS

Data from Ankylosing Spondylitis was used to inform the relationship between costs and disease severity in nr-axSpA and AS, as AbbVie is not aware of information in the literature for nr-axSpA. This approach is considered appropriate as utilities and disease severity are very similar between patients in nr-axSpA (in ABILITY-1) and AS (in the ATLAS study[86,11]). Both nr-axSpA and AS affect young male and female patients in their thirties and forties, often considered the most productive period of life; patients with AS are generally more readily identified due to the presence of radiographic sacroiliitis while nr-axSpA typically goes undiagnosed for many years. Although these are distinct conditions within the group of spondyloarthropathies, patients with nr-axSpA and radiographic axial

[8] P. 251, section 16.2. The Hospital & Community Health Services (HCHS) index (Pay and Price)).
[9] Tab (DIAGIM), the mean weighed average cost for Magnetic Resonance Imaging Scan, one area (currency codes RA01Z, RA02Z, RA03Z) was £144 with the minimum range for 50 per cent of services being £75 and the maximum £256.
[10] Tab CL, Currency code: WF01A, Service Code 410 – Rheumatology; the national average cost for follow up visit for 2012-13 was £133 with the lower quartile cost being £105 and the upper quartile cost being £150.https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
[11] Specifically, in ABILITY-1, the relationship between utilities (EQ-5D) and BASFI and BASDAI were as follows: Utility=0.922-0.03924×BASDAI-0.04117×BASFI whereas in the ATLAS, the relationship is as follows: Utility=0.948857-0.04153×BASDAI-0.03448×BASFI (including with covariate for gender and race)

SpA (AS) share a similarly high burden of disease, as shown by comparable impairments in Health-Related Quality of Life (HRQoL) and symptom severity at baseline.[7,6]

Registry data have demonstrated that patients with established AS and nr-axSpA do not significantly differ in many clinical variables such as the BASDAI, patient global assessment of disease activity, and pain scores (Table 1.1.2, reproduced below as Table 3.2.10.1). While groups did not differ in the aforementioned clinical outcomes, differences have been noted in the extent of inflammation and radiographic damage, with a higher level of both demonstrated in AS patients 6[,7].

Data from registries have also shown that the burden of disease in patients with AS and nr-axSpA are comparable in terms of fatigue and morning stiffness, which in turn is likely to result in a similar reduction in quality of life in both patient groups. 7 Further, patients with nr-axSpA and AS who are considered for anti-TNF therapy, share a similar, severe level of work productivity impairment (as measured using the WPAI)[42,9.]

Table 3.2.10.1: Baseline disease activity data from axSpA studies

Source	Registry data					RCT data		
	GESPIC[a]			Kiltz et al [b]		ATLAS[9]	ABILITY-1[42]	Haibel[10]
Disease state	**All AS**	**AS ≤5 years**	**nr-axSpA ≤5 years**	**AS**	**nr-axSpA**	**AS**	**nr-axSpA**	**nr-axSpA**
Number of patients	236	119	226	56	44	315	185	46
BASDAI, (0-10)	4.0	4.0	3.9	4.2	3.6	6.3	6.5	6.3
PtGA of disease activity VAS (0-10)	5.0	5.0	4.9	4.6	4.0	6.3	6.8	6.6
PGA of disease activity VAS (0-10)	4.5	4.4	3.6	3.5	2.7	5.7	5.7	5.9
Total pain VAS, (0-10)	5.0	4.8	4.8	4.7	4.0	-	6.8	7.2

AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; GESPIC: German Spondyloarthritis Inception Cohort; IBP: inflammatory back pain; nr-axSpA: non-radiographic axial spondyloarthritis; PGA: physician's global assessment of disease; PtGA: patient global assessment; SF-36: Short-Form 36-item questionnaire mental component summary; VAS: visual analogue scale

The costs of AS by disease severity (separately by BASDAI and BASFI levels) were obtained from the OASIS study, a longitudinal observational study of 208 patients with AS, [87] conducted in several secondary care rheumatology facilities with a two-year follow up. Patients underwent a clinical examination and completed several questionnaires at baseline and every six months. Every two months, patients completed the BASDAI and an economic questionnaire on resource use and indirect costs associated with AS. None of the patients included in the database used anti-TNFα therapies.

The aggregated resource utilisation of AS patients every year at various levels of BASDAI and BASFI scores is presented in Tables 3.2.10.2 and 3.2.10.3. It is to be noted that approximately 60% of the patients in this study had BASDAI/BASFI scores <4.0. Only 1 patient had BASDAI score >9, and only 4 patients had BASFI >9.

Table 3.2.10.2: Annual Direct Resource Use by BASDAI Score

BASDAI	N	GP visits	Specialist visits	Physio-therapy visits	Para-medical visits	Type of drugs	Hospital-isation days	Technical examin-ations	Adaptation and aids	Formal care (hrs.)
>0 < 1	30	0.89	1.57	9.93	0.04	0.80	0.14	2.00	0.03	0.00
≥1 < 2	36	0.95	1.62	11.80	0.41	1.42	0.28	3.00	0.06	6.00
≥2 < 3	35	2.16	2.44	22.78	0.31	1.44	1.00	4.00	0.09	12.00
≥3 < 4	28	2.64	2.56	26.47	0.16	1.79	2.00	4.00	0.11	0.00
≥4 < 5	30	1.37	2.62	20.18	0.41	1.37	3.00	5.00	0.18	12.00
≥5 < 6	18	3.49	4.33	28.07	0.80	0.94	2.00	6.00	0.53	58.00
≥6 < 7	17	2.82	2.63	18.73	0.92	1.65	3.00	7.00	0.74	24.00
≥7 < 8	11	4.59	5.31	31.24	0.30	2.00	11.00	8.00	0.23	0.00
≥8 < 9	2	0.82	8.13	14.07	3.33	1.50	27.00	17.00	0.25	0.00
≥9 □ 10	1	3.60	7.80	24.00	3.00	2.00	39.00	29.00	0.50	208.00

Table 3.2.10.3: Annual Direct Resource Use by BASFI Score

BASFI	N	GP visits	Specialist visits	Physio-therapy visits	Para-medical visits	Type of drugs	Hospital-isation days	Technical examin-ations	Adaptation and aids	Formal care (hrs.)
>0 < 1	49	0.85	1.26	11.10	0.17	1.20	0.15	3.05	0.03	0.00
≥1 < 2	27	1.46	1.55	16.60	0.15	1.31	0.86	2.10	0.07	0.00
≥2 < 3	25	1.93	2.81	16.72	0.31	1.32	0.63	3.10	0.10	22.88
≥3 < 4	25	1.44	3.00	18.89	0.16	1.24	1.63	3.92	0.10	16.64
≥4 < 5	25	2.18	2.54	25.50	0.93	1.56	3.53	5.41	0.24	33.28
≥5 < 6	20	5.03	5.30	22.21	0.55	1.55	3.05	7.52	0.33	0.00
≥6 < 7	14	2.24	2.61	25.94	0.09	1.29	0.97	6.01	0.21	0.00
≥7 < 8	12	1.64	3.94	24.29	0.70	1.58	6.62	9.25	0.63	17.33
≥8 < 9	7	1.53	3.06	20.22	0.34	2.14	6.34	5.37	0.14	0.00
≥9 □10	4	5.54	5.05	55.56	3.89	2.00	28.36	14.54	1.88	156.00

Each resource use (except drug cost) was priced using published tariffs (Table 3.2.10.4). Drug costs (other than adalimumab) were absent from this costing due to insufficient information on resource use. This was thought not to impact much on results, due to the type of drugs used being fairly constant across degrees of severity, and non-anti-TNF drugs used in conventional therapy of nr-axSpA patients being fairly inexpensive.

Table 3.2.10.4: Cost of Resource Uses (Direct Medical, Direct Non-Medical, and Indirect)

Resource use	Baseline value	Sources
GP visit	£45	PSSRU 2013 (p. 191, Table 10.8b) — Per clinic consultation lasting 11.7 minutes, Including direct care staff costs, with qualification costs. http://www.pssru.ac.uk/project-pages/unit-costs/2013/
Specialist visits	£133	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and NHS Foundation Trusts Consultant Led Outpatient Attendance Non-Admitted Face to Face, Follow-up. Tab CL, Currency code: WF01A, Service Code 410 – Rheumatology; the national average cost for follow up visit for 2012-13 was £133 with the lower quartile cost being £105 and the upper quartile cost being £150. https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
Physiotherapy visits	£50	National Schedule of Reference Costs Year: 2012-13 - NHS Trusts and NHS Foundation Trusts 2012; Tab CHSAHP, Currency Code A08A1 the mean average cost for an episode of Community Health Services Physiotherapy: Adult, One-to-One Services was £50 with the lower quartile being £39 and the upper quartile being £57. https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
Paramedic visit	£48	PSSRU 2013, (p. 183, Table 10.1) — Assumed to be equivalent to District Nurse Visit: £48 per hour (includes wages/salary, salary oncosts, qualifications, overheads, ongoing training, and capital overheads). N.B. In OASIS paramedical care providers included rheumatology nurse practitioner, ergotherapist, social worker, or psychotherapist. http://www.pssru.ac.uk/project-pages/unit-costs/2013/
Inpatient day	£337	National Schedule of Reference Costs Year : 2012-13 – NHS Trust and NHS Foundation Trusts Non-Elective Inpatient (Long Stay) Excess Bed Days: Tab NEI_L_XS, Currency Code HD23J - Inflammatory Spine, Joint or Connective Tissue Disorders, with CC Score 0-2, Service Code 410 – Rheumatology; the national average cost was £337 with the lower quartile cost being £194 and the upper quartile cost being £421 https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
Technical examinations	£132	£132 with the lower quartile cost being £97 and the upper quartile cost being £164, as weighted average of: National Schedule of Reference Costs Year: 2012-13 - – NHS Trust and NHS Foundation Trusts Diagnostic Imaging: Tab DIAGIM, Service Code 410 – Rheumatology; the mean weighed average cost for Magnetic Resonance Imaging Scan, one area, (currency codes RA01A, RA02A, RA03Z) was £142 with the lower quartile cost being £105 and the upper quartile cost being £176. National Schedule of Reference Costs Year : 2012-13 - – NHS Trust and NHS Foundation Trusts Diagnostic Imaging: Tab DIAGIM, Service Code 410 – Rheumatology; the mean weighed average cost for Computerised Tomography Scan, one area, (currency codes RA08A, RA09A, RA10Z) was £86 with the lower quartile cost being £61 and the upper quartile cost being £107 https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
Adaptations and aids	£178	PSSRU 2013, (p. 108) — 7.2 NHS Wheelchairs - Wheelchair cost per year £89 per self or attendant propelled chair per year; £178 per active user per chair per year; £412 per powered chair per year. http://www.pssru.ac.uk/project-pages/unit-costs/2013/
Formal care	£35	PSSRU 2013, (p. 125) Table 8.1— Homecare for elderly people with very low cost. Taken from PSS EX1 2011/12, 2 the average cost for one hour of local authority home care is £35. http://www.pssru.ac.uk/project-pages/unit-costs/2013/
Private house-hold help	£24	PSSRU 2013, (p. 202, table 11.6) per hour of face-face time — Taken from PSS EX1 2009/10, the average cost for one hour of home care worker £224 http://www.pssru.ac.uk/project-pages/unit-costs/2013/
Informal care	£13	Office for National Statistics. Labour Force Survey. Historical Quarterly Supplement Table EARN08 February 2014: Distribution of gross hourly earnings of employees, United Kingdom not seasonally adjusted (weighted average for 2013) http://www.ons.gov.uk/ons/rel/lms/labour-market-statistics/february-2014/table-earn08.xls
Exercise session	£7	UK BEAM Trial Team. United Kingdom back pain exercise and manipulation (UK BEAM) randomised trial: cost effectiveness of physical treatments for back pain in primary care. BMJ 2004, doi:10.1136/bmj.38282.607859.AE http://www.bmj.com/content/bmj/329/7479/1381.full.pdf The cost of £4.35 was inflated from 2001 prices to £6.85 (2013 prices) using: http://www.ons.gov.uk/ons/rel/cpi/consumer-price-indices/june-2014/consumer-price-inflation-reference-tables.xls (Table 10, row D7NZ, 09.4.1 Recreational and sporting services)
Hour lost	£13	Office for National Statistics. Labour Force Survey. Historical Quarterly Supplement Table EARN08 February 2014: Distribution of gross hourly earnings of employees, United Kingdom not seasonally adjusted (weighted average for 2013) http://www.ons.gov.uk/ons/rel/lms/labour-market-statistics/february-2014/table-earn08.xls

Using the resource use data in Table 3.2.10.2 and Table 3.2.10.3 and the cost information in Table 3.2.10.4 the relationship between AS-related cost in 2013 GBP and BASDAI (and BASFI) scores was derived. To estimate the incremental cost associated with a change in BASDAI or BASFI, trend lines (using transformed - exponential - data) were fitted into the estimated cost by BASDAI (Figure

3.2.10.1) and BASFI scores (Figure 3.2.10.2). In these regressions, the number of observations for each point was used as a weight.

For the purpose of the analysis, it was decided to rely primarily on the costing methodology linking the BASDAI to costs rather than the BASFI, drawing on the best fit (as measured by the R-squared), less uncertainty on the assumptions regarding the long-term change in disease severity score, and the possibility that the BASFI captures both axial SpA-related and non-axial SpA-related functional decline related to non-axial SpA comorbidities (including age-related comorbidities such as cancer, cardiovascular disease). Due to data availability issues, it was not possible to use BASDAI and BASFI scores as joint predictors of costs.

Figure 3.2.10.1: Annual Direct Medical Cost by BASDAI Score – Observed (●) and Predicted Lines

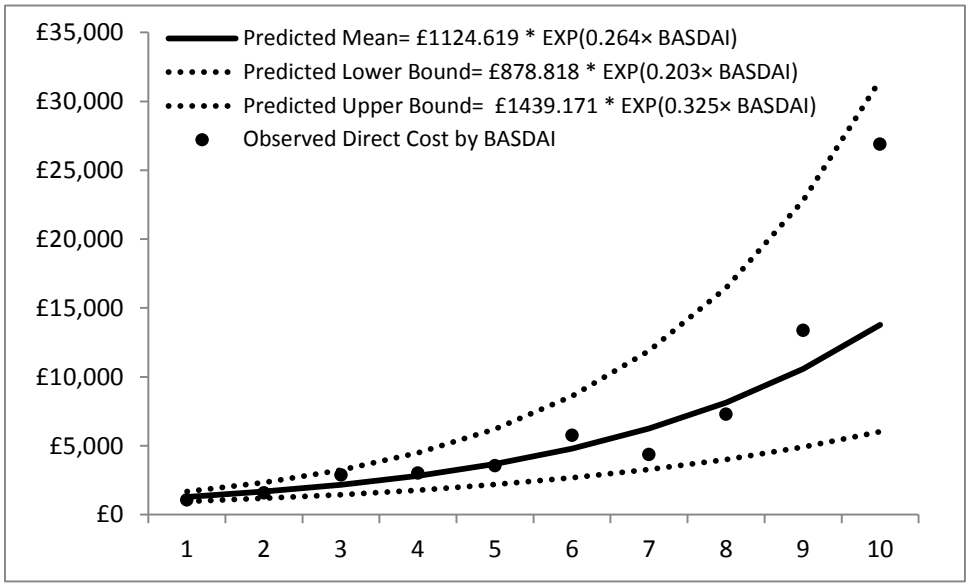
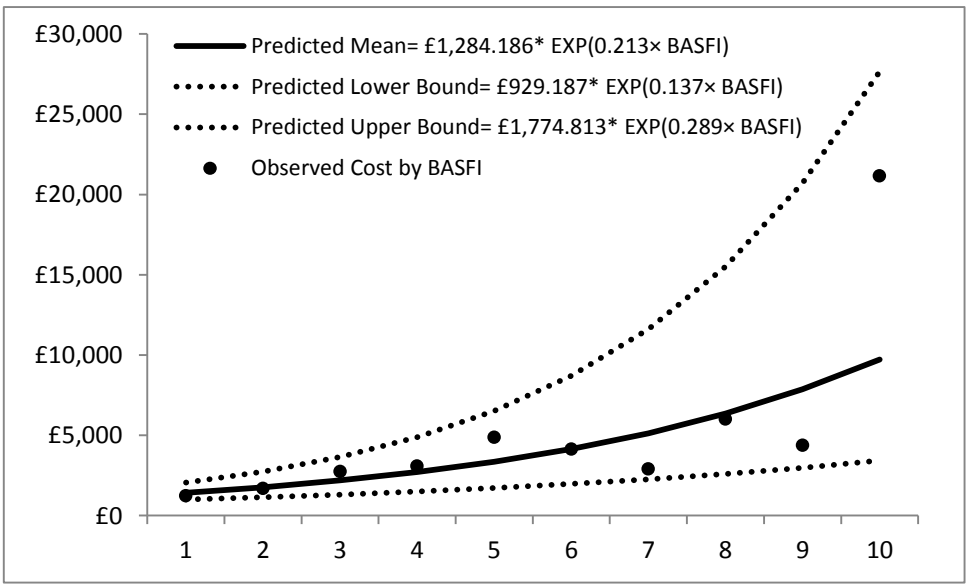


Figure 3.2.10.2: Annual Direct Medical Cost by BASFI Score – Observed (●) and Predicted Lines



3.2.11 Indirect and non-medical costs of axial SpA

Indirect and non-medical costs were included in a sensitivity analysis. The units of indirect and direct non-medical resource use were obtained from the OASIS database. Specifically, absence from paid work due to sick leave (expressed as number of working days absent from paid work) was assessed in the bimonthly economic questionnaires, and changes in working hours, work disability, and income were assessed in the six-monthly economic questionnaires. Time loss because of disease comprised the number of hours patients spent daily resting and exercising at home, time lost because of in- or outpatient health care, time lost because of participation in group physical exercise or swimming groups, and time lost because of AS-related absence at paid work. If a patient mentioned admission to hospital or health care visits and reported at the same time absence from paid work, the time absent from work was subtracted from the total loss of time.

The cost of a group exercise session was estimated at £6.85. The cost of one hour of lost time was valued according to the human capital approach at £13.03.[88] This was also the cost of an hour of informal care. The cost of an hour of private household help and informal care was assumed to be identical to the cost of one hour of formal care.

The cost of an hour of formal care was taken to be £35, corresponding to the labour component cost of the NHS / Personal Social Services worker (as shown in Table 3.2.10.4). Figures 3.2.11.1 and 3.2.11.2 present the relationship between total costs and disease severity, while Figure 3.2.11.3 compares direct costs and total costs (direct plus indirect costs).

Table 3.2.11.1: Annual Indirect and Direct Non-Medical Resource Use by BASDAI Score

BASDAI	N	Private house-hold help (hours)	Informal care (hours)	Exercise (sessions)	Time visits	Time examin-ations	Time physio-therapy	Time exercise group	Time rest	Time hosp. (corrected sick leave)	Time sick leave
>0 < 1	30	£0	£0	£27	£46	£31	£90	£39	£1,237	£20	£313
≥1 < 2	36	£216	£261	£48	£80	£42	£162	£83	£1,611	£61	£610
≥2 < 3	35	£96	£117	£69	£137	£63	£184	£304	£3,144	£261	£866
≥3 < 4	28	£624	£91	£137	£137	£58	£450	£542	£2,543	£81	£442
≥4 < 5	30	£408	£182	£103	£162	£63	£241	£404	£3,013	£717	£694
≥5 < 6	18	£216	£91	£151	£200	£85	£519	£402	£4,725	£261	£1,775
≥6 < 7	17	£1,248	£1,316	£110	£187	£104	£257	£303	£4,575	£643	£910
≥7 < 8	11	£1,032	£612	£62	£131	£103	£283	£45	£9,120	£2,724	£837
≥8 < 9	2	£0	£678	£130	£341	£300	£0	£457	£7,310	£2,114	£0
≥9 < 10	1	£0	£24,392	£0	£422	£375	£0	£0	£17,030	£12,055	£0

Table 3.2.11.2: Annual Indirect and Direct Non-Medical Resource Use by BASFI Score

BASFI	N	Private house-hold help (hours)	Informal care (hours)	Exercise (sessions)	Time visits	Time examin-ations	Time physio-therapy	Time exercise group	Time rest	Time hosp. (corrected sick leave)	Time sick leave
>0 < 1	49	£0	£138	£33	£63	£45	£99	£81	£1,013	£27	£586
≥1 < 2	27	£277	£151	£50	£72	£32	£185	£180	£1,824	£19	£537
≥2 < 3	25	£0	£108	£93	£140	£44	£224	£287	£1,632	£98	£593
≥3 < 4	25	£1,248	£813	£82	£174	£54	£236	£331	£2,797	£271	£490
≥4 < 5	25	£599	£108	£89	£150	£78	£422	£314	£5,014	£879	£1,731
≥5 < 6	20	£312	£339	£144	£228	£99	£430	£525	£5,400	£606	£910
≥6 < 7	14	£446	£145	£212	£108	£80	£399	£548	£3,677	£79	£817
≥7 < 8	12	£0	£565	£100	£136	£133	£351	£179	£7,231	£1,547	£663
≥8 < 9	7	£535	£0	£75	£148	£86	£195	£438	£3,985	£495	£50
≥9 <10	4	£1,872	£6,606	£12	£424	£190	£0	£86	£13,111	£7,327	£0

Figure 3.2.11.1: Annual Total Cost by BASDAI Score – Observed (●) and Predicted Lines

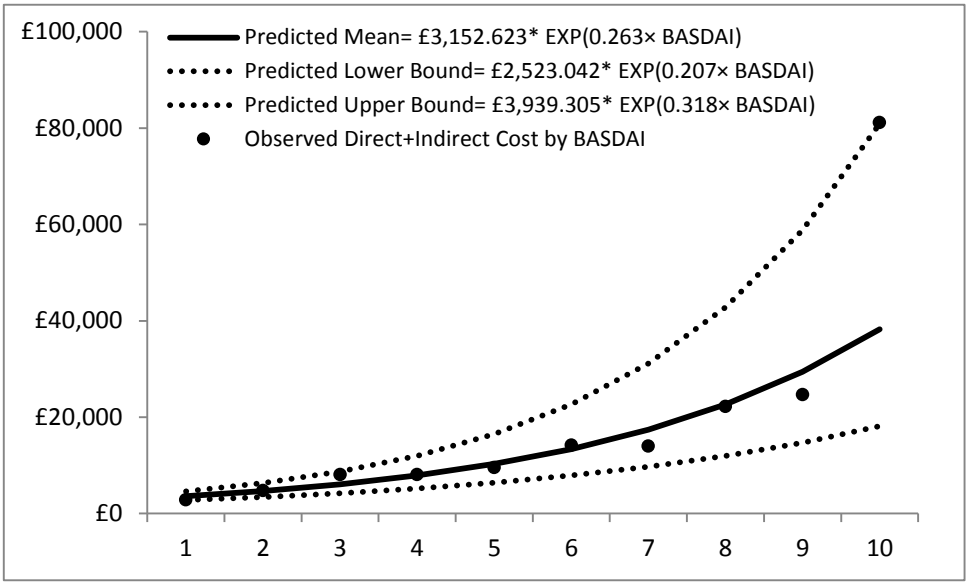


Figure 3.2.11.2: Annual Total Cost by BASFI Score – Observed (●) and Predicted Lines

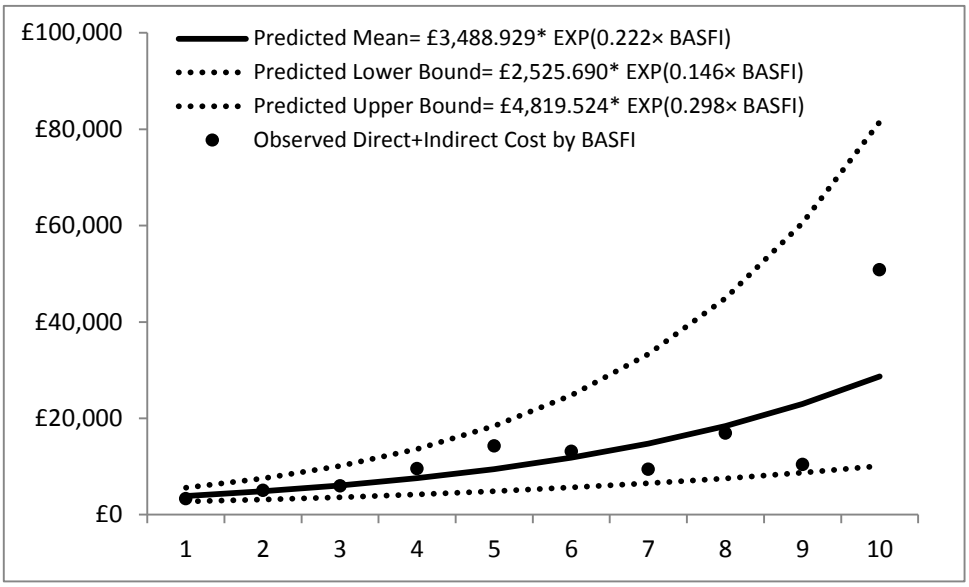
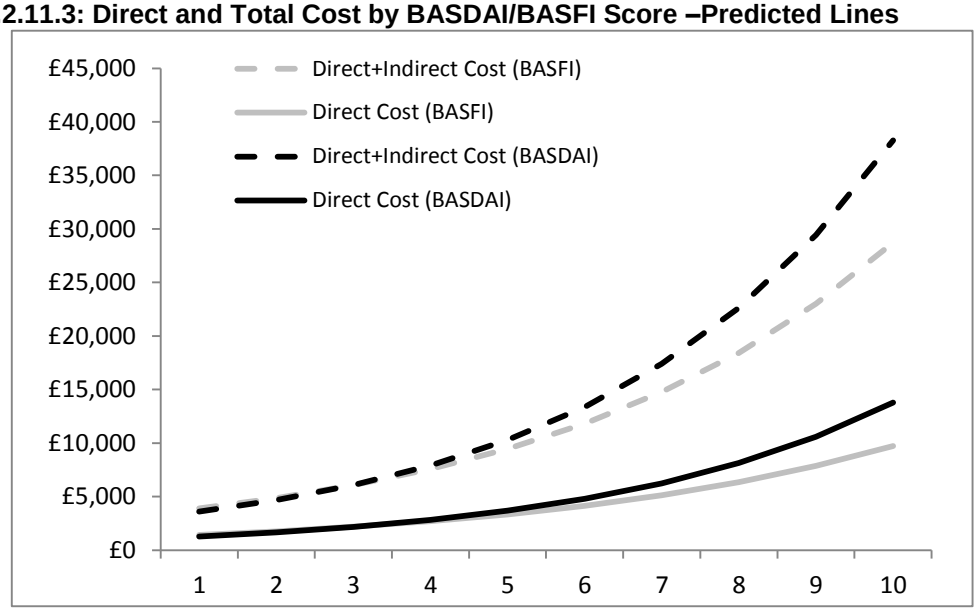


Figure 3.2.11.3: Direct and Total Cost by BASDAI/BASFI Score –Predicted Lines



3.3 Analysis and Interpretation of Results

The extensive results from the model are presented in this section with 3.3.1 providing an overview of the results and 3.3.2 introducing the exploration of uncertainty. Section 3.3.3 discusses the base case analyses conducted in both the nr-axSpA population and the AS population. Section 3.3.4 outlines the probabilistic sensitivity analyses conducted for the two populations as well as presenting results of the univariate analyses and the secondary PSAs, again for each population in turn. Finally section 3.3.5 presents the results of the extensive scenario analyses carried out both in the nr-axSpA and AS populations. In the case of the nr-axSpA population, four scenario analyses were not carried out as these were not relevant to this population.

3.3.1 Overview of results

In the base-case analysis (40 year time horizon) for AS under £30,000 per QALY willingness-to-pay (WTP) threshold, adalimumab yielded the highest net monetary benefit (£168,411) and the lowest ICER (£16,391/QALY) followed by golimumab, etanercept and certolizumab, when compared to conventional therapy. In the PSA simulations (10,000 iterations) among all comparators, adalimumab became more cost-effective after WTP increased to £18,000/QALY and stayed at this position throughout all WTP thresholds compared to other anti-TNFα. Golimumab had better NMB than certolizumab at all WTP thresholds. Certolizumab also had higher NMB than etanercept until a WTP of £33,000/QALY. Infliximab was the least cost-effective therapy across all WTP thresholds.

In Nr-AxSpA, certolizumab had the highest NMB (£162,194) and the lowest ICER (£12,866 /QALY) comparing to conventional therapy, followed by adalimumab (£13,228 /QALY). In PSA simulations, Certolizumab yielded the highest net monetary benefit when WTP was above £13,000/QALY and maintained at 60% probability for higher WTP thresholds. Adalimumab was more cost-effective than PBO for WTP>15,000/QALY and maintained at approximately 40% probability of yielding highest NMB. It should be noted that differences in the estimated effectiveness for anti-TNFs across the AS and nr-axSpA populations were taken from the NMA and are subject to considerable uncertainty given the limitations of the NMA previously highlighted.

3.3.2 Exploration of uncertainty

The uncertainty in model parameters was characterised using probabilistic sensitivity analysis. Monte Carlo sampling was used to propagate the parameter uncertainty in the cost effectiveness model, which entailed making random draws of the uncertain parameters from their probability distribution, running the model for each simulated set of parameters and collecting the outputs from each run.

Uncertainty about incremental mean costs and effectiveness of adalimumab compared to conventional therapy and certolizumab pegol (newly licensed) was also displayed in the incremental cost-effectiveness plane as a scatter plot of the Monte Carlo output samples. Decision uncertainty between different treatment strategies was presented using cost-effectiveness acceptability curves, demonstrating the probability of having the optimal net benefit given a £30,000/QALY willingness-to-pay threshold.

Univariate (one-way) sensitivity analyses were also performed for all pair-wise treatment comparisons to test the robustness of the cost-effectiveness results under the base-case assumption (i.e., conventional therapy responders lose response at week 12, BASDAI to estimate AS-related costs and BASDAI and BASFI to estimate utilities, horizon at 40 years). Due to the fact that response rates obtained from NMA indirect comparisons were correlated among treatments, it would be theoretically infeasible to examine the impact of individual response rate (e.g. independently varying only one at a time). Instead, separate probabilistic sensitivity analyses were conducted only using the 20,000 realisations of WinBUGS output which takes into account the correlation between treatments, while holding parameters other than response rates constant. Table 3.3.2.1 details the parameter ranges used in one-way sensitivity analyses. In addition, several scenarios were considered, including the consideration of societal costs (i.e., time loss valued using the human capital approach and costs borne by the patients and their families were included in analysis).

Table 3.3.2.1: Parameters included in Sensitivity Analyses

Used in Univariate & Multivariate Analyses	Non-radiographic axial SpA (Nr-AxSpA)				Ankylosing Spondylitis (AS)				Distribution
	Base Case	Low Value	High Value	Data Source	Base Case	Low Value	High Value	Data Source	
Probability of week 12 response									
Adalimumab	55.90% (ASAS40)	N/A *	N/A *	NMA Output	63.20%(ASAS20)	N/A *	N/A *	NMA Output	N/A *
Conventional therapy (placebo)	22.20% (ASAS40)				27.20% (ASAS20)				
Certolizumab pegol (200 mg/2 weeks)	58.80% (ASAS40)				46.20%(ASAS20)				
Etanercept (25 mg twice/week)	Not Licensed	N/A	N/A	N/A	60.70% (ASAS20)				
Golimumab					59.30% (ASAS20)				
Infliximab (5mg/kg per 6 weeks)					72.40% (ASAS20)				
Quarterly Prob. of discontinuation week 12+	Time dependent mean	Time dependent, CI LB	Time dependent, CI UB	ABILITY-1	Time dependent mean	Time dependent, CI LB	Time dependent, CI UB	ATLAS	LogNormal survival.
BASFI rate of progression per year if off anti-TNF therapy	0.084	0.047	0.121	ABILITY-1, Multivariate Regression (controlling for age at Axial SpA symptom onset)	0.056	0.029	0.083	ATLAS, Multivariate Regression (controlling for age at AS Diagnosis onset)	Normal
Standardized mortality ratio (SMR)	1.0	0.5	1.5	Assumption	1.5	1.0	2.0	Assumption	Uniform
BASDAI and BASFI									
Uniform Baseline BASDAI	6.432	6.191	6.672	ABILITY-1	6.297	6.109	6.484	ATLAS	Normal
Uniform Baseline BASFI	4.629	4.272	4.986	ABILITY-1	5.372	5.125	5.618	ATLAS	Normal
BASDAI									
Anti-TNFα Responder-Continuers >=12 Weeks	Observed mean till week 140 then LOCF	Observed mean CI LB till week 140 then LOCF	Observed mean CI UB till week 140 then LOCF	ABILITY-1	Observed mean till week 260 then LOCF	Observed mean CI LB till week 260 then LOCF	Observed mean CI UB till week 260 then LOCF	ATLAS	Normal
Placebo Responders At 12 Week	2.150	1.223	3.077	ABILITY-1	2.663	1.918	3.408	ATLAS	Normal

Used in Univariate & Multivariate Analyses	Non-radiographic axial SpA (Nr-AxSpA)				Ankylosing Spondylitis (AS)				Distribution
	Base Case	Low Value	High Value	Data Source	Base Case	Low Value	High Value	Data Source	
BASFI									
Anti-TNFα Responder-Continuers >=12 Weeks	Observed mean till week 140 then LOCF	Observed mean CI LB till week 140 then LOCF	Observed mean CI UB till week 140 then LOCF	ABILITY-1	Observed mean till week 260 then LOCF	Observed mean CI LB till week 260 then LOCF	Observed mean CI UB till week 260 then LOCF	ATLAS	Normal
Placebo Responders At 12 Week	1.484	0.499	2.469	ABILITY-1	2.178	1.355	3.002	ATLAS	Normal
Cost Equation BASDAI	£1124.619 × EXP(0.264× BASDAI)	£878.818 × EXP(0.203× BASDAI)	£1439.171× EXP(0.325× BASDAI)	OASIS	£1124.619 × EXP(0.264× BASDAI)	£878.818 × EXP(0.203× BASDAI)	£1439.171× EXP(0.325× BASDAI)	OASIS	Lognormal
Utility equation	EQ-5D=0.922-0.039×BASDAI-0.041×BASFI	EQ-5D=0.901-0.029×BASDAI-0.029×BASFI	EQ-5D=0.943-0.050×BASDAI-0.053×BASFI	ABILITY-1	HUI3=0.899-0.031×BASDAI-0.041×BASFI	HUI3=0.876-0.023×BASDAI-0.032×BASFI	HUI3=0.922-0.039×BASDAI-0.051×BASFI	ATLAS	Normal
Cost of initiation	£470.09	-25% x base	+25% x base	Assumptions	£470.09	-25% x base	+25% x base	Assumptions	Uniform
Cost of maintenance (per quarter)	£110.98	-25% x base	+25% x base	Assumptions	£110.98	-25% x base	+25% x base	Assumptions	Uniform
Cost of AEs (per quarter)	£13.49	-25% x base	+25% x base	Assumptions	£13.49	-25% x base	+25% x base	Assumptions	Uniform
Average Age	38.31	36.49	40.13	ABILITY-1	42.31	41.03	43.60	ATLAS	Normal
Percent male	46%	39%	53%	ABILITY-1	75%	70%	80%	ATLAS	Beta
Body Weight	Not relevant†	Not relevant†	Not relevant†	Not relevant†	81.09	79.10	83.08	ATLAS	Normal
Tested in Univariate Analyses Only									
Discount Rates (Costs)	3.5%	1.5%	6%	Assumptions	3.5%	1.5%	6%	3.5%	Assumptions
Discount Rates (QALYs)	3.5%	1.5%	6%	Assumptions	3.5%	1.5%	6%	3.5%	Assumptions

*Response rates from NMA output are correlated therefore varying rate of a single treatment is not theoretically correct and feasible. Impact of response rates on results are shown in a secondary PSA where only correlated response rates from WinBugs output is used.
†Body weight only affects the dosage of Infliximab therefore not included for Nr-AxSpA as infliximab is not licensed for this indication
CI=Confidence Interval; LB=Lower Bound; UB=Upper Bound; LOCF=Last Observation Carried Forward

3.3.3 Primary (base case) analysis

These were computed separately for patients receiving conventional therapy (PBO) and each anti-TNF therapy. The net (i.e. incremental differences) in costs and QALYs were also computed. The incremental cost-effectiveness ratio (cost per QALY gained) in the base-case analysis was computed over 40 years and results were based on cost relationships with BASDAI scores, and utility relationships with both BASDAI and BASFI scores.

Nr-axSpA

In the Nr-AxSpA comparisons over a 40 year time horizon, the net discounted gain in quality-adjusted life expectancy was 10.10, 10.16, and 8.88 QALYs for adalimumab, certolizumab and conventional therapy, respectively. Adalimumab and certolizumab incurred a net cost of £16,143 and £16,532 against conventional therapy patients, which gives an ICER for certolizumab vs. conventional therapy of £12,866/QALY, followed by £13,228/QALY for adalimumab vs. conventional therapy. When compared directly, adalimumab incurred slightly less cost and provided slightly less benefit than certolizumab. Costs of resource utilization related to axial-SpA were estimated to be approximately £113,000 for adalimumab and certolizumab, which constitute approximately 80% of the total cost. Study drug costs were similar between the two agents. Patients from all arms lived 36.75 years as the SMR of 1.0 was assumed for all treatments. It was estimated that half of week-12 ASAS40 responders would discontinue treatment at 1.63 years from week 12, which appears reasonable given the strict definition (discontinued even if losing ASAS40 only once) (Table 3.3.3.1).

Table 3.3.3.1: Base Case Results (Nr-AxSpA)

Base Case Results (per patient)	ADA	PBO	CTZ(200)	ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ
QALYs (Discounted)	10.10	8.88	10.16	1.22	1.28	(0.06)
Total Cost (Discounted)	£142,218	£126,075	£142,608	£16,143	£16,532	-£390
Axial-SpA Related Cost	£113,380	£126,075	£112,702	-£12,695	-£13,373	£678
Study Drug Cost	£26,832	£0	£27,795	£26,832	£27,795	-£964
Initiation Costs	£470	£0	£470	£470	£470	£0
Monitoring Costs	£1,167	£0	£1,228	£1,167	£1,228	-£61
AE Costs	£839	£0	£883	£839	£883	-£44
Life Years	36.75	36.75	36.75	0.00	0.00	0.00
Week-12 Responders Median Years to Anti-TNF Discontinue	1.63	NA	1.63	NA	NA	0.00
ICER (£/QALY)	-	-	-	£13,228/ QALY	£12,866/ QALY	£6,032↓/ QALY↓
Net Monetary Benefit (NMB) with WTP=£30,000/QALY	£160,646	£140,177	£162,194			

AS

For the indication of AS in the base case, results were presented in Table 3.3.3.2. Infliximab achieved the highest benefit (10.52 QALYs) followed by adalimumab (10.28 QALYs), etanercept (10.21 QALYs), golimumab (10.17 QALYs) and certolizumab pegol (9.82 QALYs). Significantly higher total cost was also incurred by infliximab (£197,100) (in most part driven by the high infusion cost), followed by relatively similar estimates of the rest of agents. At WTP threshold of £30,000 per QALY, adalimumab yielded the highest NMB (£168,411) and the lowest ICER (£16,391/QALY) compared to conventional therapy. Most other anti-TNF agents were also found to be cost-effective with the ICER well below the general threshold of £30,000 (ranged from £16,535/QALY to £17,067/QALY), except infliximab which had £44,448/QALY due to its high cost in infusion and administration, which meant that infliximab was extendedly dominated.

The major cost driver was the axial-SpA related cost, which was estimated to be approximately 45% to 70% of total cost. Average life-time cost of study drugs were generally below £50,000, except that infliximab (dosed at every 6 weeks) cost more than £100,000. Median years to discontinue for week-12 responders were estimated to be 5.22 years. The average life years per patient was estimated to be 32.70.

Table 3.3.3.2: Base Case Results (AS)

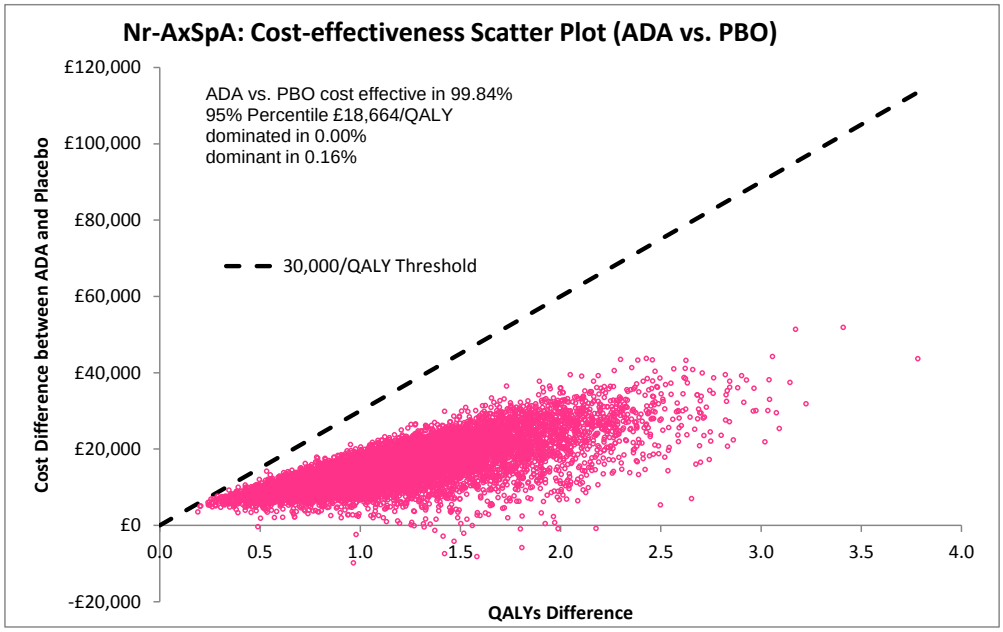
Base Case Results (per patient)	ADA	PBO	CTZ(200)	GOL	IFL6	ETN25	ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ	ADA vs. GOL	ADA vs. IFL	ADA vs. ETN	GOL vs. PBO	IFL vs. PBO	ETN vs. PBO
QALYs (Discounted)	10.28	8.62	9.82	10.17	10.52	10.21	1.65	1.20	0.45	0.10	(0.24)	0.07	1.55	1.90	1.59
Total Cost (Discounted)	£139,860	£112,762	£133,273	£138,385	£197,100	£139,574	£27,098	£20,511	£6,587	£1,475	-£57,241	£286	£25,624	£84,339	£26,812
Axial-SpA Related Cost	£92,436	£112,762	£98,026	£93,718	£89,415	£93,258	-£20,325	-£14,736	-£5,590	-£1,282	£3,021	-£821	-£19,044	-£23,347	-£19,504
Study Drug Cost	£45,299	£0	£33,694	£42,674	£105,251	£44,275	£45,299	£33,694	£11,605	£2,625	-£59,953	£1,024	£42,674	£105,251	£44,275
Initiation Costs	£470	£0	£470	£470	£470	£470	£470	£470	£0	£0	£0	£0	£470	£470	£470
Monitoring Costs	£2,062	£0	£1,508	£1,935	£2,363	£1,981	£2,062	£1,508	£555	£127	-£300	£82	£1,935	£2,363	£1,981
AE Costs	£62	£0	£46	£58	£71	£60	£62	£46	£17	£4	-£9	£2	£58	£71	£60
Life Years	32.70	32.70	32.70	32.70	32.70	32.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Week-12 Responders Median Years to Anti-TNF Discontinue	5.22	NA	5.22	5.22	5.22	5.22	NA	NA	0.00	0.00	0.00	0.00	NA	NA	NA
ICER (£/QALY)	-	-	-	-	-	-	£16,391/ QALY	£17,067/ QALY	£14,593/ QALY	£14,241/ QALY	£234,328↓ /QALY↓	£4,311/ QALY	£16,535/ QALY	£44,448/ QALY	£16,897/ QALY
Net Monetary Benefit (NMB) with WTP=£30,000 /QALY	£168,411	£145,913	£161,456	£166,779	£118,498	£166,705									

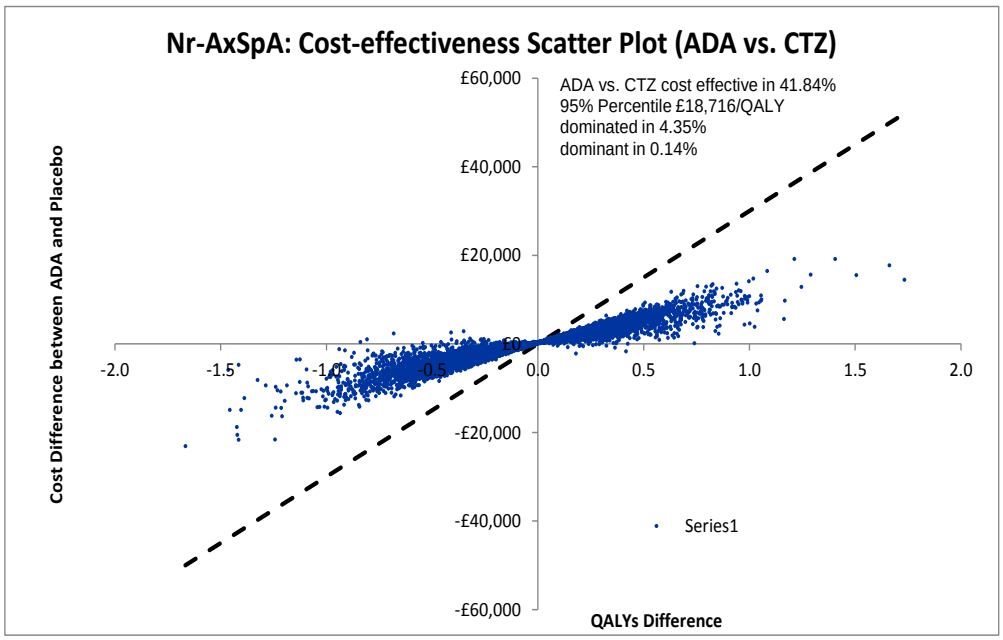
3.3.4 Probabilistic Sensitivity Analyses

Nr-axSpA

Figure 3.3.4.1 presents the scatter plot of PSA under the base case scenario (ASAS40) of nr-AxSpA comparing the differences in costs and QALYs between the ADA and conventional therapy (PBO) and between ADA and CTZ. Under the 30,000/QALY WTP threshold, the ADA was found to be cost-effective compared to conventional therapy in 99.84% of simulations, with the 95% percentile of ICER being £18,664/QALY. When compared to CTZ directly, probability was 41.94% that ADA achieved better QALYs with higher cost and below the £30,000/QALY threshold. CTZ had higher probability of dominating ADA (4.35%) compared to being dominated (0.14%). The remaining chance (e.g.53.67%= 1-41.84%-4.35%-0.14%) showed cost-saving from ADA at lower QALYs compared to CTZ.

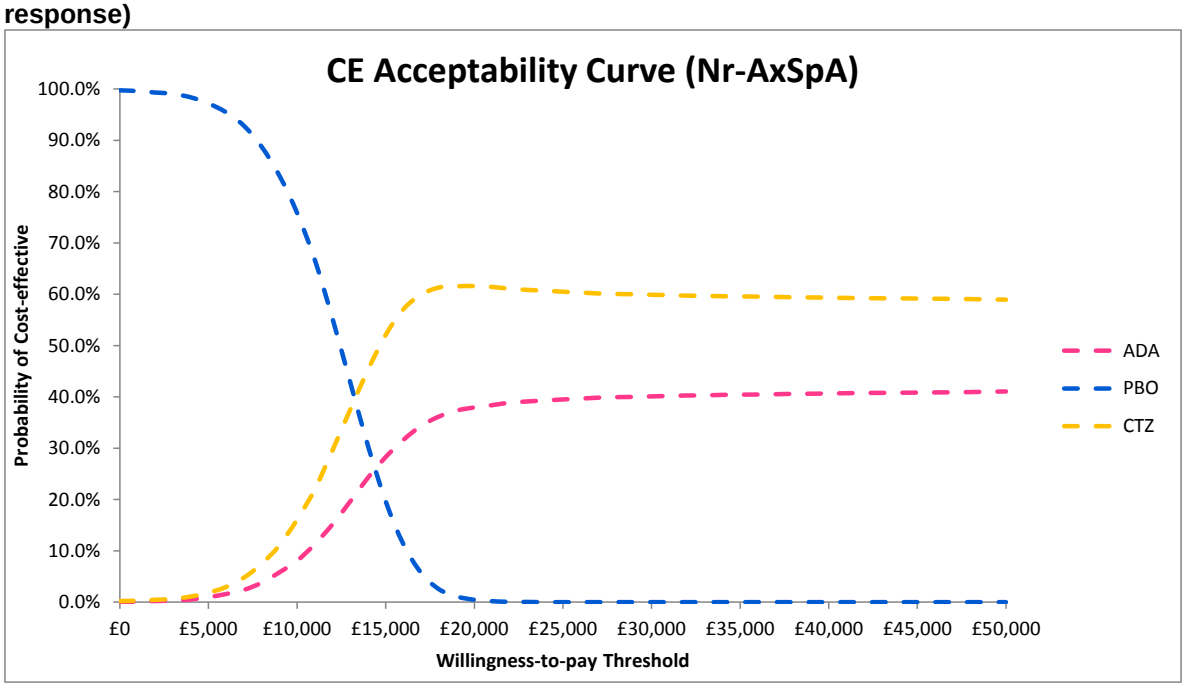
Figure 3.3.4.1: Scatter Plot of Incremental Costs and QALYs of Nr-AxSpA patients (ADA vs. PBO and CTZ)





The cost-effectiveness acceptability curve (CEAC) of nr-AxSpA shown in Figure 3.3.4.2 below indicated that both ADA and CTZ had better cost-effectiveness than PBO for WTP>£15,000/QALY. CTZ had consistently higher probability of yielding the higher net monetary benefit than ADA but differences in the estimated QALY gain were small.

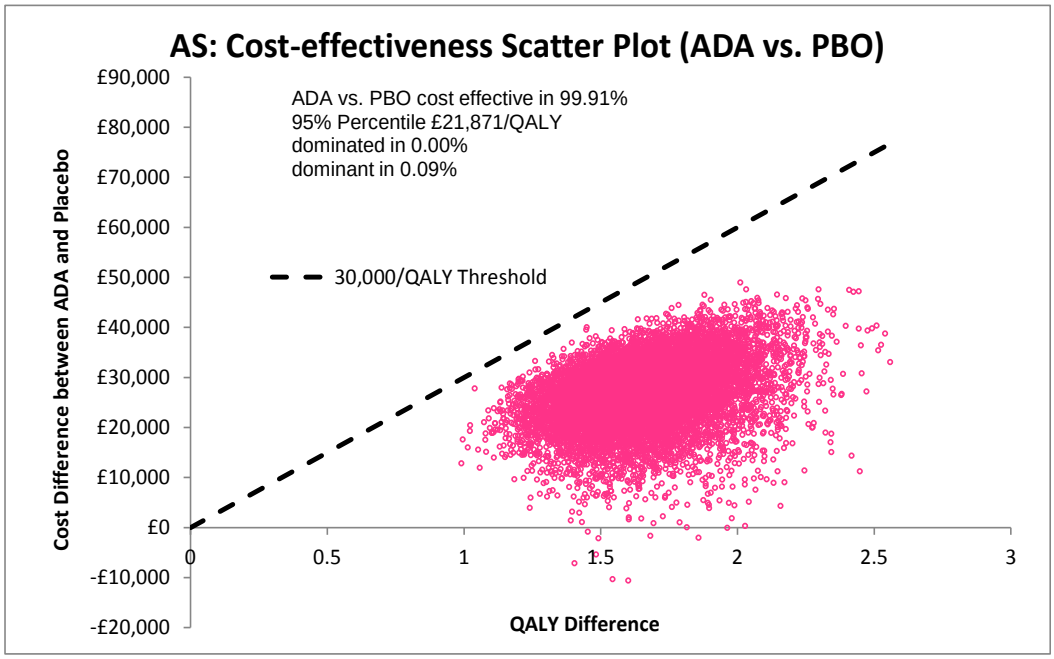
Figure 3.3.4.2: Cost Effectiveness Acceptability Curve- Nr-AxSpA (under base case ASAS40 response)

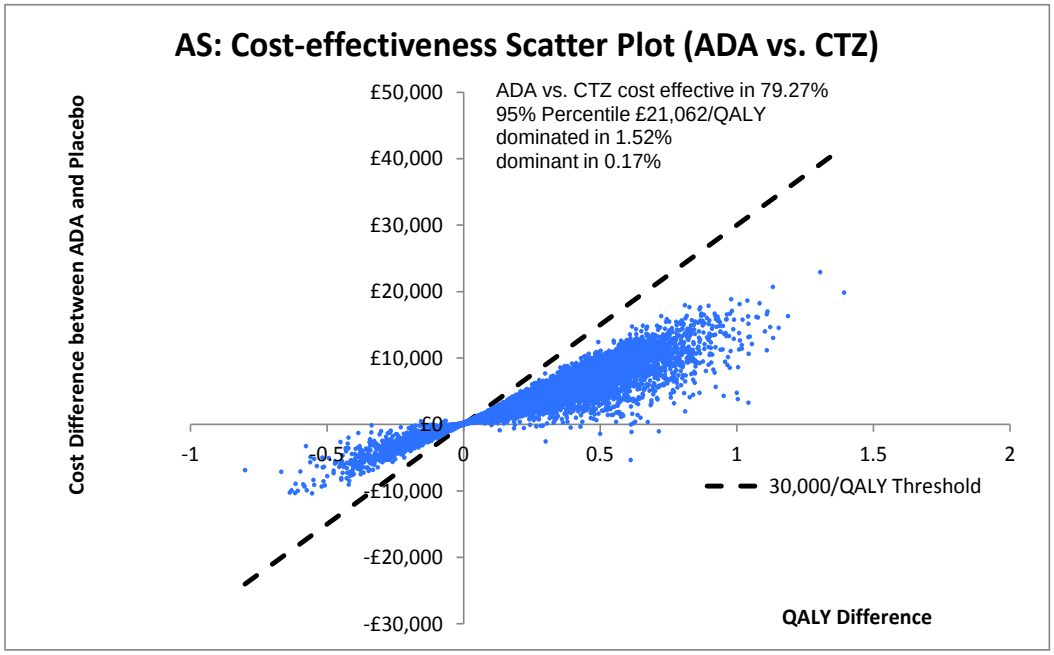


AS

Figure 3.3.4.3 below presents the scatter plot of PSA under the base case scenario (ASAS20) of AS patients comparing the differences in costs and QALYs between the ADA and conventional therapy (PBO) and between ADA and CTZ. Under the £30,000/QALY WTP threshold, the ADA was found to be cost-effective compared to conventional therapy in 99.91% of simulations, with the 95% percentile of ICER being £21,871/QALY. When compared to CTZ directly, probability was 79.27% that ADA achieved better QALYs with higher cost and below the £30,000 threshold.

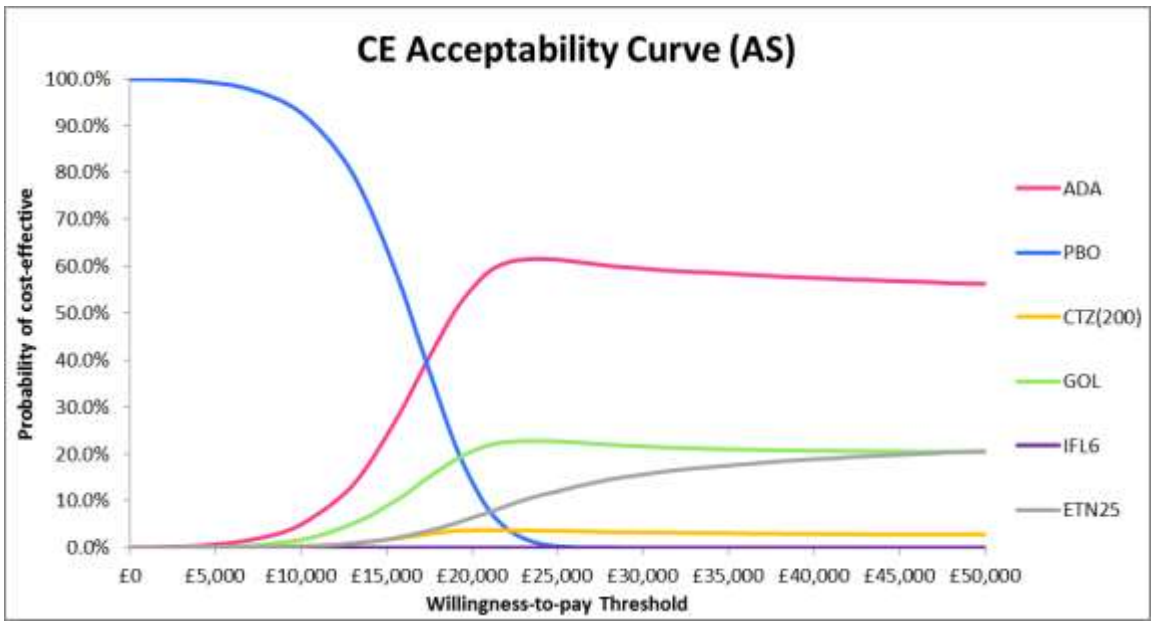
Figure 3.3.4.3: Scatter Plot of Incremental Costs and QALYs of AS patients (ADA vs. PBO and CTZ under base case ASAS20)





The CEAC demonstrated in Figure 3.3.4.4 showed that ADA had achieved better NMB than other anti-TNF agents across all WTP thresholds. Starting from WTP £18,000/QALY, adalimumab had a higher probability of being cost-effective than conventional therapy. Infliximab was the least favourable option in terms of net benefit.

Figure 3.3.4.4: Cost Effectiveness Acceptability Curve- AS (under base case ASAS20)

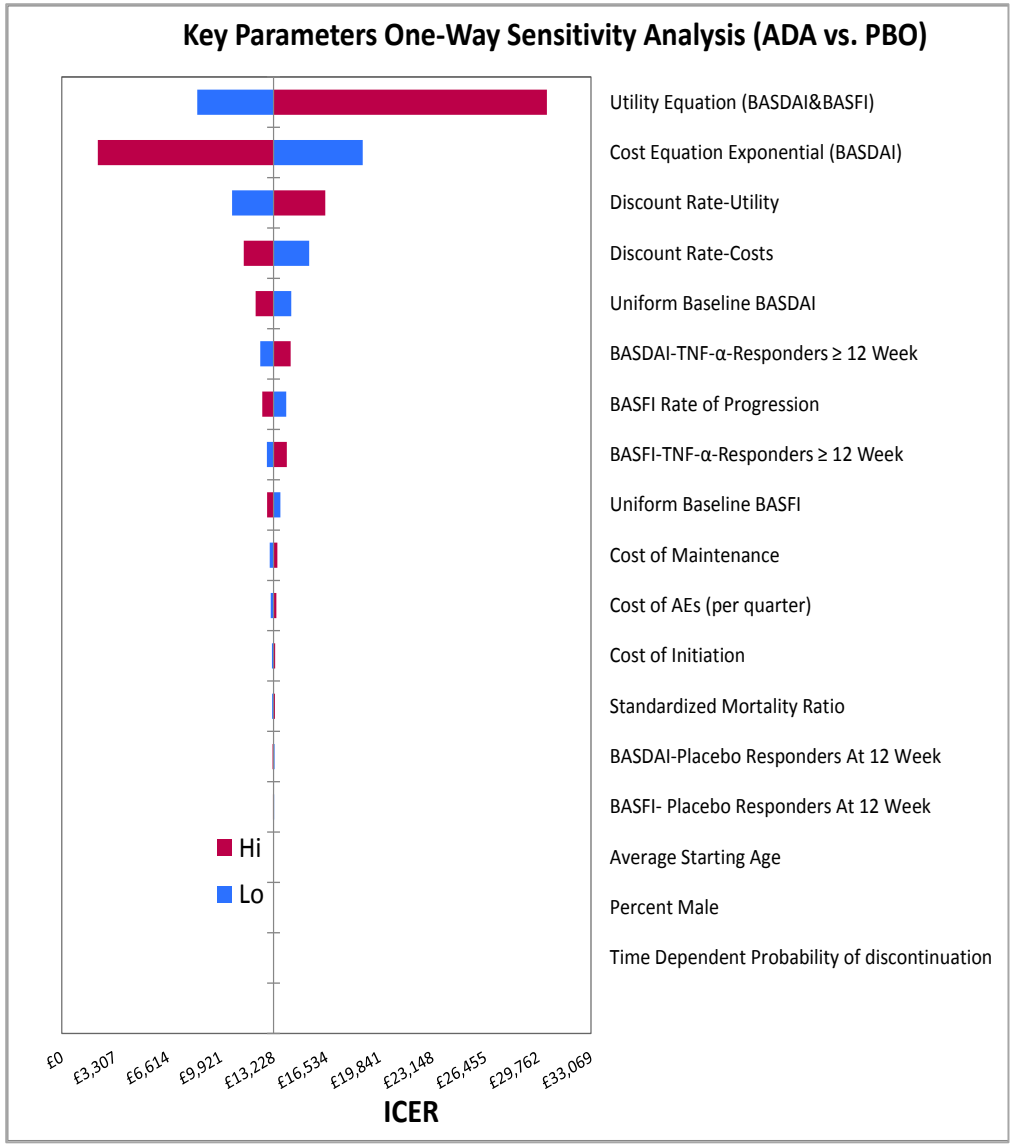


Univariate sensitivity analyses

Figure 3.3.4.5 below illustrates in the form of tornado diagrams the impact on the ICERs of changing individual model parameters within the ranges specified in Table 3.3.2.1 for nr-AxSpA. The influential factors were consistent across ICER of ADA vs PBO, CTZ vs PBO and ADA vs. CTZ: uncertainty in relationship between BASDAI/BASFI to HCRU cost and utility estimation had the most impact, followed by discount rates, baseline BASDAI, long term BASDAI/BASFI for responders and BASFI increment for patients off anti-TNF.

Tornado diagrams for AS patients were illustrated in Figure 3.3.4.6, where ADA compared to PBO and other active anti-TNFα were subject to similar factors as in nr-AxSpA. The only exception was for IFL (not shown in diagram), body weight impacted the dosage of IFL, and thus lower weight would give relatively less advantage for ADA.

Figure 3.3.4.5: Univariate Sensitivity Analysis for Key Model Parameters (Nr-AxSpA)



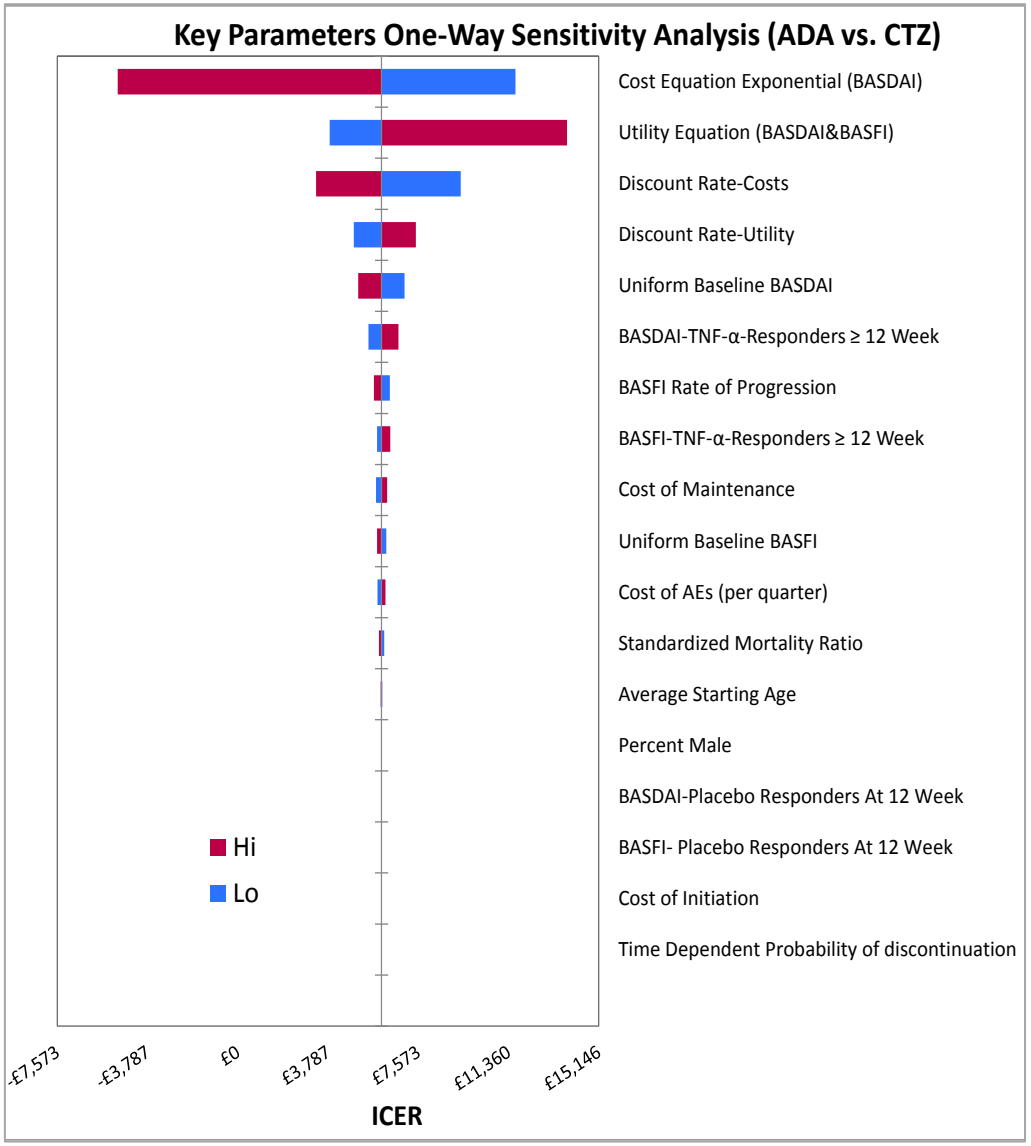
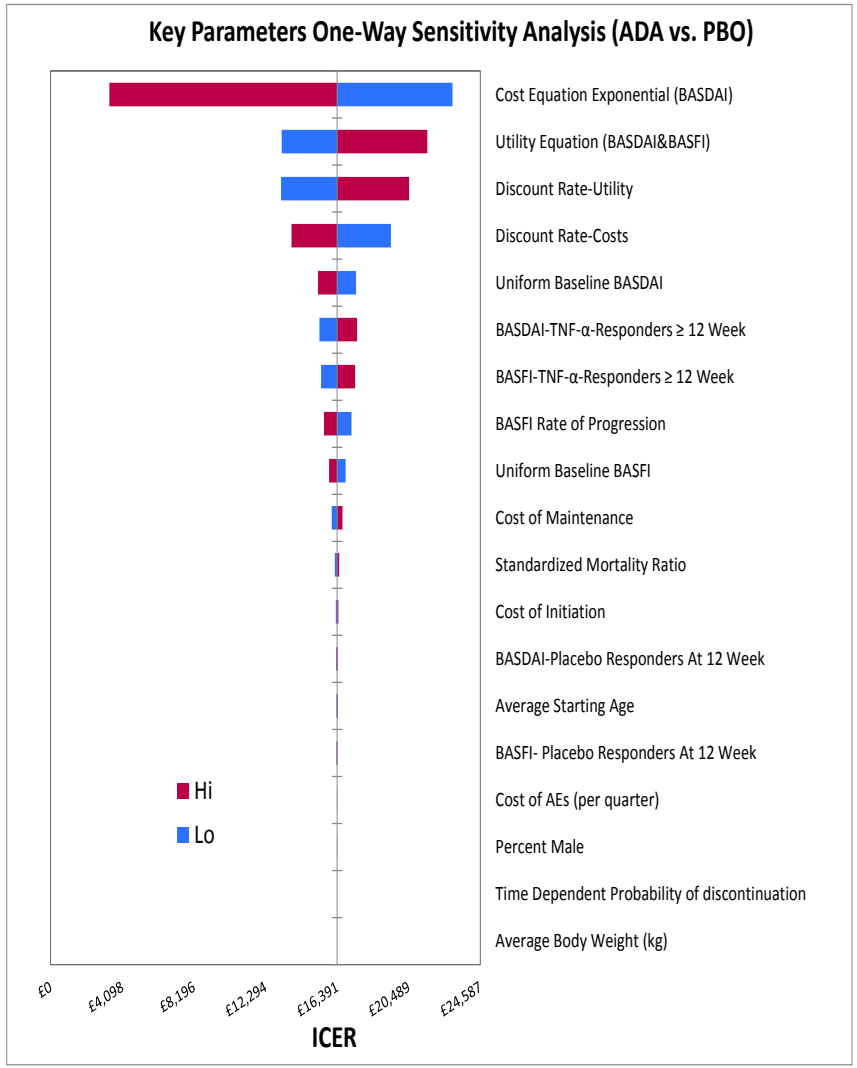


Figure 3.3.4.6: Univariate Sensitivity Analysis for Key Model Parameters (AS)



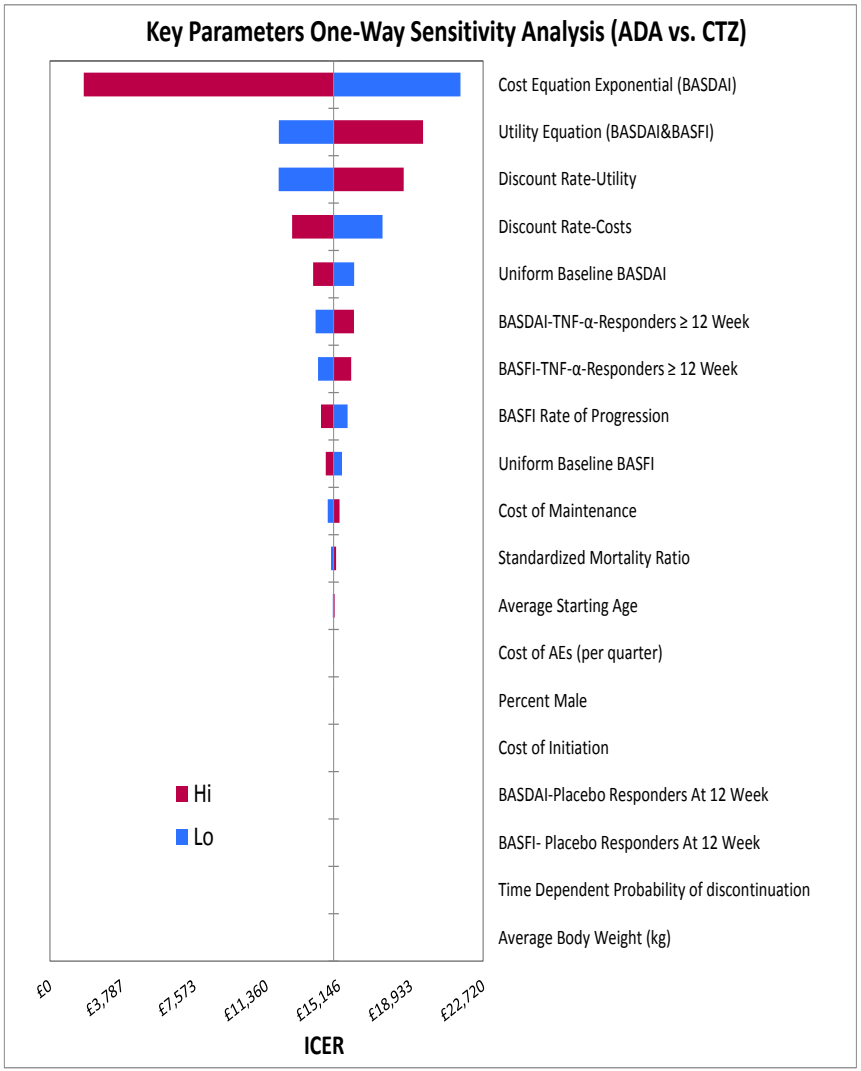
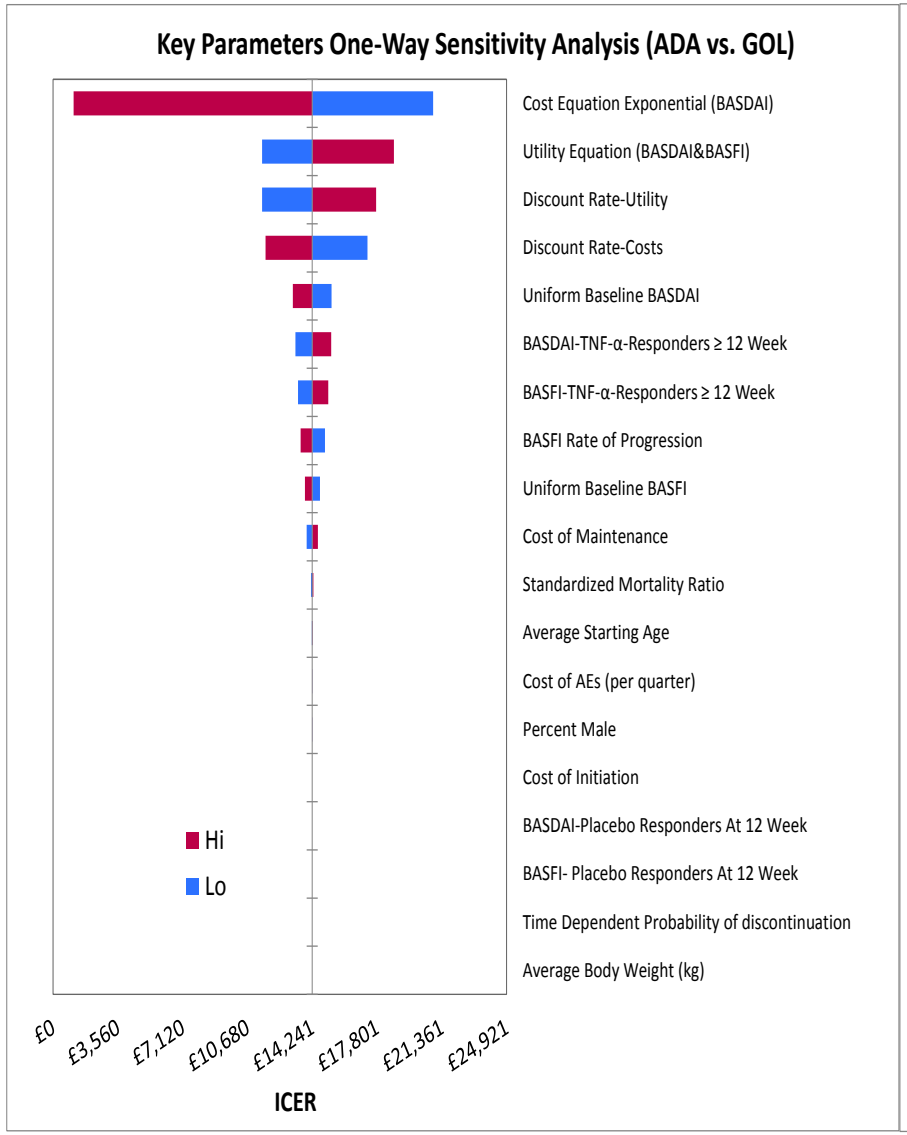


Figure 3.3.4.6: Univariate Sensitivity Analysis for Key Model Parameters (AS) (continued)



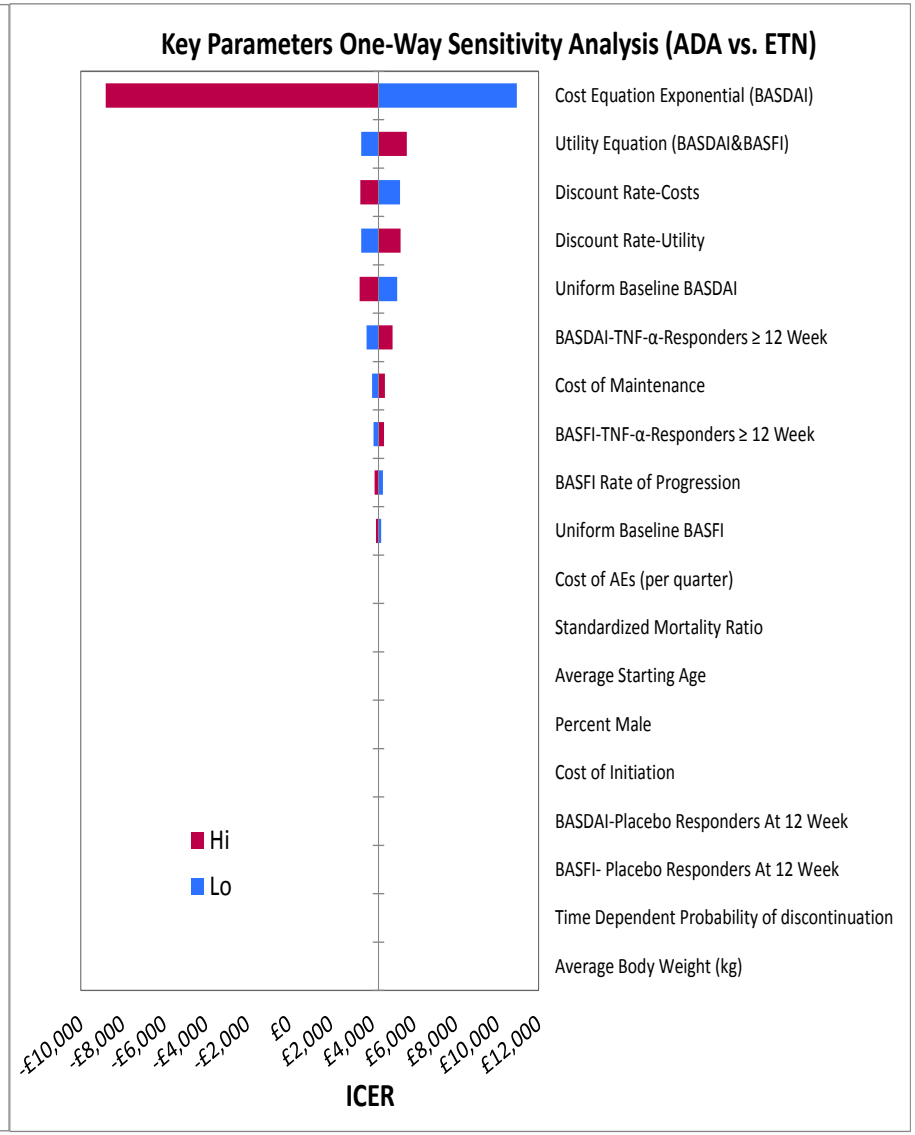
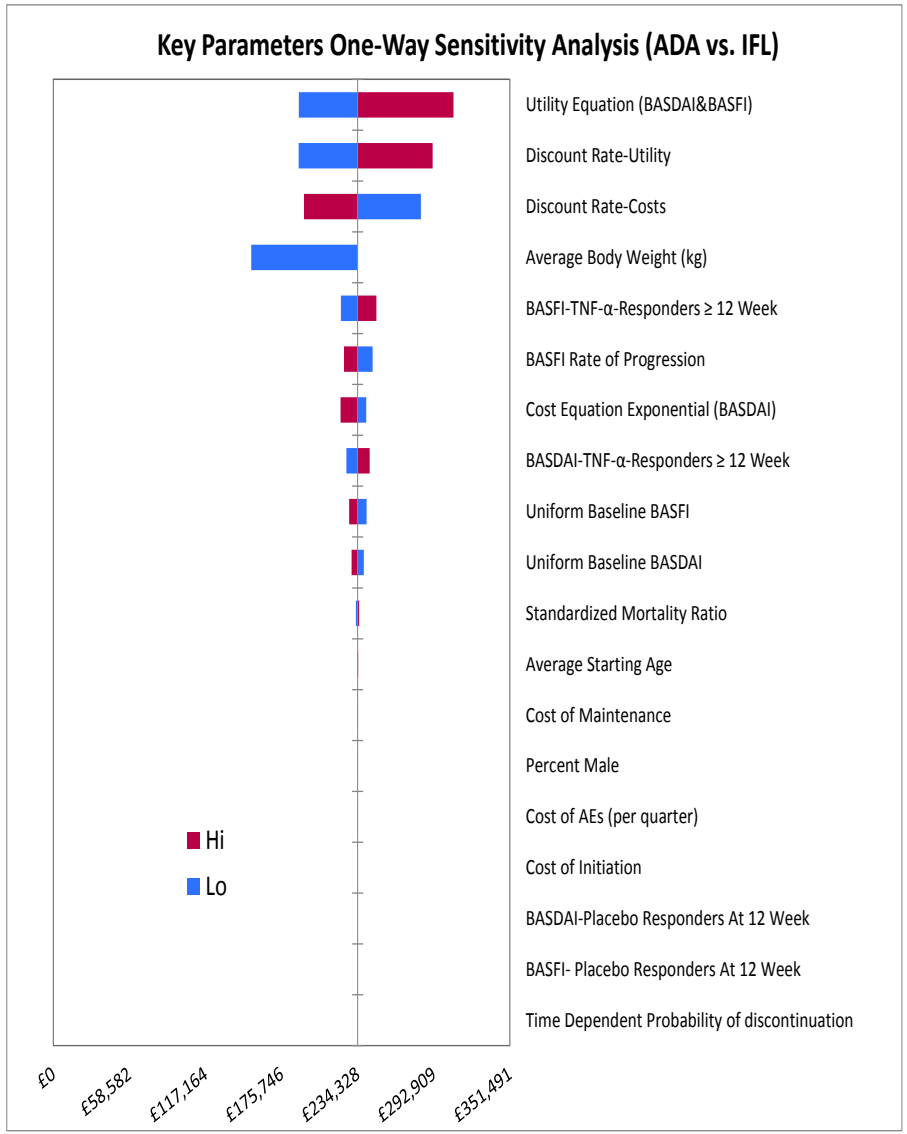


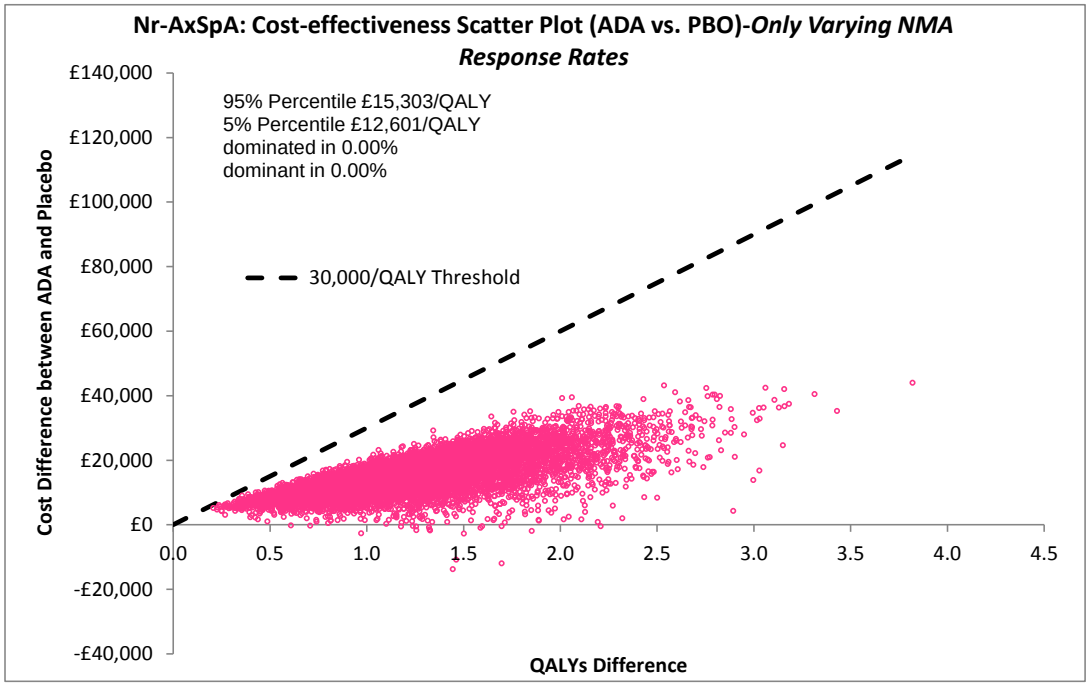
Figure 3.3.4.6: Univariate Sensitivity Analysis for Key Model Parameters (AS) (continued)

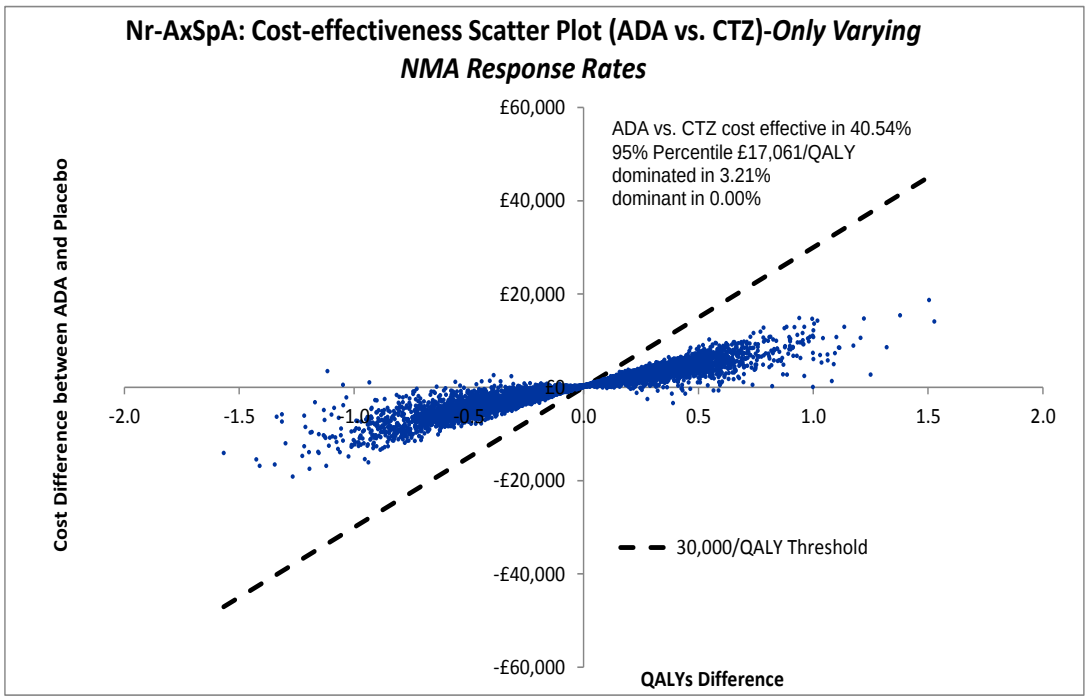


Secondary PSA analysis

The secondary PSA was also conducted to examine the impact of response rate on ICER by varying only the response rates from NMA while holding all other variables constant. Figure 3.3.4.7 showed that in nr-AxSpA, the scatterplots were similar in pattern compared to the main PSA (Figure 3.3.4.1), which indicated that out of all parameters; response rates were the main source of uncertainty.

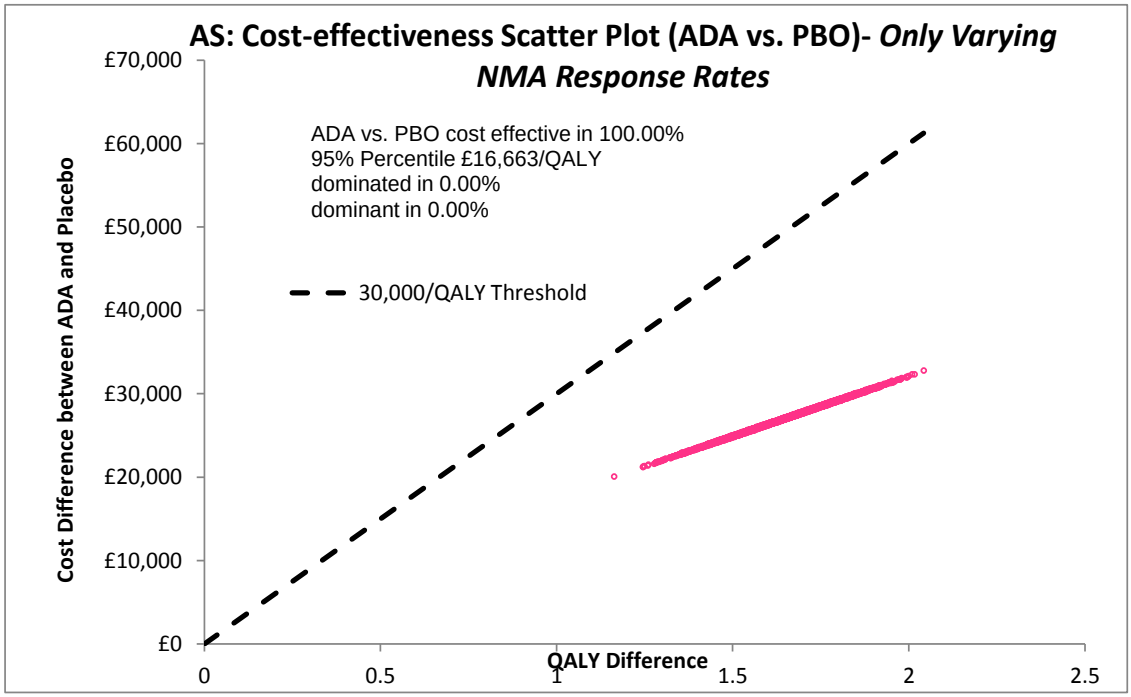
Figure 3.3.4.7: Secondary Probabilistic Sensitivity Analyses with only NMA response rates uncertainty (holding other parameters constant) for nr-AxSpA

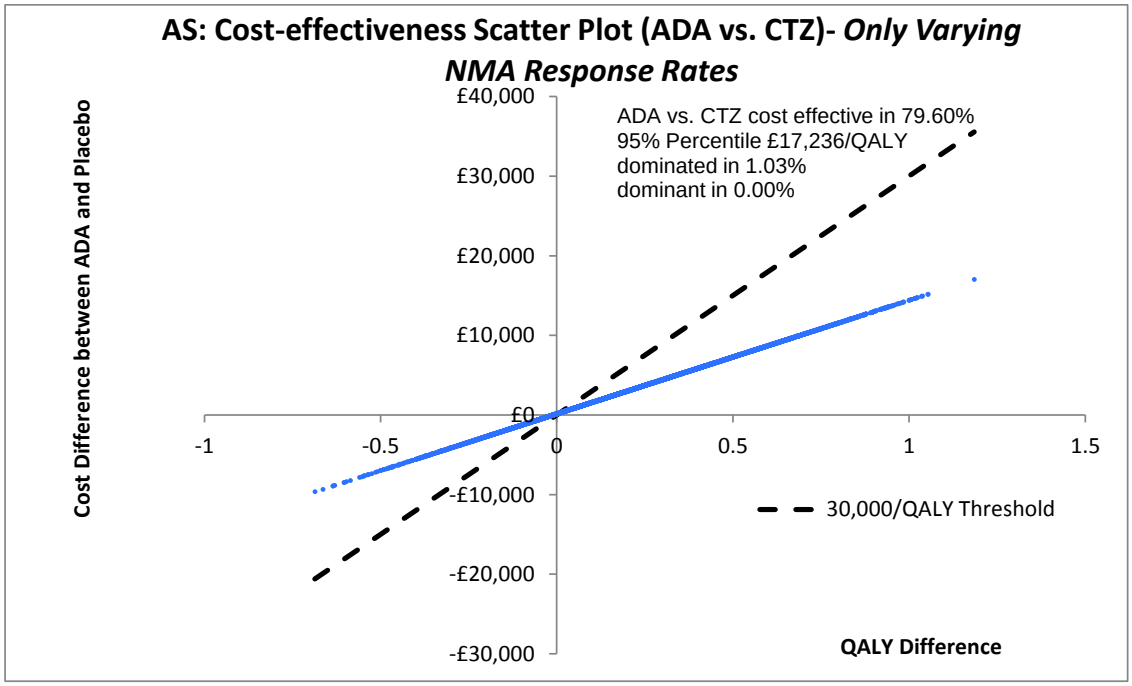




However for AS patients, Figure 3.3.4.8 shows scatterplots on the same slope with a narrower range of costs and QALYs. It follows that uncertainty from response rates for AS patients was limited in magnitude. This difference can be attributed to the fact that the number of studies available and included in the NMA was much smaller for nr-axSpA than for AS. Hence, the meta-analysed response rates yields far more uncertainty for the nr-axSpA patients.

Figure 3.3.4.8: Secondary Probabilistic Sensitivity Analyses with only NMA response rates uncertainty (holding other parameters constant) for AS





The next section (3.3.5) outlines the various scenario analyses that were conducted

3.3.5 Scenario Analyses

This section presents further details of sensitivity analyses using a number of alternative model configurations. All the scenarios and their associated assumptions are described in Table 3.3.2.1 and further specified in Table 3.3.5.1. A Summary of the values used is presented in Tables 3.3.5.2 to 3.3.5.6 for the nr-axSpA population and Tables 3.3.5.7 to 3.3.5.10 for the AS population.

Table 3.3.5.1: Assumptions used in alternate scenarios analyses.

№	Assumptions	
	Non-radiographic Axial SpA	**Ankylosing Spondylitis**
Response Criteria		
1	ASAS20	ASAS40
2	BASDAI50	BASDAI50
Off-treatment BASFI and week-12 responders' long term scores		
3	BASFI constant + All responders keep week-12 level	BASFI constant + All responders keep week-12 level
4	BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level
5	BASFI 0.08↑/yr.+ All responders keep week-12 level	BASFI 0.06↑/yr.+ All responders keep week-12 level
6	BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level
Utility Equations		
7	ABILITY-1 Trial Observed EQ-5D	ATLAS Trial Observed HUI3
8	EQ-5D=F(BASDAI)	HUI3=F(BASDAI)
9	Not Applicable*	EQ-5D=F(BASDAI, BASFI)
10	Not Applicable*	EQ-5D=F(BASDAI, BASFI, AGE, MALE)
HCRU Cost Equations		
11	Use Linear BASDAI Equation	Use Linear BASDAI Equation
12	Use Linear BASFI Equation	Use Linear BASFI Equation
13	Use Exponential BASFI Equation	Use Exponential BASFI Equation
Discount Rate		
14	6% for costs, 1.5% for Utilities	6% for costs, 1.5% for Utilities
15	3.5% for costs, 1.5% for Utilities	3.5% for costs, 1.5% for Utilities
16	1.5% for costs, 1.5% for Utilities	1.5% for costs, 1.5% for Utilities
Time Horizon		
17	5 Years	5 Years
18	10 Years	10 Years
19	20 Years	20 Years
20	30 Years	30 Years
Indirect Cost		
21	Include Indirect Cost	Include Indirect Cost
Regimen Dosage		
22	Certolizumab 400 mg/4weeks	Certolizumab 400 mg/4weeks
23	Certolizumab with PAS (first 12 weeks free)	Certolizumab with PAS (first 12 weeks free)
24	Not Applicable*	Etanercept 50 mg once per week
25	Not Applicable*	Infliximab infusion every 8 weeks
NMA output		
26	Removing Outlier Studies†	Removing Outlier Studies†
27	All Studies	Removing Asian Studies†

*Not relevant to Nr-AxSpA analysis (AS specific)
†Refer to Table E2 in Appendix B of the NMA and systematic review main document for the list of excluded studies (Appendix 1).

Table 3.3.5.2: Summary of Key Assumptions Used in Scenario Analyses for Nr-AxSpA (scenarios 1-5)

	BASE CASE	Scenario 1: ASAS20	Scenario 2: BASDAI50	Scenario 3: BASFI constant + All responders keep week-12 level	Scenario 4: BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	Scenario 5: BASFI 0.08↑/yr.+ All responders keep week-12 level
ADA w 12 responses (%)	55.9	73.3	38.8			
PBO w 12 responses (%)	22.2	45.7	13.3			
CTZ w 12 responses (%)	58.8	64.5	46.2			
Anti-TNFα Persistence rate*	a=4.4392; b=2.1479	a=5.1277; b=1.9223	a=5.2019; b=2.3695			
Uniform baseline BASDAI	6.432					
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS40-responder mean+LOCF	ASAS20-responder mean+LOCF	BASDAI50-responder mean+LOCF	1.589	1.589	1.589
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS40-responder mean+LOCF	ASAS20-responder mean+LOCF	BASDAI50-responder mean+LOCF	0.976	0.976	0.976
PBO responder BASDAI at 12 wks.	2.15	3.433	1.758			
Uniform baseline BASFI	4.629					
PBO responder BASFI at 12 wks.	1.484	2.532	1.476			
BASFI /year if off anti-TNF	0.084			0	0	
Utility function¥	BB					
HCRU Cost function ^	EB					
Discount rates cost (%)	3.5					
Discount rate QALY (%)	3.5					
Analytical Horizon (years)	40					
Indirect Costs	No					
PBO keep response	No			Yes		Yes
NMA Studies	ATP (MRI+/CRP↑)					
CTZ Dosage and PAS	200; No PAS					

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed ASAS20 responders mean till week 140 then LOCF; ¥B=BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI. **Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.3: Summary of Key Assumptions Used in Scenario Analyses for Nr-AxSpA (scenarios 6-8)

	BASE CASE	Scenario 6: BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level	Scenario 7: ABILITY-1 Trial Observed EQ-5D	Scenario 8: EQ-5D = F(BASDAI)
ADA w 12 responses (%)	55.9			
PBO w 12 responses (%)	22.2			
CTZ w 12 responses (%)	58.8			
Anti-TNFα Persistence rate*	a=4.4392; b=2.1479			
Uniform baseline BASDAI	6.432			
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS40-responder mean+ LOCF	1.589		
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS40-responder mean+ LOCF	0.976		
PBO responder BASDAI at 12 wks.	2.15			
Uniform baseline BASFI	4.629			
PBO responder BASFI at 12 wks.	1.484			
BASFI /year if off anti-TNF	0.084			
Utility function¥	BB		RCT	¥B
HCRU Cost function ^	EB			
Discount rates cost (%)	3.5			
Discount rate QALY (%)	3.5			
Analytical Horizon (years)	40			
Indirect Costs	No			
PBO keep response	No			
NMA Studies	ATP (MRI+ /CRP↑)			
CTZ Dosage and PAS	200; No PAS			

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed ASAS20 responders mean till week 140 then LOCF; ¥B=BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI. **Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.4: Summary of Key Assumptions Used in Scenario Analyses for Nr-AxSpA (scenarios 11-16)

	BASE CASE	Scenario 11: Cost Linear BASDAI Equation	Scenario 12: Cost Linear BASFI Equation	Scenario 13: Cost Exponential BASFI Equation	Scenario 14: 6% for costs, 1.5% for Utilities	Scenario 15: 3.5% for costs, 1.5% for Utilities	Scenario 16: 1.5% for costs, 1.5% for Utilities
ADA w 12 responses (%)	55.9						
PBO w 12 responses (%)	22.2						
CTZ w 12 responses (%)	58.8						
Anti-TNFα Persistence rate*	a=4.4392; b=2.1479						
Uniform baseline BASDAI	6.432						
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS40-responder mean+LOCF						
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS40-responder mean+LOCF						
PBO responder BASDAI at 12 wks.	2.15						
Uniform baseline BASFI	4.629						
PBO responder BASFI at 12 wks.	1.484						
BASFI /year if off anti-TNF	0.084						
Utility function¥	BB						
HCRU Cost function ^	EB	LB	LFI	EFI			
Discount rates cost (%)	3.5				6	3.5	1.5
Discount rate QALY (%)	3.5				1.5	1.5	1.5
Analytical Horizon (years)	40						
Indirect Costs	No						
PBO keep response	No						
NMA Studies	ATP (MRI+/CRP↑)						
CTZ Dosage and PAS	200; No PAS						

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed ASAS20 responders mean till week 140 then LOCF; ¥B=BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI. **Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.5: Summary of Key Assumptions Used in Scenario Analyses for Nr-AxSpA (scenarios 17-21)

	BASE CASE	Scenario 17: 5 Years	Scenario 18: 10 Years	Scenario 19. 20 Years	Scenario 20: 30 Years	Scenario 21: Include Indirect Cost
ADA w 12 responses (%)	55.9					
PBO w 12 responses (%)	22.2					
CTZ w 12 responses (%)	58.8					
Anti-TNFα Persistence rate*	a=4.4392; b=2.1479					
Uniform baseline BASDAI	6.432					
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS40-responder mean+LOCF					
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS40-responder mean+LOCF					
PBO responder BASDAI at 12 wks.	2.15					
Uniform baseline BASFI	4.629					
PBO responder BASFI at 12 wks.	1.484					
BASFI /year if off anti-TNF	0.084					
Utility function¥	BB					
HCRU Cost function ^	EB					
Discount rates cost (%)	3.5					
Discount rate QALY (%)	3.5					
Analytical Horizon (years)	40	5	10	20	30	
Indirect Costs	No					Yes
PBO keep response	No					
NMA Studies	ATP (MRI+/CRP↑)					
CTZ Dosage and PAS	200; No PAS					

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed ASAS20 responders mean till week 140 then LOCF; ¥B=BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI. **Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.6: Summary of Key Assumptions Used in Scenario Analyses for Nr-AxSpA (scenarios 22, 23, 26, and 27)

	BASE CASE	Scenario 22: Certolizumab 400 mg/4weeks	Scenario 23: Certolizumab with PAS (first 12 weeks free)	Scenario 26: Removing Outlier Studies	Scenario 27: All Studies
ADA w 12 responses (%)	55.9			50.4	51.2
PBO w 12 responses (%)	22.2			23.4	21.4
CTZ w 12 responses (%)	58.8	58.3		61	57.6
Anti-TNFα Persistence rate*	a=4.4392; b=2.1479				
Uniform baseline BASDAI	6.432				
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS40-responder mean + LOCF				
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS40-responder mean + LOCF				
PBO responder BASDAI at 12 wks.	2.15				
Uniform baseline BASFI	4.629				
PBO responder BASFI at 12 wks.	1.484				
BASFI /year if off anti-TNF	0.084				
Utility function¥	BB				
HCRU Cost function ^	EB				
Discount rates cost (%)	3.5				
Discount rate QALY (%)	3.5				
Analytical Horizon (years)	40				
Indirect Costs	No				
PBO keep response	No				
NMA Studies	ATP (MRI+/CRP↑)			No Outlier	All
CTZ Dosage and PAS	200; No PAS	400; No PAS	200;With PAS		

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed ASAS20 responders mean till week 140 then LOCF; ¥B=BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI. **Note: when assumptions left blank they were the same as in the base case.**

In the tables above scenarios 9, 10, 24, and 25 are missing; this is because these were not conducted in the nr-axSpA population. These scenarios were only applicable for the AS population and are shown in the tables that follow below.

Table 3.3.5.7: Summary of Key Assumptions Used in Scenario Analyses for AS (Scenarios 1-6)

	BASE CASE	1. ASAS40	2. BASDAI50	3. BASFI constant + All responders keep week-12 level	4. BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	5. BASFI 0.06↑/yr.+ All responders keep week-12 level	6. BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level
ADA w 12 responses (%)	63.2	51.2	47.7				
PBO w 12 responses (%)	27.2	15.2	15.9				
CTZ w 12 responses (%)	46.2	34	51.2				
ETN w 12 responses (%)	60.7	41.3	48.3				
GOL w 12 responses (%)	59.3	45.4	46.2				
IFL w 12 responses (%)	72.4	56.6	71.7				
Anti-TNFα Persistence rate*	a=5.6037; b=1.7965	a=5.9561; b=2.1636	a=5.7179; b=1.9138				
Uniform baseline BASDAI	6.297						
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS20-responder mean+LOCF	ASAS40-responder mean+LOCF	BASDAI 50-responder mean+LOCF	2.329	2.329	2.329	2.329
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS20-responder mean+LOCF	ASAS40-responder mean+LOCF	BASDAI 50-responder mean+LOCF	2.477	2.477	2.477	2.477
PBO responder BASDAI at 12 wks.	2.663	2.094	1.744				
Uniform baseline BASFI	5.372						
PBO responder BASFI at 12 wks.	2.178	1.973	1.467				
BASFI /year if off anti-TNF	0.056			0	0		
Utility function¥	BB→HUI						
HCRU Cost function ^	EB						
Discount rates cost (%)	3.5						
Discount rate QALY (%)	3.5						
Analytical Horizon (years)	40						
Indirect Costs	No						
PBO keep response	No			Yes		Yes	
NMA Studies	All						
CTZ Dosage and PAS	200; No PAS						
ETN Dosage	25						
IFL Frequency	6 wk.						

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed BASDAI50 responders mean till week 260 then LOCF; ¥B= BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI**. Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.8: Summary of Key Assumptions Used in Scenario Analyses for AS (Scenarios 7-12)

	BASE CASE	Scenario 7: ATLAS Trial Observed HUI3	Scenario 8: HUI3 = F(BASDAI)	Scenario 9: EQ-5D = F(BASDAI, BASFI)	Scenario 10: EQ-5D = F(BASDAI, BASFI, AGE, MALE)	Scenario 11: Cost Linear BASDAI Equation	Scenario 12: Cost Linear BASFI Equation
ADA w 12 responses (%)	63.2						
PBO w 12 responses (%)	27.2						
CTZ w 12 responses (%)	46.2						
ETN w 12 responses (%)	60.7						
GOL w 12 responses (%)	59.3						
IFL w 12 responses (%)	72.4						
Anti-TNFα Persistence rate*	a=5.6037; b=1.7965						
Uniform baseline BASDAI	6.297						
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS20-responder mean+LOCF						
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS20-responder mean+LOCF						
PBO responder BASDAI at 12 wks.	2.663						
Uniform baseline BASFI	5.372						
PBO responder BASFI at 12 wks.	2.178						
BASFI /year if off anti-TNF	0.056						
Utility function¥	BB→HUI	RCT	¥B→HUI	BB→EQ5D	(BB, Age, Male)→EQ5D		
HCRU Cost function ^	EB					LB	LFI
Discount rates cost (%)	3.5						
Discount rate QALY (%)	3.5						
Analytical Horizon (years)	40						
Indirect Costs	No						
PBO keep response	No						
NMA Studies	All						
CTZ Dosage and PAS	200; No PAS						
ETN Dosage	25						
IFL Frequency	6 wk.						

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed BASDAI50 responders mean till week 260 then LOCF; ¥B= BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI**. Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.9: Summary of Key Assumptions Used in Scenario Analyses for AS (Scenarios 13-20)

	BASE CASE	Scenario 13: Cost Exponential BASFI Equation	Scenario 14: 6% for costs, 1.5% for Utilities	Scenario 15: 3.5% for costs, 1.5% for Utilities	Scenario 16: 1.5% for costs, 1.5% for Utilities	Scenario 17: 5 Years	Scenario 18: 10 Years	Scenario 19: 20 Years	Scenario 20: 30 Years
ADA w 12 responses (%)	63.2								
PBO w 12 responses (%)	27.2								
CTZ w 12 responses (%)	46.2								
ETN w 12 responses (%)	60.7								
GOL w 12 responses (%)	59.3								
IFL w 12 responses (%)	72.4								
Anti-TNFα Persistence rate*	a=5.6037; b=1.7965								
Uniform baseline BASDAI	6.297								
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS20-responder mean+LOCF								
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS20-responder mean+LOCF								
PBO responder BASDAI at 12 wks.	2.663								
Uniform baseline BASFI	5.372								
PBO responder BASFI at 12 wks.	2.178								
BASFI /year if off anti-TNF	0.056								
Utility function¥	BB→HUI								
HCRU Cost function ^	EB	EFI							
Discount rates cost (%)	3.5		6	3.5	1.5				
Discount rate QALY (%)	3.5		1.5	1.5	1.5				
Analytical Horizon (years)	40					5	10	20	30
Indirect Costs	No								
PBO keep response	No								
NMA Studies	All								
CTZ Dosage and PAS	200; No PAS								
ETN Dosage	25								
IFL Frequency	6 wk.								

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed BASDAI50 responders mean till week 260 then LOCF; ¥B= BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI**. Note: when assumptions left blank they were the same as in the base case.**

Table 3.3.5.10: Summary of Key Assumptions Used in Scenario Analyses for AS (Scenarios 21-27)

	BASE CASE	Scenario 21: Include Indirect Cost	Scenario 22: CTZ 400 mg/4weeks	Scenario 23: CTZ with PAS (first 12 weeks free)	Scenario 24: ETN 50 mg/wk.	Scenario 25: IFL every 8 wk.	Scenario 26: Removing Outlier Studies	Scenario 27: Removing Asian Studies
ADA w 12 responses (%)	63.2						63.3	62.4
PBO w 12 responses (%)	27.2						27.2	27.1
CTZ w 12 responses (%)	46.2		54.2				46.3	46
ETN w 12 responses (%)	60.7				62.3		59.7	60.6
GOL w 12 responses (%)	59.3						59.2	66.6
IFL w 12 responses (%)	72.4						71.5	72.4
Anti-TNFα Persistence rate*	a=5.6037; b=1.7965							
Uniform baseline BASDAI	6.297							
Anti-TNFα responder BASDAI (≥12 wks.)§	ASAS20-responder mean+LOCF							
Anti-TNFα responder BASFI (≥12 wks.)§	ASAS20-responder mean+LOCF							
PBO responder BASDAI at 12 wks.	2.663							
Uniform baseline BASFI	5.372							
PBO responder BASFI at 12 wks.	2.178							
BASFI /year if off anti-TNF	0.056							
Utility function¥	BB→HUI							
HCRU Cost function ^	EB							
Discount rates cost (%)	3.5							
Discount rate QALY (%)	3.5							
Analytical Horizon (years)	40							
Indirect Costs	No	Yes						
PBO keep response	No							
NMA Studies	All						No Outlier	All
CTZ Dosage and PAS	200; No PAS		400; No PAS	200;With PAS				
ETN Dosage	25				50			
IFL Frequency	6 wk.					8 wk.		

* S(w) = 1-Φ[(Ln(w)-a)/b] where Φ is the cumulative distribution function of standard normal distribution; § Trial-observed BASDAI50 responders mean till week 260 then LOCF; ¥B= BASDAI; BB=BASDAI and BASFI; ^EB=Exponential BASDAI; EFI=Exponential BASFI; LB=Linear BASDAI; LFI=Linear BASFI**. Note: when assumptions left blank they were the same as in the base case.**

The following tables provide a summary of the results in terms of NMB and ICERs per QALY for each of the scenarios explored. Table 3.3.5.11 shows the results for the nr-axSpA population and Tables 3.3.5.12 and 3.3.5.13 provide the results for the AS population. Once again scenarios 9, 10, 24, and 25 were not applicable for the nr-axSpA population and as such are excluded from Table 3.3.5.11.

Table 3.3.5.11: Model Results (Nr-AxSpA) for Alternative Scenario Analyses

Non-radiographic Axial SpA	Base Case	Base Case NMB (WTP=£30,000/QALY)			Base Case ICER		
		ADA	PBO	CTZ(200)	ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ
		£160,646	**£140,177**	**£162,194**	**£13,228/QALY**	**£12,866/QALY**	**£6,032↓/QALY↓**
Scenarios of interest							
Scenario 1: Use ASAS20 criteria for response	ASAS40	£170,942	£140,845	£166,994	£14,310/QALY	£14,470/QALY	£13,161/QALY
Scenario 2: Use BASDAI50 criteria for response	ASAS40	£161,318	£139,733	£166,242	£13,033/QALY	£12,535/QALY	£9,954↓/QALY↓
Off-treatment BASFI and week-12 responders' long term scores							
Scenario 3: BASFI constant + All responders keep week-12 level	BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£256,406	£262,336	£257,419	£42,189/QALY	£39,235/QALY	£7,939↓/QALY↓
Scenario 4: BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£180,706	£171,080	£181,692	£19,235/QALY	£18,733/QALY	£9,324↓/QALY↓
Scenario 5: BASFI 0.08↑/yr.+ All responders keep week-12 level	BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£230,164	£231,433	£231,419	£31,977/QALY	£30,020/QALY	£6,754↓/QALY↓
Scenario 6: BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.08↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£154,465	£140,177	£155,692	£16,388/QALY	£15,963/QALY	£7,975↓/QALY↓
Utility Equations							
Scenario 7: ABILITY-1 Trial Observed EQ-5D	BASDAI/BASFI	£191,684	£173,535	N/A	£14,123/QALY	NA	NA
Scenario 8: BASDAI	BASDAI/BASFI	£182,103	£166,429	£183,402	£15,221/QALY	£14,803/QALY	£6,922↓/QALY↓
HCRU costs formula							
Scenario 11: Use Linear BASDAI Equation	Exponential BASDAI	£161,333	£139,127	£162,975	£11,804/QALY	£11,441/QALY	£4,580↓/QALY↓
Scenario 12: Use Linear BASFI Equation	Exponential BASDAI	£178,565	£158,765	£180,070	£13,776/QALY	£13,420/QALY	£6,702↓/QALY↓
Scenario 13: Use Exponential BASFI Equation	Exponential BASDAI	£189,431	£172,620	£190,777	£16,225/QALY	£15,870/QALY	£9,163↓/QALY↓

Non-radiographic Axial SpA	Base Case	Base Case NMB (WTP=£30,000/QALY)			Base Case ICER		
		ADA	PBO	CTZ(200)	ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ
		£160,646	**£140,177**	**£162,194**	**£13,228/QALY**	**£12,866/QALY**	**£6,032↓/QALY↓**
Discount rate							
Scenario 14: 6% for costs, 1.5% for Utilities	Both 3.5%	£295,987	£264,305	£298,176	£9,137/QALY	£8,812/QALY	£2,653↓/QALY↓
Scenario 15: 3.5% for costs, 1.5% for Utilities	Both 3.5%	£259,073	£229,660	£261,085	£10,631/QALY	£10,342/QALY	£4,866↓/QALY↓
Scenario 16: 1.5% for costs, 1.5% for Utilities	Both 3.5%	£210,455	£183,758	£212,253	£12,419/QALY	£12,175/QALY	£7,545↓/QALY↓
Time Horizon							
Scenario 17: 5 Years	40 Years	£45,904	£39,724	£46,910	£18,004/QALY	£16,770/QALY	Dominated
Scenario 18: 10 Years	40 Years	£78,921	£68,218	£80,085	£15,809/QALY	£15,066/QALY	£1,190↓/QALY↓
Scenario 19: 20 Years	40 Years	£123,085	£107,168	£124,445	£14,295/QALY	£13,814/QALY	£4,748↓/QALY↓
Scenario 20: 30 Years	40 Years	£148,021	£129,185	£149,499	£13,602/QALY	£13,205/QALY	£5,712↓/QALY↓
Scenario 21: Include Indirect Cost	Not Include indirect cost	-£42,290	-£84,954	-£39,548	Dominant	Dominant	Dominated
Regimen Dosage							
Scenario 22: Certolizumab 400 mg/4weeks	Certolizumab 200 mg/2weeks	Base Case	Base Case	£161,975	Base Case	£12,887/QALY	£5,122↓/QALY↓
Scenario 23: Certolizumab with PAS (first 12 weeks free)	Certolizumab without PAS	Base Case	Base Case	£164,210	Base Case	£11,297/QALY	Dominated
Response Rates Inputs (NMA)							
Scenario 26: Removing Outlier Studies	Only ATP (Licensed Population) Studies	£158,250	£140,241	£163,154	£13,577/QALY	£12,806/QALY	£9,226↓/QALY↓
Scenario 27: All Studies	Only ATP (Licensed Population) Studies	£158,598	£140,134	£161,888	£13,464/QALY	£12,875/QALY	£8,592↓/QALY↓

Table 3.3.5.12: Model Results (AS) for Alternative Scenario Analyses in terms of NMB

Ankylosing Spondylitis	Base Case	Base Case NMB (WTP=£30,000/QALY)					
		ADA	PBO	CTZ(200)	GOL	IFL6	ETN25
		£168,411	£145,913	£161,456	£166,779	£118,498	£166,705
Scenarios of interest							
Scenario 1: Use ASAS40 criteria for response	ASAS20	£170,690	£145,424	£161,142	£167,436	£123,410	£164,593
Scenario 2: Use BASDAI50 criteria for response	ASAS20	£166,997	£145,526	£168,954	£166,209	£122,850	£166,747
Off-treatment BASFI and week-12 responders' long term scores							
Scenario 3: BASFI constant + All responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£212,610	£225,034	£211,917	£212,431	£159,245	£211,837
Scenario 4: BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£167,955	£163,864	£165,952	£167,459	£115,364	£166,978
Scenario 5: BASFI 0.06↑/yr.+ All responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£199,633	£207,083	£197,602	£199,147	£146,992	£198,663
Scenario 6: BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£154,978	£145,913	£151,637	£154,175	£103,110	£153,804
Utility Equations							
Scenario 7: ATLAS Trial Observed HUI3	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£184,471	£163,704	N/A	N/A	N/A	N/A
Scenario 8: BASDAI mapping→ HUI 3 (ATLAS)	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£180,856	£160,884	£174,587	£179,381	£130,573	£179,252
Scenario 9: (BASDAI+BASFI) mapping→ EQ-5D (Ara et al)	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£160,942	£139,267	£154,211	£159,361	£110,909	£159,270
Scenario 10: (BASDAI+BASFI+Age+Male) mapping→ EQ-5D (McLeod et al)	(BASDAI+ BASFI)→ HUI 3 (ATLAS)	£151,209	£121,052	£142,163	£149,097	£102,429	£149,196

Ankylosing Spondylitis	Base Case	Base Case NMB (WTP=£30,000/QALY)					
		ADA	PBO	CTZ(200)	GOL	IFL6	ETN25
		£168,411	**£145,913**	**£161,456**	**£166,779**	**£118,498**	**£166,705**
HCRU costs formula							
Scenario 11: Use Linear BASDAI Equation	Exponential BASDAI	£167,823	£143,291	£160,305	£166,061	£118,219	£166,034
Scenario 12: Use Linear BASFI Equation	Exponential BASDAI	£174,513	£154,668	£168,325	£173,056	£124,190	£172,920
Scenario 13: Use Exponential BASFI Equation	Exponential BASDAI	£184,227	£167,524	£178,897	£182,967	£133,438	£182,760
Discount rate							
Scenario 14: 6% for costs, 1.5% for Utilities	Both 3.5%	£296,231	£257,337	£284,945	£293,587	£258,146	£293,989
Scenario 15: 3.5% for costs, 1.5% for Utilities	Both 3.5%	£262,650	£228,066	£252,444	£260,272	£214,497	£260,467
Scenario 16: 1.5% for costs, 1.5% for Utilities	Both 3.5%	£219,825	£190,331	£210,892	£217,761	£159,771	£217,711
Time Horizon							
Scenario 17: 5 Years	40 Years	£46,725	£41,247	£44,614	£46,143	£23,899	£46,043
Scenario 18: 10 Years	40 Years	£82,335	£71,248	£78,612	£81,407	£48,754	£81,295
Scenario 19: 20 Years	40 Years	£130,366	£112,752	£124,784	£129,036	£86,261	£128,932
Scenario 20: 30 Years	40 Years	£156,845	£135,846	£150,309	£155,306	£108,458	£155,220
Scenario 21: Include Indirect Cost	Not Include indirect cost	£2,585	-£55,486	-£14,194	-£1,299	-£42,016	-£564
Regimen Dosage							
Scenario 22: Certolizumab 400 mg/4weeks	Certolizumab 200 mg/2weeks	Base case	Base case	£164,797	Base case	Base case	Base case
Scenario 23: Certolizumab with PAS (first 12 week free)	Certolizumab without PAS	Base case	Base case	£163,372	Base case	Base case	Base case
Scenario 24: Etanercept 50 mg once per week	Etanercept 25 mg twice per week	Base case	Base case	Base case	Base case	Base case	£167,358
Scenario 25: Infliximab infusion every 8 weeks	Infliximab infusion every 6 weeks	Base case	Base case	Base case	Base case	£143,896	Base case
Response Rates Inputs (NMA)							
Scenario 26: Removing Outlier Studies	All Studies	£168,453	£145,913	£161,498	£166,737	£118,764	£166,297
Scenario 27: Removing Asian Studies	All Studies	£168,076	£145,908	£161,373	£169,833	£118,498	£166,665

Table 3.3.5.13: Model Results (AS) for Alternative Scenario Analyses in terms of ICER per QALY

Ankylosing Spondylitis	Base Case	Base case ICER								
		ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ	ADA vs. GOL	ADA vs. IFL	ADA vs. ETN	GOL vs. PBO	IFL vs. PBO	ETN vs. PBO
		£16,391/ QALY	**£17,067/ QALY**	**£14,593/ QALY**	**£14,241/ QALY**	**£234,328↓/ QALY↓**	**£4,311/ QALY**	**£16,535/ QALY**	**£44,448/ QALY**	**£16,897/ QALY**
Scenarios of interest										
Scenario 1: Use ASAS40 criteria for response	ASAS20	£15,065/ QALY	£15,945/ QALY	£13,350/ QALY	£13,169/ QALY	£292,595↓/ QALY↓	£11,529/ QALY	£15,310/ QALY	£41,761/ QALY	£15,923/ QALY
Scenario 2: Use BASDAI50 criteria for response	ASAS20	£15,017/ QALY	£14,782/ QALY	£11,613↓/ QALY↓	£12,743/ QALY	£90,470↓/ QALY↓	£43,686↓/ QALY↓	£15,092/ QALY	£40,483/ QALY	£15,378/ QALY
Off-treatment BASFI and week-12 responders' long term scores										
Scenario 3: BASFI constant + All responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£48,097/ QALY	£62,780 /QALY	£27,581/ QALY	£27,276/ QALY	£374,337↓/ QALY↓	£11,646/ QALY	£50,300/ QALY	£108,181/ QALY	£50,479/ QALY
Scenario 4: BASFI constant+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£26,363/ QALY	£27,440/ QALY	£23,524/ QALY	£23,009/ QALY	£344,151↓/ QALY↓	£8,520/ QALY	£26,589/ QALY	£67,522/ QALY	£27,115/ QALY
Scenario 5: BASFI 0.06↑/yr.+ All responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£38,741/ QALY	£48,186/ QALY	£23,865/ QALY	£23,601/ QALY	£323,900↓/ QALY↓	£10,077/ QALY	£40,222/ QALY	£88,262/ QALY	£40,477/ QALY
Scenario 6: BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders keep week-12 level	BASFI 0.06↑/yr+PBO responders return to baseline+TNF-α responders improve then LOCF	£22,978/ QALY	£23,891/ QALY	£20,560/ QALY	£20,110/ QALY	£300,791↓/ QALY↓	£7,447/ QALY	£23,170/ QALY	£58,872/ QALY	£23,630/ QALY
Utility Equations										
Scenario 7: ATLAS Trial Observed HUI3	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£16,984/ QALY	NA	NA	NA	NA	NA	NA	NA	NA
Scenario 8: BASDAI mapping→ HUI 3 (ATLAS)	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£17,271/ QALY	£17,985/ QALY	£15,370/ QALY	£14,999/ QALY	£246,809↓/ QALY↓	£4,540/ QALY	£17,423/ QALY	£46,831/ QALY	£17,804/ QALY

Ankylosing Spondylitis	Base Case	Base case ICER								
		ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ	ADA vs. GOL	ADA vs. IFL	ADA vs. ETN	GOL vs. PBO	IFL vs. PBO	ETN vs. PBO
		£16,391/ QALY	**£17,067/ QALY**	**£14,593/ QALY**	**£14,241/ QALY**	**£234,328↓/ QALY↓**	**£4,311/ QALY**	**£16,535/ QALY**	**£44,448/ QALY**	**£16,897/ QALY**
Scenario 9: (BASDAI+BASFI) mapping→ EQ-5D (Ara et al)	(BASDAI+ BASFI) mapping→ HUI 3 (ATLAS)	£16,668/ QALY	£17,355/ QALY	£14,838/ QALY	£14,480/ QALY	£238,263↓/ QALY↓	£4,383/ QALY	£16,814/ QALY	£45,198/ QALY	£17,182/ QALY
Scenario 10: (BASDAI+BASFI+Age+Male) mapping→ EQ-5D (McLeod et al)	(BASDAI+ BASFI)→ HUI 3 (ATLAS)	£14,199/ QALY	£14,784/ QALY	£12,640/ QALY	£12,335/ QALY	£202,973↓/ QALY↓	£3,734/ QALY	£14,323/ QALY	£38,502/ QALY	£14,636/ QALY
HCRU costs formula										
Scenario 11: Use Linear BASDAI Equation	Exponential BASDAI	£15,161/ QALY	£15,843/ QALY	£13,344/ QALY	£12,984/ QALY	£233,064↓/ QALY↓	£3,054/ QALY	£15,306/ QALY	£43,213/ QALY	£15,667/ QALY
Scenario 12: Use Linear BASFI Equation	Exponential BASDAI	£17,996/ QALY	£18,637/ QALY	£16,290/ QALY	£15,930/ QALY	£236,009↓/ QALY↓	£5,999/ QALY	£18,134/ QALY	£46,062/ QALY	£18,498/ QALY
Scenario 13: Use Exponential BASFI Equation	Exponential BASDAI	£19,897/ QALY	£20,537/ QALY	£18,192/ QALY	£17,834/ QALY	£237,916↓/ QALY↓	£7,904/ QALY	£20,035/ QALY	£47,964/ QALY	£20,399/ QALY
Discount rate										
Scenario 14: 6% for costs, 1.5% for Utilities	Both 3.5%	£11,083/ QALY	£11,549/ QALY	£9,838/ QALY	£9,413/ QALY	£155,718↓/ QALY↓	£2,768/ QALY	£11,195/ QALY	£29,657/ QALY	£11,430/ QALY
Scenario 15: 3.5% for costs, 1.5% for Utilities	Both 3.5%	£13,179/ QALY	£13,708/ QALY	£11,767/ QALY	£11,483/ QALY	£188,952↓/ QALY↓	£3,476/ QALY	£13,293/ QALY	£35,752/ QALY	£13,584/ QALY
Scenario 16: 1.5% for costs, 1.5% for Utilities	Both 3.5%	£15,655/ QALY	£16,259/ QALY	£14,042/ QALY	£13,928/ QALY	£228,240↓/ QALY↓	£4,311/ QALY	£15,770/ QALY	£42,954/ QALY	£16,128/ QALY
Time Horizon										
Scenario 17: 5 Years	40 Years	£21,409/ QALY	£22,670/ QALY	£18,158/ QALY	£15,773/ QALY	£266,701↓/ QALY↓	£4,003/ QALY	£21,795/ QALY	£53,635/ QALY	£22,155/ QALY
Scenario 18: 10 Years	40 Years	£18,913/ QALY	£19,834/ QALY	£16,495/ QALY	£15,330/ QALY	£255,079↓/ QALY↓	£4,337/ QALY	£19,155/ QALY	£49,573/ QALY	£19,529/ QALY
Scenario 19: 20 Years	40 Years	£17,342/ QALY	£18,094/ QALY	£15,349/ QALY	£14,778/ QALY	£243,903↓/ QALY↓	£4,394/ QALY	£17,514/ QALY	£46,580/ QALY	£17,886/ QALY
Scenario 20: 30 Years	40 Years	£16,682/ QALY	£17,379/ QALY	£14,830/ QALY	£14,425/ QALY	£237,530↓/ QALY↓	£4,348/ QALY	£16,833/ QALY	£45,132/ QALY	£17,199/ QALY
Scenario 21: Include Indirect Cost	Not Include indirect cost	Dominant	Dominant	Dominant	Dominant	£212,586↓/ QALY↓	Dominant	Dominant	£22,901/ QALY	Dominant

Ankylosing Spondylitis	Base Case	Base case ICER								
		ADA vs. PBO	CTZ vs. PBO	ADA vs. CTZ	ADA vs. GOL	ADA vs. IFL	ADA vs. ETN	GOL vs. PBO	IFL vs. PBO	ETN vs. PBO
		£16,391/ QALY	**£17,067/ QALY**	**£14,593/ QALY**	**£14,241/ QALY**	**£234,328↓/ QALY↓**	**£4,311/ QALY**	**£16,535/ QALY**	**£44,448/ QALY**	**£16,897/ QALY**
Regimen Dosage										
Scenario 22: Certolizumab 400 mg/4weeks	Certolizumab 200 mg/2weeks	Base case	£16,647/ QALY	£14,879/ QALY	Base case	Base case	Base case	Base case	Base case	Base case
Scenario 23: Certolizumab with PAS (first 12 week free)	Certolizumab without PAS	Base case	£15,472/ QALY	£18,838/ QALY	Base case	Base case	Base case	Base case	Base case	Base case
Scenario 24: Etanercept 50 mg once per week	Etanercept 25 mg twice per week	Base case	Base case	Base case	Base case	Base case	Dominant	Base case	Base case	£16,838/ QALY
Scenario 25: Infliximab infusion every 8 weeks	Infliximab infusion every 6 weeks	Base case	Base case	Base case	Base case	£130,358↓/ QALY↓	Base case	Base case	£31,063/ QALY	Base case
Response Rates Inputs (NMA)										
Scenario 26: Removing Outlier Studies	All Studies	£16,388/ QALY	£17,061/ QALY	£14,593/ QALY	£14,241/ QALY	£258,217↓/ QALY↓	£7,452/ QALY	£16,539/ QALY	£44,490/ QALY	£16,935/ QALY
Scenario 27: Removing Asian Studies	All Studies	£16,417/ QALY	£17,076/ QALY	£14,606/ QALY	£14,244↓/ QALY↓	£216,721↓/ QALY↓	£470/ QALY	£16,278/ QALY	£44,445/ QALY	£16,898/ QALY

Results from the scenario analyses presented above in Table 3.3.5.11 for nr-AxSpA found that for most scenarios (i.e., response criteria, utility and HCRU cost functions, discount rates, dosage and NMA studies included); the CE results do not vary substantially from the base case ICER. Adalimumab and certolizumab were found to be highly cost-effective with ICERs well below £20,000/QALY compared to conventional therapy (PBO).

The assumptions related to long-term placebo response and functional damage (scenarios 3 to 6) revealed that under extreme conservative assumptions, anti-TNF therapies have high ICERs. Specifically in scenario 3 and 5, where week-12 placebo response were maintained for the life time, adalimumab and certolizumab were associated with relatively less treatment benefit and the ICER was above £30,000/QALY compared to conventional therapy. However, as mentioned in (8), this scenario has more theoretical value as an anchor point or worst case scenario, rather than any clinical meaning or implications in the real world. It is very unlikely that a 12-week placebo response would be kept for life time.

The ICER continues to improve as the time horizons are increased from 5 to 30 years (scenarios 17 to 20); consistent with the fact that longer treatment benefit would offset the initial sunk cost at the treatment onset. Adalimumab and certolizumab dominated conventional therapy when indirect costs were included in the societal perspective.

Scenario results for AS patients shown above in Table 3.3.5.12 and 3.3.5.13, were similar to the results observed for the nr-axSpA population. Adalimumab produced the lowest ICERs compared to conventional therapy in all scenarios. Infliximab was inferior to the other anti-TNF agents with significantly higher cost and relatively similar QALY gains.

3.4 Discussion

The present analysis indicates that the use of adalimumab in nr-axSpA and AS should be cost effective from the perspective of the NICE, when using a £30,000 per QALY threshold. The results of this analysis also show that, from a societal perspective when direct non-medical and indirect costs were included, the use of adalimumab resulted in cost savings (in addition to QALY gains).

The objective of this study was to assess the cost effectiveness of adalimumab and other licensed anti-TNFα drugs in accordance with ASAS guidelines and, in particular, to quantify the cost per quality-adjusted life year (QALY) gained through the use of adalimumab compared with conventional therapy and other anti-TNFα drugs.

The cost-effectiveness results are robust. While the cost effectiveness ratio is sensitive to key parameters, it was not overly dependent on the value taken by any particular one of them. These findings were further confirmed in a series of univariate and scenario analyses. Multivariate, probabilistic sensitivity analyses also suggest that under the current model assumptions, the cost per QALY for adalimumab is <£20,000 in 95% of 10,000 model runs.

The results of the present analysis support a fundamental tenet of general treatment guidelines recommendations for the use of anti-TNFα in patients with nr and radiographic axial SpA, which require that (a) patients have sufficiently severe disease before embarking on such therapy; and (b) that those who do not exhibit (or lose) a sufficient response be discontinued from therapy.

A key strength of this analysis was that it sought to comprehensively include as many sources of costs and benefits associated with the use of adalimumab and other anti-TNFα in this patient population. In particular, the analyses included the meta-analysed response rates of all anti-TNFα, cost of TB screening, efficacy and safety monitoring, and the cost of adverse events, in addition to the savings associated with improvements in disease severity.

Despite these strengths, the present analysis has some limitations, which are now discussed.

The estimated effectiveness of the different anti-TNF drugs is based on a network meta-analysis of a limited number of trials. Differences in the trial populations and study designs would be best addressed by exclusion of studies and use of meta-regression to adjust for study level covariates. However, there are too few trials to conduct a number of these adjustments, particularly for nr-axSpA where only one pivotal trial has been conducted for adalimumab and for certolizumab.

Due to lack of access to data of other RCTs, AbbVie was only able to impose assumptions on post week-12 drug discontinuation, BASDAI/BASFI scores, utility functions and cost of adverse events, monitoring and initiation from available sources of adalimumab (ABILITY-1 and ATLAS). It is advisable that some further data analysis and assumptions using data from other anti-TNF trials (e.g. hazard ratios of discontinuation) could be obtained in the future that would resolve these issues.

The health care resource use data collected in the ABILITY-1 trial were not used for nr-AxSpA. This decision was motivated by practical considerations. In part, the health care resource use data in the trial of non-protocol-related resource use tended to be low in both treatment and placebo patients, perhaps due to the phenomenon associated with protocol driven resource use patterns (i.e., all patients are intensively monitored due to the protocol visits). All patients on placebo started open label adalimumab therapy at 12 weeks so resource utilisation data for placebo data were not available over the long term when most of the resource utilisation was expected to occur. The aggregate data from the long term AS OASIS registry study used in this model has three major limitations for nr-AxSpA: it did not include the resource use of nr-axSpA patients specifically as it was AS only; only aggregate data was available (no patient-level resource was available); it did not include UK patients.

It was not possible to develop estimates of costs that would be dependent on the joint distribution of BASFI and BASDAI. The decision to estimate costs based on the BASDAI rather than on the BASFI scores was based on three considerations:

- Unlike the BASFI, the BASDAI is used to guide treatment decisions. As such, it seems it is a more reasonable and direct anchor to estimate costs.
- The model using the BASDAI to estimate costs is arguably more robust and less subject to uncertain assumptions regarding the long-term change in disease severity score than the model relying on the BASFI to estimate costs.
- It is possible that the BASFI captures both AS-related and non-AS-related functional decline related to non-AS comorbidities (including age-related comorbidities). As such, it may be less appropriate to use the BASFI to estimate the AS-related costs which are used as proxies for the nr-axSpA related costs.

The impact of selecting one method over the other on the results was tested in scenario analyses. Although the results relying on the BASDAI costing methodology gave slightly lower ICER estimates than the results relying on the exponential BASFI methodology, the difference was generally small (ICER for ADA vs. PBO changed by £3,506 (21%) to £19,897 in AS, and changed by £2,997 (23%) to £15,654 in nr-AxSpA).

The exponential trend analyses conducted on the aggregate cost and disease severity data from the OASIS observational study may provide too narrow an estimate of the uncertainty surrounding the relationship between axial-SpA-related costs and BASDAI scores. On the other hand, given the small number of aggregated data points, it is likely that the confidence interval around the estimated relationship is overestimated. Thus, the net effect in terms of uncertainty may not be large. Nevertheless, this source of uncertainty is significant: as the univariate sensitivity analysis indicated, the shape of the relationship between cost and BASDAI is one of the more sensitive parameters of the model.

As the resource utilisation data were taken from the OASIS observational study of AS patients from the Netherlands, France and Belgium, to the extent that the resource utilisation in these countries differs from that of the UK, our analysis may over or underestimate the cost in the UK.

The method used to handle placebo response assumes that any placebo response is lost after week 12 (at randomisation). This is based on the subjectivity of the primary measure of response in the trial and in the model (ASAS40, ASAS20) and the likelihood that this effect would not be evident in clinical practice. Nevertheless, alternative assumptions could be adopted. In a scenario analysis it was assumed that the 12-week placebo response of conventional therapy patients was maintained over 40 years for those remaining as responders, which is the most stringent assumption going in the opposite direction. In that case, a patient who initially responded on anti-TNFα and who discontinued was assumed to have his/her scores return to values intermediate to the scores of placebo responders and placebo non-responders, in proportions that ensure that once all adalimumab responders are discontinued, the scores of the adalimumab and placebo arm would be equal (excluding any difference in progression due to an increase in BASFI or BASDAI scores). The detrimental effect of this alternative assumption on cost-effectiveness has been highlighted, but the likelihood that this scenario would be relevant is low. The likelihood that patients in conventional therapy benefit from a strong placebo effect at 12 weeks in clinical practice seems fairly low, for the reasons set out above, and even lower that this would be maintained beyond 12 weeks for the full 40 years of the model time period.

Disease progression in the model was based on the assumption of BASFI scores increasing over time. This assumption is comparable to the assumptions made in other models of AS and reflect the change in BASFI score over time observed in the licensed population (during the time period prior to the trial). This BASFI increase is perhaps to be expected given that a majority of patients with axial SpA experience progression towards radiographic disease (i.e., AS). Prior research has shown that in AS patients, BASFI scores are independently and positively associated with disease progression in the spine and BASDAI scores. Thus, if disease progress in the spine (i.e., patient progress from non-radiographic to radiographic axSpA), one might expect a worsening of BASFI scores (independently of BASDAI scores). However, in the present model, no attempt has been made to reconcile the change in BASFI score with possible conversion from non-radiographic to radiographic axSpA. If nr-axSpA patients progress to AS, particularly those on conventional therapy, these patients could be expected to become eligible for anti-TNF therapy (especially since most of these patients' BASDAI are >4). If this is indeed true, then the impact of disease progression in conventional therapy patients

would include increase in health care costs when patients become eligible for anti-TNF therapy and improvements in utility (and QALY gains) relative to the current model. The net effect on cost per QALY for the use of adalimumab in nr-axSpA is unclear (and likely depends on the relative cost effectiveness of treating AS vs nr-axSpA patients). This is further complicated by the uncertainty surrounding the treatment patterns that should be adopted for nr-axSpA patients who initiate adalimumab but fail to respond or respond and then discontinue. No data is available to determine whether patients who did not respond while non-radiographic would also not respond if they went on to develop AS. Answer to these questions (disease progression, radiographic progression, treatment eligibility for AS, need to consider treatment sequences) would need to be tested via additional modelling, including preferably micro-simulations.

In the model, it was calculated, based on observed data from the trial, that patients on adalimumab do not experience worsening on BASFI while remaining on therapy. This is also consistent with published evidence on the effectiveness of adalimumab**Error! Bookmark not defined.**. However, revious studies have shown that the relationship between anti-TNF use and the rate of radiographic progression in AS within 2 years [89] is different from the relationship between anti-TNF use and radiographic progression in rheumatoid arthritis [90]. Hence, it may be legitimate to question whether it is appropriate to assume no BASFI increase while on adalimumab while assuming an increase in BASFI while not on adalimumab. Yet, at the same time, both the results of the ABILITY-1 and the results of other trials in AS do show at least maintenance if not deepening of response among axSpA patients receiving anti TNF. Modelling the discontinuation of patients who lose response allows inclusion in the model of a deepening in response.

The definition of response in the analysis was based on the ASAS40. The choice of the ASAS40 was made on the basis that this measure is consistent with the primary endpoint of the ABILITY-1 trial. However, alternative definitions have been used in past economic analyses of AS. Nevertheless the results of the present analysis were not affected substantially by the use of these alternative methods.

Cost savings due to adalimumab may be underestimated. It is possible that the cost equation used in the base case and most other scenarios, which links costs to BASDAI scores, ignores the cost associated with extra-articular manifestations of nr-axSpA (e.g. uveitis or IBD), since the BASDAI may not correlate well with these manifestations.

Finally, the cost of adalimumab has decreased by 1.5% in terms of its list price since it was assessed by the NICE for the AS indication, while the costs associated with monitoring and treating AS have consistently increased since 2005, so adalimumab could be considered to have increased value in the present day NHS.

3.5 Equity implications

Dealing exclusively with patients with nr-axSpA who have failed NSAIDs therapies, the model results do not highlight equity problems within this population. It should however be reiterated that, while patients with nr-axSpA share a similar burden of disease to patients with AS, they currently have, contrary to patients with AS, delayed or no access to anti-TNF drug therapies. Alleviating this instance of limited/delayed access from patients with nr-axSpA who have failed NSAIDs therapies to adalimumab would, apart from reducing the economic burden associated with nr-axSpA, promote equity in access to resources deployed in the NHS between patients suffering from conditions which are different in their clinical nature but are associated with similar economic burden. There may be an equity implication given the observation that patients with AS are more commonly male whereas the male: female ratio is more evenly split in nr-axSpA, based on the observed demographic characteristics of the ATLAS and ABILITY-1 studies.

Appendix 1 – Network Meta-Analysis (NMA) - full report

Copies of the full NMA report and its associated appendices have been attached as separate documents.

The appendices include details of the search strategies for the systematic literature review, excluded citations and examples of the WinBUGS code used for the network meta-analysis.

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