Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Etanercept

Proprietary Product Name: Enbrel

Sponsor: Pfizer Australia Pty Ltd

First round CER report: 15 May 2014
Second round CER report: 24 October 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AS	Ankylosing Spondylitis
ASAS	Assessment in Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASspiMRI-a	Ankylosing Spondylitis spine MRI score for activity
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI	Ankylosing Spondylitis spine Magnetic Resonance Imaging
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity
AS-WIS	Ankylosing Spondylitis Work Instability Index
AST	Aspartate Aminotransferase
AxSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BAS-G	Bath Ankylosing Spondylitis Patient Global Assessment Score
BL	Baseline
BP	Blood Pressure
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DMARDs	Disease-Modifying Anti-rheumatic Drugs
DNA	Deoxyribonucleic acid
DVU	Discovertebral units

Abbreviation	Meaning
EIU	Exposure In Utero
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EQ-5D	EuroQol EQ-5D Health State Profile
FDA	Food and Drug Administration
F/U	Follow-up
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen B27
hsCRP	High Sensitivity C-Reactive Protein
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
MASES	Maastricht Anklyosing Spondylitis Entheses Score
MCII	Minimum Clinically Important Improvement
MCS	Mental Component Score
MFI	Multidimensional Fatigue Inventory
mITT	Modified Intent-to-Treat
MOS	Medical Outcomes Study (MOS) Sleep Scale

Abbreviation	Meaning
MRI	Magnetic Resonance Imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spine Score
NA	Not Assessed
nr-AxSpA	Non-radiographic Axial Spondyloarthritis
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NY	New York
PASS	Patient Acceptable Symptom State
PBO	Placebo
PCS	Physical Component Score
PGA	Physician Global Assessment
PPD	Purified protein derivative
RA	Rheumatoid Arthritis
RASSS	Radiographic Ankylosing Spondylitis Spine Score
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneously
SD	Standard Deviation
SE	Standard Error
SF-36	36-Item Short-Form Health Survey
SI	Sacroiliac
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	Tuberculosis
TNFα	Tumor Necrosis Factor alpha

Abbreviation	Meaning
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WPAI	Work Productivity and Activity Impairment Questionnaire
VAS	Visual Analogue Scale

1. Background

1.1. Submission type

This is a type C application to extend the indication of etanercept (Enbrel) powder for injection/solution for injection to include the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA).

1.2. Drug class and therapeutic indication

The approved indication for etanercept submitted in the dossier was:

Enbrel is indicated for the treatment of:

- *Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Enbrel can be used in combination with methotrexate.*
- *Severe, active, adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see CLINICAL TRIALS).*
- *Active polyarticular-course juvenile chronic arthritis in patients (4 to 17 years) who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. Enbrel has not been studied in children less than 4 years of age.*
- *The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Enbrel has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (see CLINICAL TRIALS).*
- *The signs and symptoms of active ankylosing spondylitis in adults.*
- *Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.*
- *Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.*

The current approved indication for etanercept (PI dated 12 February 2014) following a recent evaluation of data in relation to juvenile idiopathic arthritis (JIA) is as follows:

Enbrel is indicated for the treatment of:

Adults

Rheumatoid Arthritis

- *Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Enbrel can be used in combination with methotrexate.*
- *Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see CLINICAL TRIALS).*

Psoriatic Arthritis

- *The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate.Enbrel has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (see CLINICAL TRIALS).*

Ankylosing Spondylitis

- *The signs and symptoms of active ankylosing spondylitis in adults.*

Plaque Psoriasis

- *Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.*

Children and Adolescents

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.*[1]
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*[1]
- *Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.*[1]
- *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*[1]

Enbrel has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

- *Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.*

After one takes into account the recently approved extension of indication in JIA, the final wording of the indications resulting from this current submission will be (new wording for nr-axSpA underlined): Enbrel is indicated for the treatment of:

Adults

Rheumatoid Arthritis

Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Enbrel can be used in combination with methotrexate.

Severe, active, adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see CLINICAL TRIALS).

[1] Extension of indication approved by the TGA on 12 February 2014.

Psoriatic Arthritis

The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Enbrel has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (see CLINICAL TRIALS).

Ankylosing Spondylitis

The signs and symptoms of active ankylosing spondylitis in adults.

Plaque Psoriasis

Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Axial spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy (see CLINICAL TRIALS).

Children and Adolescents

Juvenile Idiopathic Arthritis

- *Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.*[1]
- *Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*[1]
- *Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.*[1]
- *Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.*[1]

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Paediatric Plaque Psoriasis

Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

1.2.1. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Enbrel (Etanercept) 25 mg and 50 mg powder for injection and water for injections
- Enbrel (Etanercept) 25 mg and 50 mg solution for injection in pre-filled syringe
- Enbrel (Etanercept) 50 mg solution for injection in Auto-injector

There are no new dosage forms or strengths proposed.

[1] Extension of indication approved by the TGA on 12 February 2014.

1.2.2. Dosage and administration

There is no proposed change, apart from the addition of the new indication (underlined), to the dosage and administration in the PI which is as follows:

> *Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.*
>
> ***Adults***
>
> ***Rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis and ankylosing spondylitis***
>
> *The recommended dose of Enbrel is 50 mg per week, given as a subcutaneous injection, EITHER once weekly as a single 50 mg injection OR twice weekly as two separate 25 mg injections given 3-4 days apart.*

2. Clinical rationale

Etanercept (Enbrel) is a recombinant human tumour necrosis factor alpha (TNFα) antagonist which binds to TNFα and blocks its interaction with the cell surface TNFα receptor. It is currently approved for the treatment of ankylosing spondylitis (AS) as well as several other conditions. The sponsor stated the following rationale for the proposed extended indication in their covering letter:

> *Spondyloarthritis (SpA) encompasses closely related but clinically heterogeneous inflammatory diseases including ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease-related arthritis, reactive arthritis, and other 'undifferentiated' SpA. In general, patients are classified by whether they have predominantly axial involvement (axial SpA [axSpA]) or predominantly peripheral involvement (peripheral SpA). The severity of axSpA can span from self-limited inflammation to bony destruction of the spine whose most devastating clinical manifestation is the loss of mobility.*
>
> *While AS is a well-characterised chronic and progressive form of axSpA, the natural history of nr-axSpA is not well known. Available evidence suggests that the majority of patients with newly diagnosed axSpA can be expected to be nr-axSpA patients and if left untreated, nr-axSpA may progress to AS. It should be noted however that while a subset of patients with nr-axSpA may have early AS, it is currently unknown what proportion of patients with nr-axSpA will progress to AS. It may take years from the onset of inflammatory back pain symptoms until the appearance of radiographic sacroiliitis and there are no established criteria to identify patients who are likely to progress. Nevertheless, the burden of disease on patients can be equally severe in the presence or absence of radiographic sacroiliitis and early therapeutic intervention may potentially impact the natural history of the disease progression.*
>
> *Non-steroidal anti-inflammatory drugs (NSAIDs) are currently recommended for patients with axSpA, including those with nr-axSpA. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine are sometimes used but have demonstrated minimal efficacy in treating axSpA. Thus, there is an unmet medical need for patients with nr-axSpA whose disease is not responsive to NSAIDs.*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One Phase III study (B1801031)
- Literature references.

3.2. Paediatric data

The submission did not include paediatric data and the extended indication is not sought for paediatric patients.

3.3. Good clinical practice

The clinical study report for B1801031 included a statement that the study was conducted in accordance with GCP guidelines as well as local ethical and regulatory requirements.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

There were no submitted pharmacokinetic studies.

4.2. Summary of pharmacokinetics

The following information has been taken and summarised from the approved PI.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH2 and CH3 regions but not the CH1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. Etanercept is now manufactured using a serum-free process.

4.2.1. Absorption

Etanercept is slowly absorbed from the site of subcutaneous (SC) injection, reaching maximum concentration between 24 and 96 hours after a single dose. The absolute bioavailability is 76% as calculated in a population pharmacokinetic analysis of several studies. With twice weekly doses, it is anticipated that steady-state concentrations may be two to five fold greater than those observed after single doses. After a single SC dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was 1.65±0.66 mg/L, and area under the curve was 235±96.6 mg.hr/L. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

4.2.2. Distribution

A bi-exponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 L, while the volume of distribution at steady state is 10.4 L. After continued dosing of RA patients (n = 25) with Enbrel for 6 months with 25 mg twice weekly, the median observed level was 3.0 mg/L (range 1.7 to 5.6 mg/L).

4.2.3. Excretion

Etanercept is cleared slowly from the body. The half-life is approximately 80 hours. Clearance is approximately 0.066 L/hr in patients with RA, somewhat lower than the value of 0.11 L/hr observed in healthy volunteers. Additionally, the pharmacokinetics of etanercept in rheumatoid arthritis patients, plaque psoriasis and ankylosing spondylitis patients are similar.

Serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg Enbrel powder for injection once weekly and those treated with 25 mg Enbrel powder for injection twice weekly. A single 50 mg/mL injection of Enbrel was also found to be bioequivalent to two simultaneous injections of 25 mg/mL. The mean (± standard deviation) Cmax, Cmin and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L and 297 ± 166 mg.h/L, respectively, for patients treated with 50 mg Enbrel once weekly (n = 21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L and 316 ± 135 mg.h/L for patients treated with 25 mg Enbrel twice weekly (n = 16). Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between men and women.

No formal pharmacokinetic studies have been conducted to examine the metabolism of etanercept or the effects of renal or hepatic impairment. Methotrexate has no effect on the pharmacokinetics of etanercept. The effect of Enbrel on the human pharmacokinetics of methotrexate has not been investigated.

In the Clinical Overview, the sponsor stated that: Population pharmacokinetic analyses in adults have not identified pharmacokinetic differences that can be linked to specific disease observed in the subjects studied. These data were based on patients with rheumatoid arthritis and ankylosing spondylitis (Zhou et al 2011).

4.2.4. Pharmacokinetics in other special populations

Elderly (> 65 years)

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

4.3. Evaluator's overall conclusions on pharmacokinetics

There was no new clinical pharmacology data submitted. There is no reason to believe that the PK of etanercept would be altered in the proposed new patient population compared to those adult populations already studied.

The formulation of etanercept used in Study B1801031 is the same as the 50 mg/mL pre-filled syringe that is currently approved in the EU. The dosage regimen used in Study B1801031 (50 mg SC once weekly) is the same as that approved for the treatment of adults with RA, AS, psoriatic arthritis, or psoriasis.

Evaluators comment: As the data were not available to the evaluator, the sponsor needs to confirm that the formulation of etanercept registered in Australia is the same as that used in Study B1801031.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were no submitted pharmacodynamic studies.

5.2. Summary of pharmacodynamics

The following information is taken from the approved PI.

Etanercept binds specifically to tumour necrosis factor alpha (TNFα) and blocks its interaction with cell surface TNFα receptors.

Pro-inflammatory molecules that are linked in a network controlled by TNF mediate much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNF receptor, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biological responses controlled by additional downstream molecules (for example, cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

5.3. Evaluator's overall conclusions on pharmacodynamics

There were no new clinical pharmacology data submitted.

Anti-etanercept antibodies were not assessed in the Study B1801031.

6. Dosage selection for the pivotal studies

There is no proposed change to the approved dosage as the dosage regimen used in Study B1801031 was the approved regimen of 50 mg SC once weekly.

7. Clinical efficacy

7.1. Non-radiographic axial spondyloarthritis

7.1.1. Pivotal efficacy study

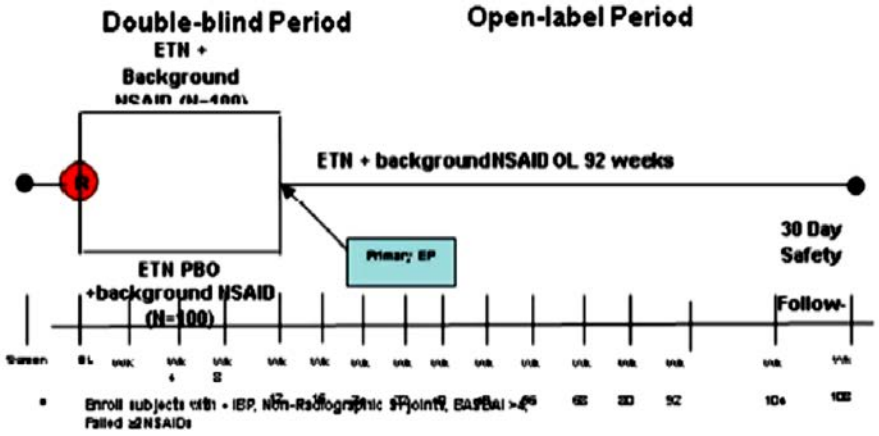
7.1.1.1. Study B1801031

7.1.1.1.1. Study design, objectives, locations and dates

This was a Phase III, multicentre, 12 week double-blind, placebo-controlled, randomised study with a 92 week open label extension period, which evaluated the efficacy of etanercept on background NSAID therapy in adults with active AxSpA despite optimal NSAID therapy. Non-radiographic sacroiliitis was defined as those subjects who did not meet the modified New York (NY) criteria. The study was conducted between May 2011 and February 2013 at 48 centres in 14 countries in South America, east and west Europe and Asia.

After a 4 week screening period, eligible subjects were randomised in a 1:1 ratio to ETN or placebo on a background of stable, optimal dose NSAID. Subjects were stratified based on positive or negative sacroiliitis on MRI. Subjects who successfully completed the 12 week double-blind period entered a 92 week open label period of with ETN and NSAID therapy (Figure 1). Subjects discontinuing early had a 30 day follow up.

Figure 1: Study B1801031 Study design and plan



BL=baseline, EP=endpoint, ETN= etanercept 50 mg, NSAID=nonsteroidal anti-inflammatory drugs, OL=Open-label, PBO=placebo, Wk=week.

The dossier included the interim CSR which contained data to the end of the 12 week double-blind and 12 week open label periods (24 weeks total). The study is ongoing to Week 92 of the open label period.

There was a central reading of X-rays and MRIs and a central laboratory for all samples (except ESR and urine pregnancy test which were performed using supplied kits). MRI scores were given by two independent readers with adjudication by a third if results were discordant.

The primary objective was to compare the efficacy of ETN against placebo in improving symptoms of early nr-AxSpA at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose.

Secondary objectives were:

- To assess the efficacy and safety of ETN and background NSAID over 104 weeks.
- To compare the effect of ETN 50 mg once weekly versus placebo on inflammation seen in MRI of the spine at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose.
- To compare the quality of life between those subjects treated with ETN 50 mg once weekly versus placebo over 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose.

An exploratory objective was to evaluate the effect of ETN plus background NSAID on radiographic and MRI changes for up to 104 weeks.

7.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria were:

- Diagnosis of AxSpA, as defined by the ASAS criteria (Figure 2)[2], with a duration of symptoms of > 3 months and < 5 years.
- Active symptoms defined by a BASDAI ≥ 4 at the screening.

[2] The ASAS classification criteria for axial spondyloarthritis requires patients to have ≥3 months of back pain and age of onset <45 years. Additional requirements are EITHER sacroiliitis on imaging plus 1 or more SpA features OR HLA-B27 plus 2 or more SpA features. SpA features include: inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's or colitis, good response to NSAIDs, family history of SpA, HLA-B27 and elevated CRP. Sacroiliitis on imaging required active inflammation on MRI highly suggestive of sacroiliitis associated with SpA or defined radiographic sacroiliitis according to the Modified New York criteria (Figure 2).

- Axial symptoms of back pain with a less than favourable response to current intake of NSAID at the optimal dose as determined by the Investigator. Subjects should have failed at least 2 NSAIDs (including the current one) taken separately at the optimal dose with a total combined duration of > 4 weeks.
- Taking a stable dose of NSAID for at least 14 days before baseline.
- ≥ 18 years and < 50 years.
- No contraindication to MRI examination, able to self-inject drug and store injectable study drug under refrigerated conditions.
- Negative serum pregnancy test and use of effective contraception.
- Adequate screening for TB in accordance with local country guidelines.
- In Germany only: subjects who were not eligible to get new spine and/or pelvic X-rays due to local regulations should have had these X-rays taken within 12 months prior to screening. The central reader was to consider the X-rays to be acceptable for evaluation of sacroiliitis, mSASSS and RASSS.

Figure 2: ASAS Classification criteria for Axial Spondyloarthritis in patients with ≥3 months of Back pain and Age onset <45 years.

Sacroiliitis on imaging* Plus ≥1 SpA Feature #	OR	**Positive HLA-B27 Plus ≥2 other SpA Features #**

# SpA Features	*Sacroiliitis on Imaging
Inflammatory back pain	Active inflammation on MRI highly suggestive of sacroiliitis associated with SpA
Arthritis	Defined radiographic sacroiliitis according to the Modified New York criteria
Enthesitis (heel)	
Uveitis	
Dactylitis	
Psoriasis	
Crohn's or Colitis	
Good response to NSAIDs	
Family history of SpA	
HLA-B27	
Elevated CRP	

Reference: Sieper J, Rudwaleit M, Baraliakos X, et al. Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68(Suppl 2):ii1-44.
Abbreviations: AxSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; SpA=spondyloarthritis.

Exclusion criteria were:

- Previous treatment with TNFα inhibitor or other biologic agent or immunosuppressive agent.
- Any orthopedic or medical condition that could cause chronic back pain such as spondylodiscitis, tumour or advanced discopathy.

- IBD flare within 6 months, current or recent episodes of uveitis within 6 months.
- Radiological evidence of sacroiliitis Grade 3-4 unilaterally or grade ≥ 2 bilaterally as defined by the Modified NY Criteria for ankylosing spondylitis[3]. Only results from the central imaging reader determined eligibility. In all countries (except Germany) historical X-rays obtained within 4 months of screening may have been utilised, however, these subjects with historical X-rays had to exhibit radiological sacroiliitis Grade 0-1 unilaterally or Grade 0 bilaterally. In Germany historical X-rays were accepted if obtained within 12 months of screening (country specific protocol amendment).

Evaluators Comment: It is therefore assumed from these criteria that 'non-radiographic' sacroiliitis would be sacroiliitis on screening X-ray of either Grades 0, 1 or 2 unilaterally or Grades 0 or1 bilaterally. However if historical X-rays were used, the grading requirement was lower at 0-1 unilaterally or Grade 0 bilaterally. The sponsor has been asked to confirm this.

- Known or suspected allergy, hypersensitivity, or contraindication to ETN or related compounds.
- Concurrent treatment with more than one NSAID or the dose had changed within 14 days at baseline (aspirin use at daily doses up to 325 mg for cardiovascular protection was allowed).
- DMARDS other than methotrexate, sulfasalazine and hydroxychloroquine within 4 weeks of baseline.
- Dose of prednisone > 10 mg/day (or equivalent) or had a dose changed, or had received an intra-articular, intravenous, intramuscular, or SC corticosteroid within 4 weeks before baseline.
- Pregnancy or breastfeeding.
- Current or recent (within 2 years) active TB infection or untreated latent TB.
- TB chemoprophylaxis during screening with ALT or AST > 2x ULN.
- Serious infection within 1 month or current active infection.
- Live vaccine within 4 weeks.
- Abnormal haematology or blood chemistry: white blood cell (WBC) count ≤ 3.5 x 10^9/L; haemoglobin ≤ 85 g/L or ≤ 5.3 mmol/L; haematocrit ≤ 27%; platelet count ≤ 125 x 10^9/L; serum creatinine level ≥ 175 µmol/L (≥ 1.98 mg/dL); AST or ALT level ≥ 2 x ULN.
- Clinically relevant medical history including: hepatitis B; hepatitis C; HIV; Class III or IV heart failure; uncontrolled hypertension; MI, CABG or PTCA within 12 months; unstable angina within 6 months; severe pulmonary disease; blood dyscrasias; multiple sclerosis or other demyelinating disorder; history of cancer; uncontrolled diabetes mellitus; rheumatoid arthritis, SLE, scleroderma or polymyositis; cutaneous ulcers; and liver cirrhosis or fibrosis.

7.1.1.1.3. Study treatments

Treatment was with weekly ETN 50 mg SC injections or matching placebo. All subjects received optimal anti-inflammatory theray. Eligible subjects who continued into the open-label period were treated with ETN 50 mg SC injection weekly plus a stable background NSAID at optimal

[3] Modified New York criteria grades for radiographic sacroiliitis. Grade 0: normal. Grade 1: suspicious changes. Grade 2: minimal abnormality - small localised areas with erosion or sclerosis, without alteration in the joint width. Grade 3: unequivocal abnormality - moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis. Grade 4: severe abnormality - total ankylosis.

dose. ETN or placebo was provided in 1.0 mL (50 mg/mL) prefilled syringes which was stored under refrigerated conditions.

Only one NSAID was allowed at a time with a stable dose through the double-blind period. The NSAID could be ceased or lowered during open label treatment. DMARDs of sulphasalazine, hydroxychlorquine or methotrexate were allowed at a stable dose during the double-blind period. Oral corticosteroids needed to be ≤ 10 mg/day of prednisolone.

Prohibited medications included: live vaccines; other TNF antagonists, biologics or immunosuppressants; multiple NSAIDs; DMARDs other than those listed above; IV, IM or SC corticosteroids (CCS); intra-articular CCS during double-blind treatment; and long acting analgesics or narcotics.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was the proportion of subjects who achieved Assessment in Ankylosing Spondylitis (ASAS) 40 at Week 12. ASAS 40 was derived from 4 AS assessments: subject assessment of disease activity, pain, physical function and inflammation. If a subject had a missing evaluation for any 1 of the 4 AS assessment domains, the subject was to be considered a non-responder for analysis.

ASAS 40 responders were defined as subjects who satisfied the following criteria:

1. An improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 cm scale (converted from 0 to 100 mm) or an improvement of 100% for those domains that had a baseline score < 2 in at least 3 of the following four domains:

    a. Subject Assessment of Disease Activity,

    b. Mean of subject assessment of nocturnal pain and total back pain,

    c. Function represented by the BASFI score,

    d. Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.

2. No worsening at all in any of the domains.

Other efficacy endpoints included:

a. Proportion of subjects who achieve ASAS 40 at time points other than 12 weeks.

b. Proportion of subjects who achieve ASAS 20[4].

c. Proportion of subjects who achieve ASAS 5/6[5].

[4] ASAS 20 responders were defined as subjects who satisfied the following criteria:

- An improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 cm scale (converted from 0 to 100 mm) in at least 3 of the following 4 domains:
  - Subject Assessment of Disease Activity,
  - Mean of subject assessment of total back pain,
  - Function represented by the BASFI score,
  - Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.
- Absence of deterioration (of at least 20% and absolute change of at least 1 unit) in the potential remaining domain.

[5] The ASAS 5/6 required a 20% improvement in 5 of 6 criteria - the 4 domains of the ASAS response, a measure of spinal mobility (lateral spinal flexion), and hsCRP.

d. Changes from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS)[6].

e. Proportion of subjects with ASAS partial remission[7].

f. Time to ASAS partial remission.

g. Changes from baseline in Subject Assessment of Disease Activity (visual analogue scale [VAS])[8].

h. Changes from baseline in the VAS Physician Global Assessment (PGA)[9].

i. Changes from baseline in VAS nocturnal and total back pain over time.

j. Changes from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI)[10] and its components.

k. Changes from baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[11] and its components.

l. Proportion of subjects who achieved BASDAI 20 and BASDAI 50.

m. Changes in Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G)[12].

n. Changes from baseline in spinal mobility as measured by Bath Ankylosing Spondylitis Metrology Index (BASMI)[13] (and its individual components), and occiputo-wall distance, and chest expansion.

o. Changes in inflammation at Week 12 as measured by MRI of the spine at Week 12.

p. Changes from baseline in tender and swollen joint counts (44 count).

q. Changes from baseline in dactylitis and enthesitis score (Maastricht Anklyosing Spondylitis Entheses Score [MASES]).

r. Changes from baseline in the acute phase reactants high sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR).

s. Health Outcomes Assessments using the following instruments: WPAI, HADS, EQ-5D, SF-36, ASQoL, AS-WIS, MOS, MFI, PASS, and MCII.

t. Exploratory endpoints included:

[6] Assessment in Ankylosing Spondylitis (ASDAS) scores were calculated from the following:
1. Total back pain (BASDAI question 2),
2. Subject Assessment of Disease Activity,
3. Peripheral pain/swelling (BASDAI question 3),
4. Duration of morning stiffness (BASDAI question 6),
5. hsCRP in mg/L (or ESR)

[7] Partial remission was defined as a score of 2 or less (on a scale of 0-10 cm) for each of the 4 domains.
[8] Subjects assessed their overall disease activity over the last 48 hours using a pain scale between 0 mm (none) and 100 mm (severe), which corresponded to the magnitude of their pain.
9 The Investigator estimated the subject's overall disease activity over the previous 48 hours (this was independent of the Subject Assessment of Disease Activity) using a scale between 0 mm (none) and 100 mm (severe).
[10] The BASFI was a set of 10 questions designed to determine the degree of functional limitation in those with AS. It used a VAS and assessed level of ability.
[11] The BASDAI consisted of a 0 through 100 mm scale (zero being no problem and 100 being very severe) which was used to answer 6 questions pertaining to the 5 major symptoms of AS: fatigue; spinal pain; joint swelling and pain; morning stiffness duration; morning stiffness severity.
[12] The BAS-G was a 2 question assessment evaluating the effect of AS on the subject's wellbeing over the last week and last 6 months.
[13] The BASMI consists of 5 clinical measurements to reflect axial status: intermalleoloar distance, cervical rotation, modified Schober's test, lateral flexion and tragus to wall distance.

u. Changes from baseline in inflammation of the SI joint at 12 weeks, and in the spine and SI joint at 48 weeks and 104 weeks as measured by MRI. Scoring of the SI joints used the SPARCC[14] method and also the AS spine MRI score (ASspiMIR-a).

v. Changes from baseline in spinal X-ray at 104 weeks as measured by Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and Radiographic Ankylosing Spondylitis Spine Score (RASSS).

7.1.1.1.5. Randomisation and blinding methods

Subjects were randomised in a 1:1 ratio, stratified by MRI results (positive or negative sacroiliitis) using an IVRS.

7.1.1.1.6. Analysis populations

Primary analysis was on the modified intent-to-treat (mITT) population which was defined as all randomised subjects who took at least one dose of study medication, had at least one on-therapy evaluation and met the ASAS classification criteria for AxSpA. Data were analysed using the LOCF.

If more than 20% of the items on a scale were missing the total score was considered missing. If 20% or less items were missing a derived total score was calculated using the average of available items.

7.1.1.1.7. Sample size

The sponsor assumed an ASAS 20 response rate of at least 55% in the ETN + NSAID group and up to 30% in the placebo + NSAID group based on historical data. With this response, a sample of 100 subjects per group would give the study 90% power at a 0.05 significance level (2 sided). The sponsor stated that the ASAS 40 response rate would be lower but expected the difference between groups to still be 25% which gave the sample size of 200 the same power.

7.1.1.1.8. Statistical methods

The comparison between 2 treatment groups was performed using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by positive or negative sacroiliitis on MRI and geographic region. The test was 2 sided at a 0.05 significance level. A sensitivity analysis was conducted where subjects who discontinued before Week 12 were counted as non-responders (instead of using an LOCF). A further sensitivity analysis used a generalised estimating equations (GEE) model.

It was noted that there was an alteration to the planned analysis of the primary endpoint in relation to EMA guidelines on AS. The sponsor made the following statement:

> *The primary endpoint was the ASAS 40 response (that is, responder or non-responder) at Week 12. This ASAS 40 and all other ASAS endpoints were planned in the SAP using the 2005 EMA guideline on clinical investigation of medicinal products for the treatment of AS. After data base lock, it was brought to the Sponsor's attention by external experts that current convention was to use the 2009 EMA guideline on clinical investigation of medicinal products for the treatment of AS, where 'nocturnal pain and total back pain' was replaced by 'nocturnal or total back pain'. Therefore, following advice from clinical experts consulted, a decision was made to use the more recent guidelines including 'total back pain'. For completeness the primary endpoint was analyzed both ways (in accordance with 2005 and 2009 EMA guidelines).*
>
> *Secondary endpoints were analysed like the primary endpoint using the CMH chi-square test. Time to partial remission used the Kaplan-Meier method. Continuous variables were analysed using ANCOVA. There were no adjustments for multiplicity.*

[14] SPARCC is the Spondyloarthritis Research Consortium of Canada.

There were 4 protocol amendments. Amendments 1 and 3 were specific for Germany and related to limiting X-ray exposure. Amendment 2 changed the primary endpoint from response rate on ASAS 20 to ASAS 40. Amendment 4 updated standard safety language.

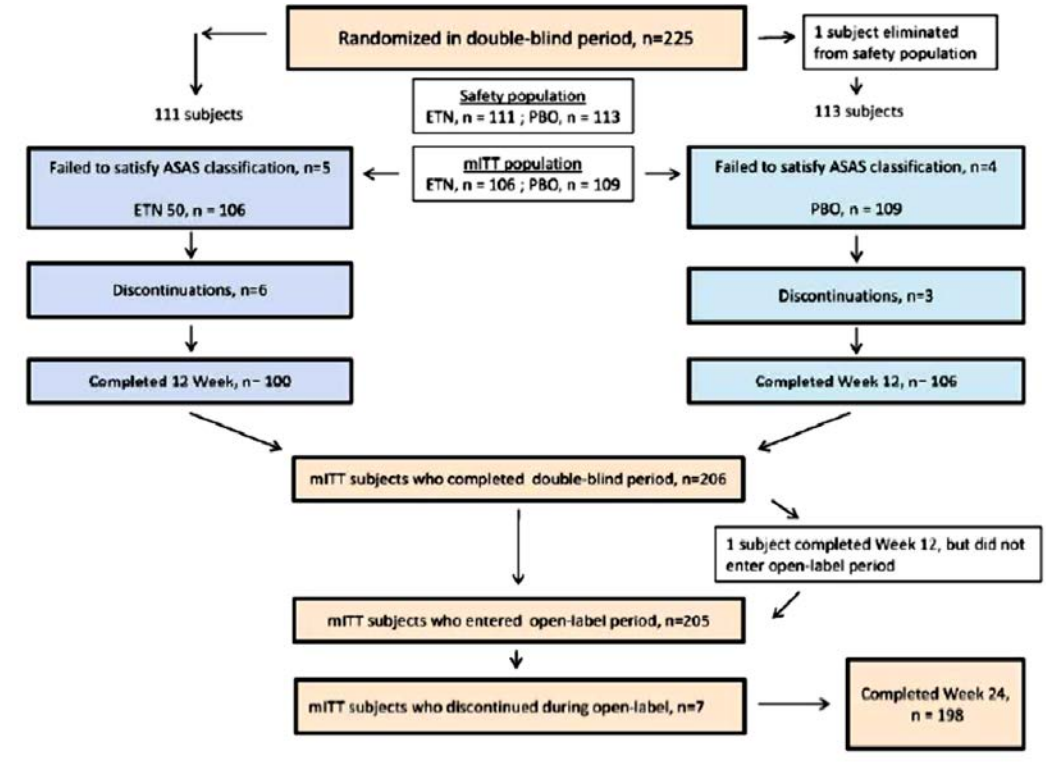
7.1.1.1.9. Participant flow

There were 369 subjects with SI joint X-rays read centrally, 71 did not meet eligibility criteria as they had AS by the Modified NY Criteria and 73 did not have AS on X-ray (that is, met the X-ray criteria) but did not meet other inclusion/exclusion criteria. There were 225 subjects randomised with 224 receiving study drug, 111 in the ETN 50 mg and 113 in the placebo group (Safety Population). For the 225 randomised subjects, the SI joint findings were as follows: 80 with Grade 2 unilateral; 53 with Grade 1 bilateral; 47 with Grade 0 bilateral; and 45 with Grade 1 unilateral.

There were 15 subjects who discontinued during the double-blind period (9 [8.1%] and 6 [5.3%] in the ETN and placebo groups, respectively), 209 subjects completed double-blind treatment and 208 entered the open label period. At Week 24 there were 200 subjects (98 and 102 from the ETN and placebo groups, respectively) with 4 subjects from each original group discontinuing. The reasons for discontinuation of the double-blind and open label treatment were similar between groups.

The mITT population excluded 10 subjects (4.4%) who did not meet the ASAS classification for axial SpA (Figure 2) leading to a total of 215 subjects (106 and 109 in the respective groups) with 206 completing the double-blind and 198 completing the week 24 open label period (Figure 3).

Figure 3: Subject disposition



Source: Section 14.1, Double-blind: Table 14.1.1.1, Table 14.1.1.3, and Table 14.1.1.5, and Open-label: Table 14.1.2.4 and 14.1.2.5, and Appendix 16.5 (file note).
ASAS= assessment in ankylosing spondylitis, ETN= etanercept 50 mg, mITT=modified intent-to-treat, n=number of subjects with data.

7.1.1.1.10. Major protocol violations/deviations

A listing of protocol deviations showed that there were 5 subjects (2.2%) who took > 1 DMARD and 10 subjects (4.4%) who did not meet ASAS criteria. Many subjects did not have measurements performed properly (40%) although this was not exclusionary from the per protocol (PP) population. The PP population included 206 (91.5%) subjects (Table 1).

Table 1: Study B1801031 Subject populations

	ETN	PBO	Total
Double-blind period			
Full analysis population	111	114	225
Safety population	111	113	224
mITT population[a]	106	109	215
Per protocol population	101	103	204
mITT population excluding site 1004	102	105	207
Open-label period	**ETN/ETN**	**PBO/ETN**	**Total**
Safety population	102	106	208
mITT population[b]	100	105	205

[a]Two additional subjects (one in ETN group and one in PBO group) were excluded from the mITT population from most of the efficacy analyses. Subject 10041004 did not technically meet the definition for an on-therapy evaluation because the subject did not have an assessment within 15 days of dose of study drug. Subject 10291002 did not have baseline BASFI data due to a data entry error.
[b]The open-label mITT population was not defined in the protocol. However, any subject in the original mITT population with Week 12 data or later efficacy and dosing in the open-label period was included as 'mITT' for the open-label period.
BASFI= Bath Ankylosing Spondylitis Functional Index, ETN=etanercept 50 mg weekly, mITT=modified intent-to-treat, N=number of subjects randomized, PBO=placebo.

The analysis of the primary endpoint was conducted on 213 of the 215 subjects in the mITT population. There were 2 subjects excluded, one from each treatment group. One subject had a single post-baseline assessment at a discontinuation visit 28 days post their only ETN dose which was outside the 15 day assessment window. The second did not have a baseline BASFI value.

There was one site in Taiwan which was noted to have GCP non-compliance issues. This site included 4 subjects and primary and key secondary endpoint analysis was also conducted excluding these subjects (n = 209).

7.1.1.1.11. Baseline data

The groups were balanced on baseline demographic and disease characteristics. In the mITT population, the mean age was 32 years, 60% were male, 73% white, 22% Asian with a mean BMI of 25 kg/m^2. Most subjects (82% of the ETN group and 80% of the placebo group) met inclusion criteria based on ASAS imaging rather than clinical criteria (that is, had a positive MRI for sacroiliitis with at least one SpA feature).

Evaluators comment: The sponsor has been asked to verify the gradings on X-ray of the included subjects to ensure that all did meet the criteria of having 'non-radiographic' axial SpA.

The mean disease duration was 2.4 years, mean baseline BASDAI total score was 5.96 (SD 1.8) and mean baseline BASFI score was 4.0 (SD 2.5). Mean baseline hsCRP level was 6.6 (SD 10.5). The mean baseline SPARCC MRI SI score was 7.9 (SD 9.9) and 81% of subjects were positive for sacroiliitis on MRI by ASAS criteria. Between 23 and 25% of subjects reported prior use of DMARDs. Concomitant medication use during the study was similar between groups for DMARDs (19-21%) but higher in the placebo group for CCS (10% compared to 5% in the

etanercept group. Scoring of NSAIDs based on potency showed similar levels between baseline and end of double-blind treatment.

Study drug compliance was reported as high with all except one subject with ≥ 80% compliance and 100% compliance reported in 88% of subjects during double-blind treatment. Reported compliance during the open label period was 98%.

7.1.1.1.12. Results for the primary efficacy outcome

In the mITT population with LOCF, the proportion of subjects achieving ASAS 40 at Week 12 was 32.4% versus 15.7% in the ETN and placebo groups respectively. The difference of 16.6% (95% CI: 5.4, 27.9) was significant (p = 0.0062). When the data were analysed using the 2009 EMA guideline criteria, the week 12 response rates were similar: 33.3% versus 14.8% with a significant difference of 18.5% (95% CI: 7.3, 29.8, p = 0.0023) (Table 2).

Table 2: Proportion of subjects achieving ASAS 40 (mITT Population, LOCF)

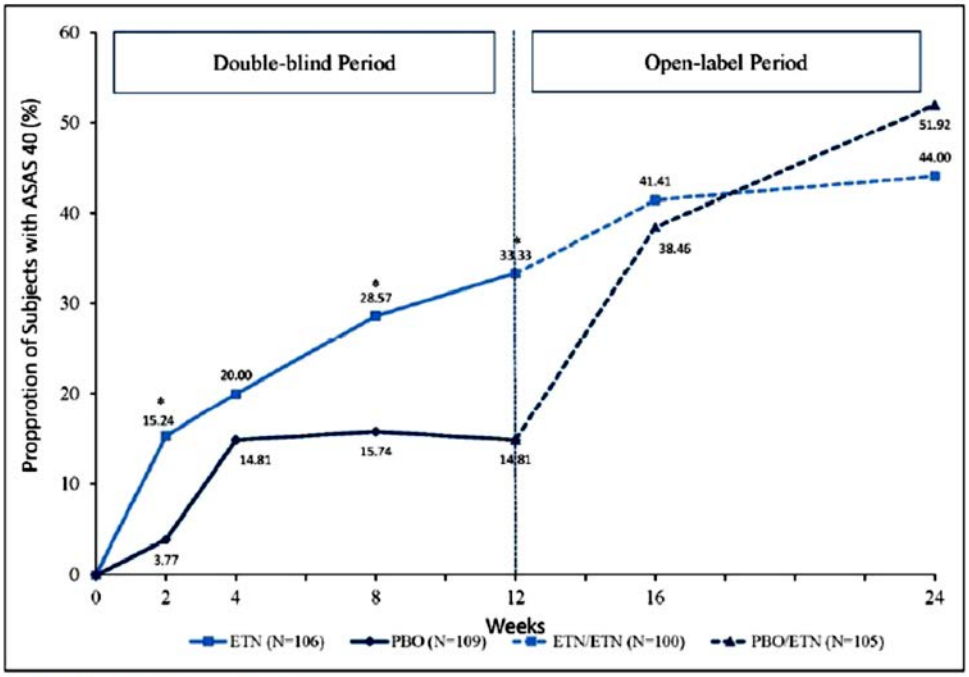
Double-blind Period	**N=105**	**N=108**		
Time Point	**ETN n/N (%)**	**PBO n/N (%)**	**P-value (CMH)***	**Difference in proportions % (95% CI)**
Week 2	16/105 (15.24)	4/106 (3.77)	0.0059	11.46 (3.69, 1 9.24)
Week 4	21/105 (20.00)	16/108 (14.81)	0.3786	5.19 (-4.98, 15.35)
Week 8	30/105 (28.57)	17/108 (15.74)	0.0304	12.83 (1.79, 23.87)
Week 12	35/105 (33.33)	16/108 (14.81)	0.0023	18.52 (7.29, 29.75)
Open-label Period[a]	**N=100**	**N=104**		
Time Point	**ETN/ETN n/N (%)**	**PBO/ETN n/N (%)**		
Week 16	41/99 (41.41)	40/104 (38.46)	NA	NA
Week 24	44/100 (44.00)	54/104 (51.92)	NA	NA

*Cochran-Mantel-Haenszel chi-square test, stratified by positive/negative sacroiliitis by MRI and geographic region.
[a]All subjects were receiving etanercept 50 mg weekly in the open-label period
ASAS= Assessment in Ankylosing Spondylitis, CMH=Cochran-Mantel-Haenszel, CI=confidence interval, ETN=etanercept 50mg weekly, LOCF=last observation carried forward, mITT=modified intent-to-treat, MRI= magnetic resonance imaging, n=number of subjects with an observation, N=the total number of subjects in the treatment group in the indicated population, NA=not assessed, PBO=placebo.

Evaluators comment: the achieved response rate difference between active and placebo groups of 17% was less than the anticipated rate of 25%.

By Week 24 the ASAS 40 response rates were 44.0% and 51.9% in the ETN/ETN and placebo/ETN groups, respectively (Table 2). Achievement of ASAS 40 over time is shown in Figure 4.

Figure 4: Study B1801031 Proportion of subjects achieving ASAS 40 mITT population (double-blind and open-label periods)



*p<0.05 (Double-blind period only).
ASAS= Assessment in Ankylosing Spondylitis, ETN=etanercept 50mg weekly, mITT=modified intent-to-treat, N= number of subjects randomized, PBO=placebo.

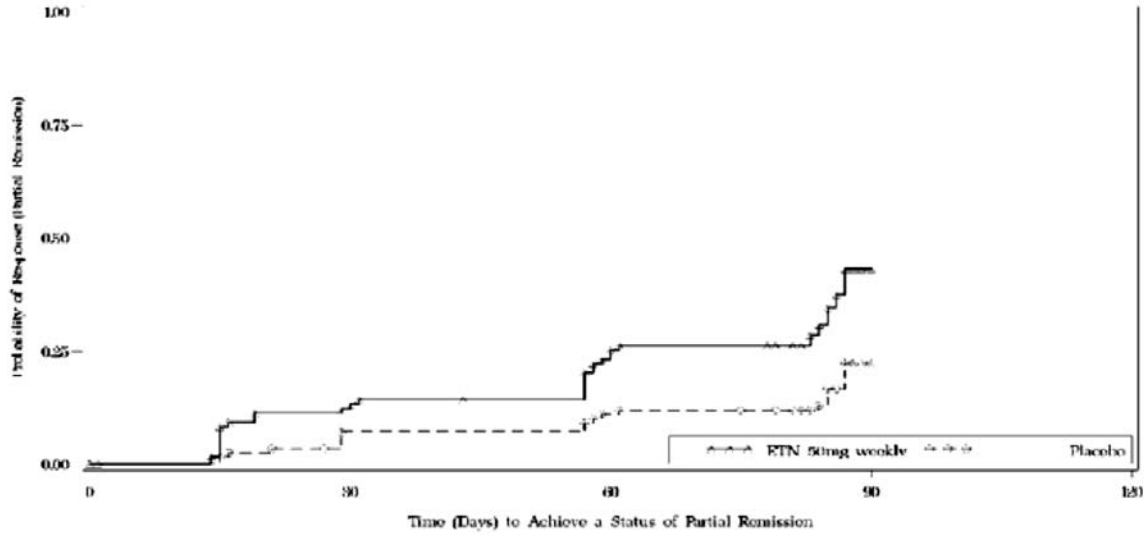
Evaluators comment: The response in the placebo group who switched to etanercept in the open label period is higher than in the ETN/ETN group with a rapid response in the first 4 weeks of treatment. The sponsor has been asked to comment on these findings.

7.1.1.1.13. Results for other efficacy outcomes

In the mITT population with LOCF, a significantly higher proportion of the ETN group achieved of ASAS 20 at Weeks 2 and 12, but not at Weeks 4 and 8. The rates in the ETN and placebo groups at Week 12 were 52.4% and 36.1%, respectively, with a difference of 16.3% (95% CI: 3.1, 39.4, p = 0.0195).

ASAS partial remission rates at Week 12 showed a significantly greater rate with etanercept with a between group difference of 12.8% (95% CI: 2.6, 23.1, p = 0.021). The Kaplan Meier plot of cumulative partial remission rates also shows a response in favour of etanercept (Figure 5).

Figure 5: Study B1801031 Cumulative partial remission (%) mITT population (double-blind period)



ETN=etanercept 50 mg weekly, mITT=modified intent-to-treat

Achievement of ≥ 20% improvement in 5 of 6 ASAS criteria followed a similar positive trend to ASAS 40 through double-blind and open label periods (Table 3).

Table 3: Study B1801031 Proportion of subjects achieving ASAS 5/6 by time point (mITT population LOF)

Double-blind Period[a]	N=103	N=107		
Time Point	ETN n/N (%)	PBO n/N (%)	P-value (CMH)*	Difference in proportions % (95% CI)
Week 2	16/102 (15.69)	3/105 (2.86)	0.0021	12.83 (5.09, 20.57)
Week 4	24/103 (23.30)	9/107 (8.41)	0.0020	14.89 (5.18, 24.60)
Week 8	34/103 (33.01)	12/107 (11.21)	<0.0001	21.79 (10.92, 32.67)
Week 12	34/103 (33.01)	11/106 (10.38)	<0.0001	22.63 (11.85, 33.41)
Open-label Period[a]	**N=97**	**N=103**		
Time Point	ETN/ETN n/N (%)	PBO/ETN n/N (%)		
Week 16	35/97 (36.08)	35/103 (33.98)	NA	NA
Week 24	39/97 (40.21)	43/103 (41.75)	NA	NA

*Cochran-Mantel-Haenszel chi-square test, stratified by positive/negative sacroiliitis by MRI and geographic region.
[a]All subjects were receiving etanercept 50 mg weekly in the open-label period.
ASAS= Assessment in Ankylosing Spondylitis, CMH=Cochran-Mantel-Haenszel, CI=confidence intervals, ETN=etanercept 50 mg weekly, LOCF=last observation carried forward, MRI=magnetic resonance imaging, mITT=modified intent-to-treat, n=number of subjects with an observation, N=the total number of subjects in the treatment group in the indicated population, NA=not assessed, PBO=placebo.

There were multiple other secondary endpoints, the results of which are summarised in Table 4.

Table 4: Study B1801031 Summary of selected secondary end points

Variable	Week 12			Week 24	
	ETN	Placebo	p-Value	ETN/ETN	Placebo/ ETN
Clinical Outcomes - mITT	N=106	N=109		N=100	N=105
ASAS 20, % of subjects	52.38	36.11	0.0195	65.00	71.15
ASAS Partial Remission, % of subjects	24.76	11.93	0.0209	32.00	42.86
ASAS 5/6, % of subjects	33.01	10.38	<0.0001	40.21	41.75
Subject Assessment Disease Activity, mean change (% improvement)	-2.06 (35.4)	-1.26 (21.9)	0.0102	-2.92 (50.6)	-3.21 (55.5)
Nocturnal back pain, mean change (% improvement)	-1.96 (35.3)	-1.03 (19.2)	0.0091	-2.79 (50.4)	-3.25 (60.4)
Total back pain, mean change (% improvement)	-1.99 (35.9)	-1.12 (20.5)	0.0064	-2.76 (50.0)	-2.92 (53.7)
BASDAI morning stiffness (2 items), mean change (% improvement)	-2.26 (34.6)	-1.43 (22.2)	0.0134	-3.71 (57.1)	-4.00 (61.9)
BASMI Lateral Side Flexion, mean change (% improvement)	1.63 (10.3)	0.45 (2.7)	0.0450	1.97 (12.4)	0.92 (5.5)
hsCRP, mean change (% improvement)	-2.98 (43.7)	0.14 (2.2)	0.0038	-4.62 (64.9)	-4.56 (72.0)
ASDAS hsCRP Inactive Disease, % of subjects	40.00	17.43	0.0004	42.86	58.10
ASDAS hsCRP, mean change (% improvement)	-1.10 (36.6)	-0.49 (16.6)	<0.0001	-1.48 (49.0)	-1.55 (52.7)
BASDAI 50, % of subjects	43.81	23.85	0.0029	50.00	62.86
BASDAI Total score, mean change (% improvement)	-1.96 (32.7)	-1.31 (22.0)	0.0186	-2.86 (48.0)	-3.26 (54.5)
BASFI Total score, mean change (% improvement)	-1.41 (33.4)	-0.84 (21.6)	0.0164	-1.89 (44.5)	-1.85 (48.3)
PGA, mean change (% improvement)	-2.74 (48.5)	-2.04 (40.0)	0.0156	-3.66 (63.9)	-3.26 (63.0)
BASMI, mean change (% improvement)	-0.31 (22.7)	-0.25 (21.3)	0.6871	-0.48 (35.7)	-0.32 (27.1)
Imaging endpoints - mITT					
SPARCC Sacroiliac Joint Score, mean change (% improvement)	-3.77 (46.9)	-0.84 (10.9)	<0.001	NA	NA
SPARCC-Spine 6 Discovertebral Units (DVU) Total Score, mean change (% improvement)	-2.12 (45.4)	-1.16 (33.4)	0.0414	NA	NA
ASspiMRI-a Total Score, mean change (% improvement)	-0.73 (40.9)	-0.33 (25.6)	0.0132	NA	NA

Abbreviations: ASAS=Assessment in Ankylosing Spondylitis; ASDAS=Ankylosing Spondylitis Disease Activity Score; ASspiMRIa=Ankylosing Spondylitis spine MRI score for activity; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index; DVU=Discovertebral units; ETN=etanercept; hsCRP=highly sensitive C-reactive protein; mITT=modified intent-to-treat, N=the total number of subjects in the treatment group in the indicated population; NA=not assessed; PGA=physician global assessment; SPARCC=Spondyloarthritis Research Consortium of Canada.

Components of ASAS.

For subject assessment of disease activity, the mean percentage change from baseline in the VAS score was 35.4% versus 21.9% in the ETN and placebo groups, respectively. By week 24, the mean change from baseline was similar at 50.6% and 55.%% in the ETN/ETN and placebo/ETN groups, respectively. The mean change from baseline in VAS for nocturnal back pain and total back pain as well as the BASDAI level of morning stiffness all showed significant changes in favour of etanercept (Table 4). At Week 12, the change from baseline in BASMI lateral side flexion score was 10.3% and 2.7% , respectively, with an adjusted mean difference of 1.18 (95% CI: 0.03, 2.33) which just reached statistical significance (p = 0.045). At Week 24, the improvement in lateral side flexion was 12.4% and 5.5% in the ETN/ETN and placebo/ETN groups respectively. ETN treatment led to a positive response in hsCRP with an adjusted mean difference at Week 12 of -3.12 (95% CI: -5.23, -1.02, p = 0.0038).

ASDAS.

The proportion of subjects with ASDAS hsCRP 'inactive disease' was greater with ETN (40.0% versus 17.4%) at Week 12 (p = 0.004). This was maintained to week 24 (47.0% and 58.1%). The mean change from baseline in ASDAS hsCRP at Week 12 showed a significant difference in favour of ETN (-0.6, 95% CI: -0.83,-0.37, p < 0.001).

Response on the BASDAI total score followed similar trend with a mean percentage change from baseline to Week 12 of 32.7% and 22.0% in the etanercept and placebo groups, respectively. At Week 24 the response showed ongoing improvement (48.0% and 54.5%). The proportion of subjects achieving BASDAI 50 was 43.8% versus 23.9% (difference 19.96%, 95% CI: 7.5, 32.4, p=0.003). The proportion responding was maintained to Week 24 in etanercept-treated subjects (50.0%) and increased in those switching to etanercept (62.9%).

Physical function

As measured by the BASFI total score physical function was significantly greater with etanercept at Week 12 with a mean percentage change from baseline of 33.6% versus 21.6% and an adjusted mean difference of -0.57 (95% CI -1.04, -0.11, p = 0.0164). There was some ongoing improvement to week 24 (mean change from baseline of 44.5% and 48.3%).

There was a small but statistically significant improvement in the Physician Global Assessment (PGA) VAS score (mean percentage change of 48.5% versus 39.6%, adjusted mean difference of -0.70, p=0.0156). This improved to week 24 (mean percentage change of 63.9% and 63.0%).

Spinal mobility

As measured by the BASMI total score found no statistically significant difference between groups at Week 12 (mean percent change from baseline of 22.7% versus 21.3%, adjusted mean difference -0.06, p = 0.687) (Table 5). There was a trend for improvement to Week 24 (mean percentage change from baseline of 35.7% and 27.1%). There were no statistically significant differences between group at Week 12 in the BASMI component scores (cervical rotation, tragus-to-wall distance, modified Schober's test, intermalleolar distance and lateral side flexion) nor in other mobility measures of chest expansion and occiput-to-wall test.

Table 5: Study B1801031 Change from baseline in BASMI total score by time point (mITT population LOCF)

Double-blind Period[a]						
Time Point	Treatment	n	Raw mean score (SD)	Change within group	Change between group	
				Adjusted mean (SE)*	Adjusted difference of mean (95% CI)*	P-values*
Baseline	ETN	104	1.36 (1.34)			
	PBO	109	1.17 (1.27)			
Week 2	ETN	103	1.24 (1.34)	-0.08 (0.12)	0.05 (-0.18, 0.28)	0.6741
	PBO	108	1.07 (1.09)	-0.13 (0.11)		
Week 4	ETN	103	1.00 (1.28)	-0.30 (0.12)	-0.10 (-0.33, 0.13)	0.3896
	PBO	109	0.98 (1.16)	-0.20 (0.11)		
Week 8	ETN	103	1.05 (1.35)	-0.36 (0.14)	0.04 (-0.22, 0.31)	0.7468
	PBO	109	0.89 (1.12)	-0.41 (0.13)		
Week 12	ETN	103	1.01 (1.31)	-0.31 (0.15)	-0.06 (-0.35, 0.23)	0.6871
	PBO	109	0.98 (1.20)	-0.25 (0.14)		
Open-label Period[b]						
Time Point	Treatment	n	Mean score (SD)	Change from baseline Mean (SE)		
Week 16	ETN/ENT	98	0.91 (1.25)	-0.44 (0.14)	NA	NA
	PBO/ETN	105	0.83 (1.14)	-0.35 (0.10)		
Week 24	ETN/ETN	98	0.87 (1.05)	-0.48 (0.13)	NA	NA
	PBO/ETN	105	0.86 (1.18)	-0.32 (0.10)		

*ANCOVA model used for 'adjusted' values and between group P-values: Change = baseline score + treatment + region + SI status.
[a] Source: Section 14.2, Double-blind: Table 14.2.1.351.
[b] Source: Section 14.2, Open-label: Table 14.2.2.200.
ANCOVA=analysis of covariance, BASMI=Bath Ankylosing Spondylitis Metrology Index, CI=confidence intervals, ETN=etanercept 50 mg weekly, LOCF=last observation carried forward, mITT=modified intent-to-treat, n=number of subjects with an observation, NA=not assessed, PBO=placebo, SD=standard deviation, SE=standard error, SI=sacroiliac.
Note: open-label period results include unadjusted mean changes and standard errors, no covariate adjustments was applied.

Imaging

Changes in inflammation using MRI of the spine was measured using the SPARCC score for the SI joint. The mean change from baseline to week 12 in this score was -3.77 and -0.84 in the ETN and placebo groups, respectively. The adjusted mean difference of -2.93 (95% CI: -4.16, -1.70) was statistically significant ($p < 0.001$) (Table 4). The SPARCC-Spine 6 discovertebral units (DVU) total score was also in favour of etanercept (adjusted mean difference of -0.96, 95% CI: -1.88, -0.04, $p = 0.041$) as was the ASspiMRI-a total score (Table 4).

Health outcomes.

For sites in Russia and the Czech Republic only certain questionnaires were translated (BASDAI, BASFI, Subject Assessment of Disease, total pain and nocturnal back pain assessments) resulting in lower numbers in some analyses.

Evaluators comment: The sponsor has been asked to clarify this issue, the numbers involved and if there was any impact on other outcomes.

The EuroQoL-5D VAS score was significantly improved with etanercept at Week 12 and showed ongoing improvement to Week 24 (Table 6). There was, however, no significant difference between groups at Week 12 in the proportion of subjects with a score >82 (26.2% versus 17.4%, $p = 0.148$) and the proportion remained steady to Week 24 (28-30%) (Table 7). There was no significant difference between groups at Week 12 in the EQ-4D utility score (difference 0.06, $p = 0.135$).

Table 6: Study B1801031 Change from baseline in EQ-5D VAS score (mm) by time point (mITT population, Observed Cases)

Double-blind Period[a]						
Time Point	Treatment	n	Raw mean score (SD)	Change within group Adjusted mean (SE)*	Change between group Adjusted difference of mean (95% CI)*	P-values*
Baseline	ETN	90	56.50 (21.00)			
	PBO	96	56.36 (20.61)			
Week 4	ETN	86	62.49 (20.76)	4.76 (2.20)	-0.01 (-4.39, 4.37)	0.9965
	PBO	93	61.94 (18.34)	4.77 (2.03)		
Week 8	ETN	85	64.87 (19.03)	6.66 (2.84)	3.61 (-1.89, 9.10)	0.1970
	PBO	93	60.76 (21.69)	3.05 (2.65)		
Week 12	ETN	84	67.43 (21.20)	9.33 (2.97)	6.07 (0.30, 11.84)	0.0394
	PBO	92	60.89 (22.31)	3.26 (2.77)		
Open-label Period[b]						
Time Point	Treatment	n	Mean score (SD)	Change from baseline Mean (SE)		
Week 16	ETN/ETN	82	69.59 (19.18)	13.06 (2.16)	NA	NA
	PBO/ETN	90	67.71 (22.21)	11.43 (2.47)		
Week 24	ETN/ETN	82	70.37 (20.08)	13.21 (2.23)	NA	NA
	PBO/ETN	90	72.41 (19.13)	16.61 (2.26)		

*ANCOVA model used for 'adjusted' values and between group P-values: Change = baseline score + treatment + region + SI status.
[a]Source: Section 14.2, Double-blind: Table 14.2.1.101.
[b]Source: Section 14.2, Open-label: Table 14.2.2.76.
ANCOVA=analysis of covariance, CI=confidence intervals, EQ-5D=The EuroQol EQ 5D Health State Profile, ETN=etanercept 50 mg weekly, mITT=modified intent-to-treat, n=number of subjects with an observation, NA=not assessed, PBO=placebo, SD=standard deviation, SE=standard error, SI=sacroiliac.
Note: open-label period results include unadjusted mean changes and standard errors, no covariate adjustments was applied.

Table 7: Study B1801031 Proportion of subjects ache9iving EQ-5D VAS score of >82 (mITT population; Observed Cases.

Double-blind Period	N=90	N=96		
Time Point	ETN n/N (%)	PBO n/N (%)	P-value (CMH)*	Difference in proportions (95% CI)
Baseline	7/90 (7.78)	8/96 (8.33)	0.8506	-0.56 (-8.38, 7.27)
Week 4	14/86 (16.28)	9/93 (9.68)	0.1879	6.60 (-3.25, 16.45)
Week 8	14/85 (16.47)	15/93 (16.13)	0.9855	0.34 (-10.52, 11.21)
Week 12	22/84 (26.19)	16/92 (17.39)	0.1477	8.80 (-3.38, 20.98)
Open-label Period[a]	**N=82**	**N=90**		
Time Point	ETN/ETN n/N (%)	PBO/ETN n/N (%)		
Week 16	18/82 (21.95)	29/90 (32.22)	NA	NA
Week 24	23/82 (28.05)	27/90 (30.00)	NA	NA

*Cochran-Mantel-Haenszel chi-square test, stratified by positive/negative sacroiliitis by MRI and geographic region.
[a]All subjects are receiving etanercept 50 mg weekly in the open-label period.
CMH=Cochran-Mantel-Haenszel, CI=confidence intervals, ETN=etanercept 50 mg weekly, EQ-5D= EuroQol EQ-5D Health State Profile, MRI=magnetic resonance imaging, mITT=modified intent-to-treat, n=number of subjects with an observation, N=the total number of subjects in the treatment group in the indicated population, NA=not assessed.

On the SF-36 Physical Component Summary (PCS), the mean change from baseline was 16.4% and 10.2% in the etanercept and placebo groups, respectively (p = 0.013).There was no further improvement with ongoing etanercept treatment to Week 24 (17.7% in the ETN/ETN group) (Table 8). There was no significant difference in the proportion of subjects with improvement in the SF-36 general physical function (SF-36 PCS) of ≥ 2.5 (68.2% versus 56.4%, p = 0.164) while

those with SF-36 PCS improvement of ≥5 reached statistical significance (51.8% versus 35.1%, p = 0.036). There was no significant difference between groups in the general mental function component.

Table 8: Study B1801031 Change from baseline in SF-36 PCS by time point (mITT population, Observed cases)

Double-blind Period[a]						
Time Point	Treatment	n	Raw mean score (SD)	Change within group	Change between group	
				Adjusted mean (SE)*	Adjusted difference of mean (95% CI)*	P-values*
Baseline	ETN	90	37.77 (8.89)			
	PBO	96	37.18 (8.14)			
Week 4	ETN	89	41.04 (9.10)	4.04 (0.79)	1.31 (-0.27, 2.90)	0.1035
	PBO	96	39.43 (7.36)	2.72 (0.74)		
Week 12	ETN	85	43.65 (8.87)	6.18 (0.97)	2.38 (0.50, 4.26)	0.0134
	PBO	94	41.00 (7.83)	3.80 (0.91)		
Open-label Period[b]						
Time Point	Treatment	n	Mean score (SD)	Change from baseline Mean (SE)		
Week 24	ETN/ETN	83	44.36 (9.19)	6.67 (0.93)	NA	NA
	PBO/ETN	91	44.55 (8.89)	7.29 (0.78)		

*ANCOVA model used for 'adjusted' values and between group P-values: Change = baseline score + treatment + region + SI status.
a Source: Section 14.2, Double-blind: Table 14.2.1.165.
b Source: Section 14.2, Open-label: Table 14.2.2.108.
ANCOVA=analysis of covariance, CI=confidence intervals, ETN=etanercept 50 mg weekly, mITT=modified intent-to-treat, n=number of subjects with an observation, NA=not assessed, PBO=placebo, PCS=physical component summary, SD=standard deviation, SE=standard error, SI=sacroiliac, SF-36=36-Item Short-Form Health Survey.
Note: open-label period results include unadjusted mean changes and standard errors, no covariate adjustments was applied.

There was also no significant difference between groups in the AS QoL score (Table 9). On the Work Productivity and Activity Impairment questionnaire (WPAI) at Week 12 there was no difference in the proportion of subjects employed, percent of work time missed, or overall work impairment due to health problems. On the Hospital Anxiety and Depression Scale (HADS) there were no significant differences on the anxiety or depression scores during the double-blind period.

Table 9: Study B1801031. Change from baseline in ASQoL score by time point (mITT population, Observed cases).

Double-blind Period[a]						
Time Point	Treatment	n	Raw mean score (SD)	Change within group	Change between group	
				Adjusted mean (SE)*	Adjusted difference of mean (95% CI)*	P-values*
Baseline	ETN	90	8.60 (4.81)			
	PBO	96	8.40 (4.82)			
Week 12	ETN	88	6.31 (4.80)	-1.93 (0.54)	-0.52 (-1.55, 0.52)	0.3286
	PBO	94	6.62 (4.93)	-1.42 (0.51)		
Open-label Period[b]						
Time Point	Treatment	n	Mean score (SD)	Change from baseline Mean (SE)		
Week 24	ETN/ETN	83	5.48 (4.77)	-3.12 (0.47)	NA	NA
	PBO/ETN	91	5.04 (4.55)	-3.16 (0.41)		

*ANCOVA model used for 'adjusted' values and between group P-values: Change = baseline score + treatment + region + SI status.
[a]Source: Section 14.2, Double-blind: Table 14.2.1.57.
[b]Source: Section 14.2, Open-label: Table 14.2.2.56.
ASQoL=ankylosing spondylitis quality of life, ANCOVA=analysis of covariance, CI=confidence intervals, ETN=etanercept 50 mg weekly, mITT=modified intent-to-treat, n=number of subjects with an observation, NA=not assessed, PBO=placebo, SD=standard deviation, SE=standard error, SI=sacroiliac.
Note: open-label period results include unadjusted mean changes and standard errors, no covariate adjustments was applied.

There was no significant difference in the mean change from baseline in the Bath AS patient global assessment score (BAS-G) (29.3% versus 21.5% at Week 12, p = 0.06).

7.1.1.1.14. Other outcomes

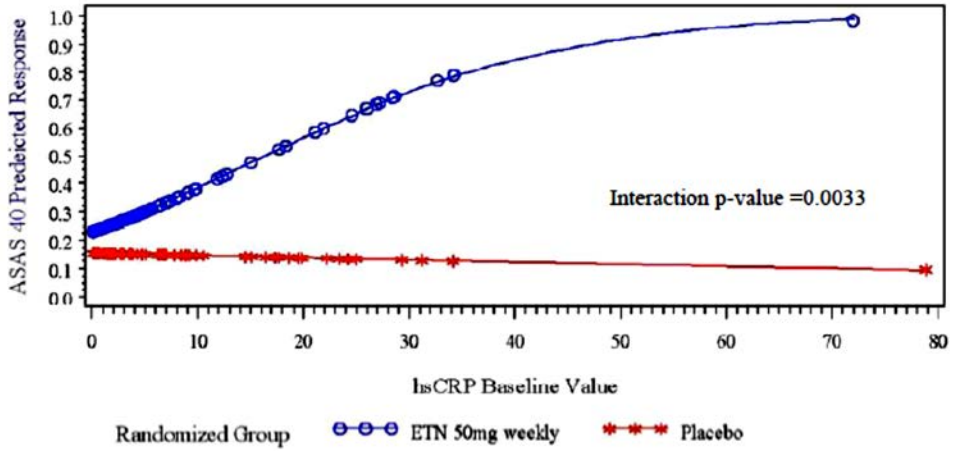
The mean percentage change in ESR from baseline to week 12 was 44.5% and 15.1% in the ETN and placebo groups respectively. There were no differences in peripheral articular involvement, number of tender joints or dactylitis score while there was a trend in favour of greater reduction in the enthesitis (MASES change from baseline of 44.2% versus 25.4%).

7.1.1.1.15. Subgroup analyses

There were no subgroups, as based on demographic and disease characteristics, with significant interaction on logistic regression of the primary endpoint (ASAS 40). ASAS 40 response rates for males and females (35.3% versus 28.9%), Whites and non-Whites (35.4% versus 25.9%), weight under or over 70 kg (32.5% versus 33.3%) and use or not of DMARD at baseline (28.6% versus 34.1%) were similar between groups with differences no greater than that seen in the placebo subgroup.

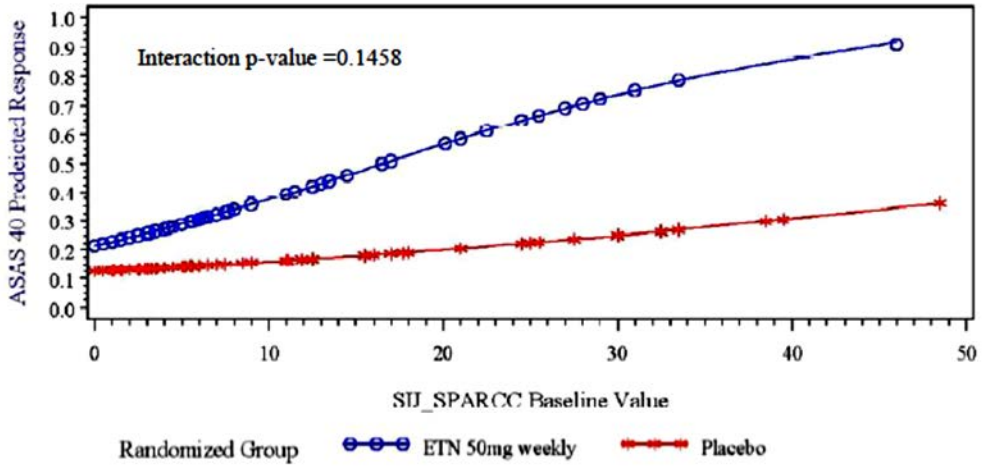
In subjects treated with etanercept, those with a high baseline hsCRP (≥ 3 mg/L) compared to a normal level (< 3mg/L) had a greater ASAS 40 response at Week 12 (47.9% versus 20.7%). A post-hoc analysis of baseline hsCRP level showed a significant interaction (p = 0.003) (Figure 6).

Figure 6: Study B1801031 Fitted Logistic Regression of ASAS 40 on Baseline hsCRP



Due to the low numbers of subjects that were negative MRI at baseline, a further post-hoc analysis of baseline SPARCC SIJ score (≥ 2 versus < 2) was undertaken. This found a trend for better response to etanercept on ASAS 40 in those with higher SPARCC scores (41.8% versus 17.9%) although the interaction was not statistically significant on categorical or continuous variable analysis (Figure 7).

Figure7: Study B1801031 Fitted Logistic Regression of ASAS 40 on baseline SPARRC SIJ



There were also trends for a greater etanercept response in subjects with HLA-B27 positive status (39.4% versus 21.2%), in those aged <40 years (36.8% versus 15.8%) and those with a history of uveitis (62.5% versus 30.6%). There was little difference if positive or negative for sacroiliitis on MRI as screening (33.3% versus 31.6%) although there were few negative subjects.

Evaluators comment: The small numbers in many of the subgroups make interpretation of differing results problematic. Nonetheless, there are definite trends for greater response in those with evidence of inflammation.

7.1.1.1.16. Sensitivity analyses

Analysis of the primary endpoint using the GEE model produced similar results as did analysis using the differing populations (per protocol, excluding the site 1004, with non-responder imputation) (Table 10).

Table 10: Study B1801031. Proportion of subjects achieving ASAS 40 Sensitivity analysis (Week 12)

Time Point	ETN n/N (%)	PBO n/N (%)	P-value (CMH)*	Difference in proportions % (95% CI)
Sensitivity Analyses				
Per-Protocol Population, LOCF	N=101	N=103		
Week 2	14/101 (13.86)	3/101 (2.97)	0.0103	10.89 (3.38, 18.40)
Week 4	19/101 (18.81)	14/103 (13.59)	0.3702	5.22 (-4.87, 15.31)
Week 8	27/101 (26.73)	17/103 (16.50)	0.0844	10.23 (-0.99, 21.45)
Week 12	31/101 (30.69)	15/103 (14.56)	0.0085	16.13 (4.85, 27.41)
All Treated, LOCF	N=110	N=112		
Week 2	16/110 (14.55)	4/110 (3.64)	0.0055	10.91 (3.45, 18.37)
Week 4	21/110 (19.09)	16/112 (14.29)	0.3606	4.81 (-4.99, 14.60)
Week 8	30/110 (27.27)	17/112 (15.18)	0.0282	12.09 (1.44, 22.74)
Week 12	35/110 (31.82)	16/112 (14.29)	0.0021	17.53 (6.68, 28.38)
Non Responder Imputataions	N=106	N=109		
Week 2	16/106 (15.09)	4/109 (3.67)	0.0047	11.42 (3.75, 19.10)
Week 4	21/106 (19.81)	16/109 (14.68)	0.3607	5.13 (-4.95, 15.22)
Week 8	30/106 (28.30)	17/109 (15.60)	0.0281	12.71 (1.75, 23.66)
Week 12	35/106 (33.02)	16/109 (14.68)	0.0022	18.34 (7.19, 29.49)
mITT Population, LOCF – excluding Site 1004	N=102	N=105		
Week 2	15/102 (14.71)	4/103 (3.88)	0.0098	10.82 (3.00, 18.64)
Week 4	20/102 (19.61)	16/105 (15.24)	0.4768	4.37 (-5.96, 14.70)
Week 8	28/102 (27.45)	17/105 (16.19)	0.0624	11.26 (0.10, 22.43)
Week 12	33/102 (32.35)	16/105 (15.24)	0.0053	17.11 (5.73, 28.50)
Time Point	**ETN n/N (%)**	**PBO n/N (%)**	**P-value****	
mITT Population, GEE analysis summary	N=104	N=106		
Week 2	17/103 (16.50)	3/106 (2.83)	0.0036	NA
Week 4	23/104 (22.12)	15/106 (14.15)	0.1411	NA
Week 8	34/102 (33.33)	17/106 (16.04)	0.0051	NA
Week 12	34/101 (33.66)	17/104 (16.35)	0.0052	NA

Source: Section 14.2, Double-blind: Table 14.2.1.6, Table 14.2.1.14, Table 14.2.1.1.4, and Table 14.2.1.7.
*Cochran-Mantel-Haenszel chi-square test, stratified by positive/negative sacroiliitis (assessed by MRI) and geographic region.
**=from generalized estimating equations. Model includes positive/negative sacroiliitis status, geographic region, treatment, visit and treatment by visit interaction
ASAS= Assessment in Ankylosing Spondylitis, CMH=Cochran-Mantel-Haenszel, CI=confidence interval, hsCRP=high sensitivity C-reactive Protein, GEE=generalized estimating equations, ETN=etanercept 50 mg weekly, LOCF=last observation carried forward, mITT=modified intent-to-treat, MRI=magnetic resonance imaging, n=number of subjects with an observation, N=the total number of subjects in the treatment group in the indicated population, NA=not assessed, PBO=placebo.

7.1.2. Other efficacy studies

No other studies were submitted in the dossier.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled analyses.

7.1.4. Evaluator's conclusions on clinical efficacy for nr-AxSpA

There was one pivotal efficacy study submitted in the dossier and no other supporting studies. Study B1801031 was a Phase III, randomised, placebo-controlled, double-blind study of 12 weeks etanercept treatment in 215 adult patients with active axial spondyloarthritis despite optimal NSAID therapy but without meeting criteria for AS. At baseline, the mean BASDAI was 6.0 indicating high disease activity and 81% of subjects had sacroiliitis on MRI. The study had a

second open label period of 92 weeks for which data to a total treatment duration of 24 weeks were submitted.

Etanercept 50 mg SC weekly was compared to placebo on a background of stable, optimal dose NSAID treatment. Subjects were required to have active symptoms and inadequate response to at least 2 NSAIDs. X-rays at study entry were read centrally to confirm the patients did not have findings of AS and MRIs, also read centrally, confirmed the presence or absence of sacroiliitis.

The study met its primary endpoint as the proportion of subjects with ASAS 40 response at Week 12 was significantly greater with etanercept + NSAID compared to placebo + NSAID (32% versus 16%). This treatment difference was less, however, than the anticipated 25%. The positive responses were found on the individual components of the ASAS (subject assessment of disease activity, nocturnal back pain, total back pain, BASFI, morning stiffness and lateral side flexion). The result was supported by sensitivity analyses and positive results across secondary endpoints of ASAS 20, ASAS 5/6, ASAS partial remission, BASDAI total score and BASDAI 50.

There was no significant effect on BASDAI 20, dactylitis or mobility endpoints (BASMI) (except lateral flexion). The sponsor claimed the lack of effect on mobility was related to the study population having little mobility restriction at baseline. Etanercept was seen to result in a positive response on imaging of the SI joints and spine. The reading was central and blinded to treatment which is important due to variability in reading of radiological images. The response on health outcomes showed a positive effect on measures of physical function (SF-36 PCS) but little positive impact on quality of life (ASQoL) or well-being (BAS-G).

There was persistence and maintenance of effect with treatment to Week 24, however longer term efficacy data to two years from the open label study are not yet available. Withdrawal of treatment and possible rebound in disease were not assessed.

A major issue with the submitted data was that there was no adjustment for multiple comparisons undertaken on the numerous secondary endpoints. A question on this has been raised. While subgroup analyses were hampered by small sample size, the main finding, on post-hoc analyses, was that there was a notably greater treatment effect (in terms of ASAS 40) in those with higher baseline hsCRP level (≥ 3mg/L) (48% versus 21%). There was also a greater response in those with a higher baseline SPARCC score (≥ 2) (42% versus 18%). The Sponsor has been asked to discuss these findings further.

The efficacy data submitted indicated that the treatment is symptomatic and there is no evidence that there is any impact on disease progression. Due to the age cut-off of 50 years there are no efficacy data in the elderly population.

The study design was in accordance with EMA guidelines for AS. The study's primary endpoint (ASAS response criteria) was in line with 2005 EMA draft guidelines on clinical investigation of medicinal products for the treatment of ankylosing spondylitis (EMA 2005). With the introduction of the 2009 guideline, the primary endpoint was also analysed according to its criteria which differed on the pain assessment domain (total or nocturnal pain scores rather than total and nocturnal pain). Results for analysis using both criteria were concordant.

Overall, the pattern of results in patients with nr-AxSpA are consistent with data from etanercept studies in AS patients although the degree of response is less and the positive response appears confined to those with evidence of inflammation on MRI or with elevated CRP.

8. Clinical safety

8.1. Studies providing evaluable safety data

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) and SAEs, AEs of particular interest, including investigator identified infection (a treated infection and/or serious infection), malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression, autoimmune disorders, Inflammatory bowel disease (IBD) and liver function abnormalities;
- Laboratory tests, including blood chemistry, fasting glucose and lipids, haematology, urinalysis;
- Physical examination and vital signs;
- IBD, psoriasis and uveitis evaluations.

8.2. Patient exposure

In Study B1801031, there were 225 randomised subjects and 224 received study drug, 111 etanercept and 113 placebo. The median exposure was 85 days in both groups with a total exposure of 24.1 and 25.3 subject-years in the etanercept and placebo groups, respectively in the double-blind period. In the open label period of Weeks 12 to 24, the median exposure was 78.0 days in both the ETN/ETN group (n = 102) and the placebo/ETN group (n = 106). The total exposure to etanercept from baseline to Week 24 was 47.4 subject years in the ETN/ETN group and 24.1 subject-years in the placebo/ETN group.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal study

In the double-blind period, the rate of TEAEs was 56.8% and 45.1% in the etanercept and placebo groups, respectively. General disorders and administration site conditions (mainly injection site reactions) were notably higher with etanercept (18.0% versus 3.5%) as were Musculoskeletal and connective tissue disorders (10.8% versus 5.3%) and Skin disorders (12.6% versus 4.4%) (Table 11). The rate of Infections/infestations was similar between groups (23.4% versus 22.1%). There was a significantly higher rate of injection site erythema and injection site reactions with etanercept (Table 12).

Table 11: Study B1801031 Incidence of treatment emergent adverse events reported in ≥1% of subjects in either treatment group during the double-blind period

MedDRA System Organ Class[a] MedDRA Preferred Term	ETN (N=111) n (%)	Placebo (N=113) n (%)
Any adverse event	63 (56.8)	51 (45.1)
Eye disorders	4 (3.6)	0
Dry eye	2 (1.8)	0
Gastrointestinal disorders	11 (9.9)	11 (9.7)
Abdominal Pain	2 (1.8)	0
Abdominal Pain Upper	3 (2.7)	1 (0.9)
Constipation	2 (1.8)	0
Diarrhoea	4 (3.6)	3 (2.7)
Nausea	1 (0.9)	3 (2.7)
General disorders and administration site conditions	20 (18.0)	4 (3.5)
Injection Site Erythema	7 (6.3)	1 (0.9)
Injection Site Rash	3 (2.7)	0
Injection Site Reaction	6 (5.4)	0
Infections and infestations	26 (23.4)	25 (22.1)
Gastroenteritis	3 (2.7)	2 (1.8)
Influenza	1 (0.9)	3 (2.7)
Nasopharyngitis	11 (9.9)	7 (6.2)
Sinusitis	1 (0.9)	2 (1.8)
Upper Respiratory Tract Infection	2 (1.8)	5 (4.4)
Bronchitis	0	2 (1.8)
Musculoskeletal and connective tissue disorders	12 (10.8)	6 (5.3)
Spondyloarthropathy	2 (1.8)	0
Arthralgia	0	2 (1.8)
Nervous system disorders	6 (5.4)	3 (2.7)
Dizziness	3 (2.7)	0
Headache	4 (3.6)	3 (2.7)
Respiratory, thoracic and mediastinal disorders	2 (1.8)	4 (3.5)
Oropharyngeal Pain	1 (0.9)	2 (1.8)
Skin and subcutaneous tissue disorders	14 (12.6)	5 (4.4)
Erythema	3 (2.7)	0
Pruritus	2 (1.8)	1 (0.9)
Rash	4 (3.6)	1 (0.9)

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more events within the higher level category.
Abbreviations: ETN=etanercept, n=number of subjects with an observation, MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects in treatment group.
Treatment-emergent includes events up to 15 days after last dose of study drug.
Medical Dictionary for Regulatory Activities (MedDRA) (v15.0) coding dictionary applied.

Table 12: Study B1801031 Incidence of Adverse Events reported in ≥5% of subjects in either treatment group during the double-blind period

System Organ Class[a] Preferred Term	ETN (N=111) n (%)	Placebo (N=113) n (%)	Total (N=224) n (%)	Risk Difference	95% Confidence Interval (Lower; Upper)	p-Value
General disorders and administration site conditions						
Injection site erythema	7 (6.3)	1 (0.9)	8 (3.6)	0.0542	(-0.0779; 0.1865)	0.0288
Injection site reaction	6 (5.4)	0	6 (2.7)	0.0541	(-0.0784; 0.1863)	0.0122
Infections and infestations						
Nasopharyngitis	11 (9.9)	7 (6.2)	18 (8.0)	0.0372	(-0.0928; 0.1698)	0.3065

Abbreviations: ETN=etanercept; MedDRA=Medical Dictionary for Regulatory Activities, n=number of subjects with an observation, N=number of subjects.
Medical Dictionary for Regulatory Activities (MedDRA) (v15.0) coding dictionary applied.
95% confidence intervals were provided to help gauge the precision of the estimates for risk difference. They were not adjusted for multiplicity and should be used for estimation purpose only.
Risk difference was computed as ETN versus placebo.

In the open label period (Week 12 to 24) the rates of TEAEs were 34.3% and 50.0% in the ETN/ENT and placebo/ETN groups, respectively (Table 13).

Table 13: Study B1801031 Incidence of Treatment Emergent Adverse Events reported in ≥1% of subjects in either treatment group during the open-label period

MedDRA System Organ Class[a] MedDRA Preferred Term	ETN/ETN (N=102) n (%)	Placebo/ETN (N=106) n (%)
Any adverse event	35 (34.3)	53 (50.0)
Ear and labyrinth disorders	1 (1.0)	2 (1.9)
Vertigo	0	2 (1.9)
Gastrointestinal disorders	4 (3.9)	8 (7.5)
Diarrhoea	2 (2.0)	1 (0.9)
Nausea	0	2 (1.9)
General disorders and administration site conditions	7 (6.9)	20 (18.9)
Fatigue	2 (2.0)	1 (0.9)
Injection Site Erythema	1 (1.0)	4 (3.8)
Injection Site Pruritus	0	4 (3.8)
Injection Site Reaction	0	5 (4.7)
Infections and infestations	20 (19.6)	25 (23.6)
Bronchitis	2 (2.0)	1 (0.9)
Gastroenteritis	2 (2.0)	0
Nasopharyngitis	4 (3.9)	5 (4.7)
Pharyngitis	1 (1.0)	2 (1.9)
Tinea Pedis	2 (2.0)	1 (0.9)
Upper Respiratory Tract Infection	2 (2.0)	2 (1.9)
Onychomycosis	0	2 (1.9)
Urinary Tract Infection	0	3 (2.8)
Viral Infection	0	2 (1.9)
Musculoskeletal and connective tissue disorders	8 (7.8	6 (5.7)
Back Pain	1 (1.0)	2 (1.9)
Myalgia	3 (2.9)	1 (0.9)
Nervous system disorders	2 (2.0)	4 (3.8)
Headache	0	3 (2.8)
Psychiatric disorders	2 (2.0)	2 (1.9)
Insomnia	1 (1.0)	2 (1.9)
Respiratory, thoracic and mediastinal disorders	3 (2.9)	1 (0.9)
Cough	2 (2.0)	0
Vascular disorders	0	2 (1.9)
Hypertension	0	2 (1.9)

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more events within the higher level category.

Abbreviations: ETN=etanercept, n=number of subjects with an observation, MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects in treatment group.

Treatment-emergent includes events up to 15 days after last dose of study drug.

Medical Dictionary for Regulatory Activities (MedDRA) (v15.0) coding dictionary applied.

8.3.1.2. AEs of special interest

There were no reported cases of malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression or IBD up to week 24 of the study.

The rate of investigator-identified treatment emergent infections was 9.9% and 8.8% in the respective groups during the double-blind period. The most common were nasopharyngitis and sinusitis. One case (placebo group) was serious (anal abscess). In the open label period the rate of these infections was 12.0% with the most frequent being bronchitis and UTI (1.4% each).

After week 24 data cutoff, the sponsor reported one opportunistic infection (herpes zoster) and one demyelinating disorder (multiple sclerosis). The case of zoster was in a 50 year old female subject on etanercept. The zoster was diagnosed nearly 6 months post etanercept commencement. Treatment was ceased temporarily and the zoster resolved with valaciclovir

therapy. The case of MS was in a 41 year old female in the placebo/ETN group who was diagnosed with MS on day 357. Etanercept was discontinued.

In the double-blind period there was one case of uveitis (SAE) in a placebo-treated subject. In the open label period there were two subjects (one ETN/ETN and one placebo/ETN group) with acute anterior uveitis. In neither case was study drug ceased.

8.3.2. Treatment-related adverse events (adverse drug reactions)

A breakdown of TEAE by whether they were treatment related or were not treatment related was not undertaken.

8.3.3. Deaths and other serious adverse events

There were no deaths through to Week 24 of the study.

There were 4 subjects (2 [1.8%] in each group) with SAEs during the double-blind period. In the etanercept group, the SAEs were spondyloarthopathy and cholelithiasis. In the placebo group, the SAEs were uveitis, anal abscess (in the same subject) and laceration wound. There was one subject with 3 SAEs during the open label period (motor vehicle accident with resultant contusion, cervical sprain and shoulder sprain).

8.3.4. Discontinuation due to adverse events

In the double-blind period there were 3 discontinuations due to AEs in subjects treated with etanercept: hepatitis; worsening spondyloarthropathy and asthenia. There was also one AE-related discontinuation in the placebo group due to an anal abscess. There was one AE-related discontinuation in the open label period which was due to acute bronchitis.

8.4. Laboratory tests

8.4.1. Liver function

In the double-blind period, there were 5 subjects with Grade 3 or 4 laboratory test results, 3 in the etanercept and 2 in the placebo group (2.7% versus 1.8%). All were related to raised levels of LFTs. Two subjects in the placebo group had elevated bilirubin related to Gilbert's syndrome and hepatic steatosis. One case in the etanercept group with Grade 3 elevated ALT and AST also had an AE of hepatitis. The rate of subjects with ALT >2xULN was 6.3% versus 2.7% and AST > 2xULN was 2.7% versus 1.8% in the etanercept and placebo groups, respectively.

In the open label period, there were 9 subjects (4.3%) with Grade 3 or 4 laboratory results. There were four cases of increased bilirubin (two continued from the double-blind period) and one case of Grade 3 increased ALT. The rate of AST >2x ULN and ALT >2xULN was 2.8% and 0.5% respectively.

There were five subjects with AEs of elevated liver enzymes. In the double-blind period there were three cases: one in the placebo group (ALT < 3x ULN and no treatment change) and 2 in the etanercept group. The first case in the etanercept group had AST > 3x ULN and ALT > 10x ULN but no increase in bilirubin. This was reported as hepatitis and the subject was discontinued. In the second case (ALT and ALT < 5xULN) treatment was temporarily discontinued and was ceased later due to a protocol deviation. There was one case in the open label period (ALT < 5x ULN) which resolved after temporary treatment discontinuation and the subject remained on study. In the second case in the open label period, the elevated ALT was transient and mild (< 3xULN) with no resultant change to treatment.

There were no cases of abnormal LFTs which met Hy's Law criteria.

8.4.2. Kidney function

No details reported.

8.4.3. Other clinical chemistry

There were two cases (1%) of Grade 4 potassium increase in the open label period were reported to be transient and not clinically significant.

8.4.4. Haematology

There were two cases (1%) of Grade 3 decreased neutrophils in the open label period which were transient and reported to return to normal at the next visit.

8.4.5. Electrocardiograph

Not done.

8.4.6. Vital signs

There were no reported clinically significant differences between groups in SBP, DBP or pulse rate.

8.5. Post-marketing experience

Etanercept has been on the market since 1998 and patient exposure to February 2013 was estimated at 3.6 million patient-years. Most treatment is for rheumatoid arthritis. The most frequent serious events reported are pneumonia, sepsis, myocardial infarction and worsening of the condition for which the etanercept was used. The most frequent causes of death are infections, neoplasms and cardiac disorders. The sponsor conducted a review of the safety database for cases with axial spondyloarthritis as the indication for etanercept. There were 125 cases of spondylitis with 4 cases of AxSpA (the other 121 were reported to be non-specific SpA, peripheral AxSpA or AS). The events reported were lack of effect, uveitis, herpes zoster, increased ALT, increased ALT, hepatic steatosis and Sjorgren's syndrome.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

See Section 8.4.1 Liver function above.

8.6.2. Unwanted immunological events

Anti-etanercept antibody concentrations were not assessed in Study B1801031.

Evaluators comment: It would be expected that the immunological risks in the nr-AxSpA population would be the same as in other populations already studied.

8.7. Other safety issues

8.7.1. Safety in special populations

No pregnancies were reported in Study B1801031.

8.7.2. Safety related to drug-drug interactions and other interactions

Not assessed.

8.7.3. Withdrawal

Withdrawal and disease rebound were not assessed.

8.8. Evaluator's overall conclusions on clinical safety

The safety database for the nr-AxSpA population was derived from the one Phase III clinical trial in which there were 111 patients exposed to double-blind etanercept. The median duration of

exposure in the double-blind phase was 85 days with a total of 24.1 subject-years. The median exposure duration in the open label phase was 78 days. The total exposure to etanercept from baseline to Week 24 was 47.4 subject years in the ETN/ETN group and 24.1 subject-years in the placebo/ETN group.

There were no deaths in the study to Week 24. SAEs were infrequent (2 [1.8%] in each group during double-blind treatment). In the etanercept group, the SAEs were spondyloarthopathy and cholelithiasis. There were three discontinuations due to AEs in subjects treated with etanercept (hepatitis, worsening spondyloarthropathy and asthenia) during double-blind treatment with a higher rate than placebo (2.7% versus 0.9%). There was one AE-related discontinuation (acute bronchitis) during open label treatment.

During double-blind treatment, TEAEs were more frequent with etanercept than placebo (56.8% and 45.1%). The notable increased risk was injection site reactions. The overall rate of infections was similar between groups (23% versus 22%) while treated or serious infections were slightly higher in the etanercept group (9.9% versus 8.8%).

Up to Week 24 of the study, there were no reported cases of malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression or IBD. After Week 24 data cut-off, the sponsor reported one opportunistic infection (herpes zoster) and one demyelinating disorder (multiple sclerosis). In the open label period there were two subjects with acute anterior uveitis and in neither case was study drug ceased.

Grade 3 or 4 laboratory test results were higher with etanercept (2.7% versus 1.8%) and in particular a higher rate of raised ALT and AST. There was one etanercept-treated subject with hepatitis (which led to discontinuation) but no cases meeting the Hy's Law criteria. Transient neutropaenia (Grade 3) was also reported in 2 (1%) patients during open label treatment. There was some lack of detail on laboratory assessments and question on this has been raised.

There were no reported pregnancies. Anti-etanercept antibodies were not assessed nor was safety in relation to treatment withdrawal.

Overall the safety risks appeared in line with current knowledge for etanercept. However the database was small and the maximum treatment duration was only 24 weeks which is shorter than the recommended minimum of 12 months.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of etanercept in the proposed usage are:

- Efficacy compared to placebo on ASAS 40 of 32% versus 16% after 12 weeks treatment. The efficacy appeared largely confined to those with elevated hsCRP and possibly also those with evidence of inflammation on MRI.
- Efficacy is supported by positive results across secondary endpoints of disease activity and function. There was, however, little effect on mobility or quality of life.
- Efficacy was maintained to Week 24.
- No new safety signals.
- Safety data which is supported by a large existing safety database.

9.2. First round assessment of risks

The risks of etanercept in the proposed usage are:

- Injection site reactions.
- Infections and sepsis.
- Elevated liver enzymes and hepatitis.
- CNS disorders including demyelinating disorders.
- Other serious risks as outlined in the product information such as: opportunistic infections and tuberculosis; haematological reactions including pancytopaenia; reactivation of hepatitis B, worsening of hepatitis C, allergic reactions, worsening of congestive heart failure; malignancy and lymphoproliferative disorders, autoimmune antibody formation; new onset psoriasis; interstitial lung disease; risk in patients with alcoholic hepatitis; hypoglycaemia in diabetic patients; risks during pregnancy and lactation; and drug interactions with anakinra and abatacept.
- A small safety database in the nr-AxSpA population.
- Lack of efficacy and safety data beyond 24 weeks.
- No data on effects on disease progression.
- No efficacy data in patients aged ≥ 50 years (exclusion criteria in the pivotal study).

9.3. First round assessment of benefit-risk balance

Spondyloarthritis (SpA), formerly termed spondyloarthropathy, refers to a group of diseases that share certain clinical features, including axial inflammation (spinal and/or sacroiliac), enthesitis (inflammation of ligament/tendon attachment to bone), dactylitis, oligoarthritis, inflammatory eye disease, inflammatory bowel disease, an association with prior or ongoing infection, mucocutaneous lesions typically affecting the genital regions, and, importantly, the human leukocyte antigen HLA-B27.

Subsets of SpA include ankylosing spondylitis; undifferentiated spondyloarthritis (USpA), which includes non-radiographic axial SpA (nr-axSpA); reactive arthritis (formerly called Reiter syndrome); psoriatic arthritis; inflammatory bowel related disease; and SpA in children.

An alternate scheme classifies SpA according to whether the joint involvement is predominantly axial or peripheral: axial SpA which is SpA with predominantly axial involvement; and peripheral SpA where the SpA has predominantly peripheral involvement. Axial SpA patients who do not show defined radiographic changes of sacroiliitis are classified as having non-radiographic axial SpA (nr-axSpA). Patients with nr-axSpA were formerly classified among patients who have undifferentiated SpA (USpA).

The clinical manifestations of SpA include: musculoskeletal findings; eye involvement; skin, genital and mucosal lesions; and bowel mucosal inflammation. A family history of SpA and related conditions may also be present. A good response to NSAIDs is common and is supportive of the diagnosis.

Acute phase reactants may be increased. Plain radiographs are used to assess sacroiliitis but patients with axial involvement may have normal radiographs in early disease. Plain radiographs of the sacroiliac joints are normal in patients with UspA and nr-axSpA, in contrast to ankylosing spondylitis (AS) patients, whose sacroiliac joints would invariably show sclerosis, joint space widening, or erosion. Magnetic resonance imaging of the sacroiliac joint is indicated in patients with clinically-suspected axial SpA who have negative or indeterminate plain radiographic findings at the sacroiliac joints.

The Assessment of Spondyloarthritis International Society (ASAS) criteria for the classification of AxSpA require patients to have back pain for at least three months and age of onset less than 45 years with sacroiliitis on imaging (MRI or X-ray) along with at least one SpA feature or be HLA-B27 positive and have at least two other SpA features. SpA features include inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA, and elevated C-reactive protein (CRP) (Figure 2). The sensitivity and specificity of these criteria were 83% and 84%, respectively in study of 649 patients (Rudwaleit M 2009). With these criteria 'sacroiliitis on imaging' is defined as active (acute) inflammation on magnetic resonance imaging that is highly suggestive of sacroiliitis associated with SpA or as definite radiographic sacroiliitis according to the modified New York Criteria. While it can be deduced that non-radiographic axSpA is a diagnosis of exclusion (axSpA patients who do not have ankylosing spondylitis on X-ray according to the modified NY criteria) it is not clear to the evaluator if this is a widely and consistently utilised classification and the ASAS Handbook (Sieper J et al 2009) does not clearly set out a specific definition for the non-radiographic subgroup of axial spondyloarthritis.

The management of nr-axSpA is similar to the management of patients with ankylosing spondylitis. Initial therapy is with NSAIDs. Secondary options include local glucocorticoid injections and DMARDs, although the latter have not been shown to be effective for patients with only pure axial disease. For those with inadequate response to NSAIDs and continuing pain and evidence of inflammation (for example, elevated CRP or inflammation on MRI) TNF inhibitors have been suggested. Adalimumab has been approved in the EU for severe axial SpA in patient without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and/or MRI and who have inadequate response to or are intolerant of NSAIDs. The evaluator has noted that the application in Australia for this usage of adalimumab was withdrawn in 2013.

The design of the submitted study was in accordance with European guidelines and the endpoints are validated and have been accepted by the European regulators (ASAS 40 response being the primary endpoint for the submission for adalimumab). The use of centralised, blinded radiologists was important for ensuring reliable radiological assessments. It is noted that there has been discussion on whether the selected population of nr-AxSpA is a separately identified disease with established diagnostic criteria. In the submitted clinical trial there were 10/225 (4.4%) of subjects who were randomised yet did not meet the ASAS criteria. Thus, even with specific training, specialist physicians may not accurately apply the ASAS criteria. While it appears that this classification system is being accepted by rheumatologists, a question has been raised for the sponsor to address this issue and the diagnosis of nr-AxSpA within the Australian clinical practice context.

The efficacy of etanercept was demonstrated in one clinical trial with statistically significant results to 12 weeks, maintenance of effect to 24 weeks and support from secondary endpoints. There were however several issues with the efficacy of etanercept in the proposed population. For a chronic condition, the data to 24 weeks are felt to be insufficient for establishing long term efficacy. Secondly, the evaluator believes the degree of response in the total population (16% placebo-corrected difference on the ASAS 40) may be of limited clinical benefit particularly given the treatment risks. Post-hoc analyses pointed towards increase benefit in those with higher CRP (placebo-corrected difference for those with hsCRP ≥ 3 mg/L was 27%) and more SI joint inflammation on MRI (SPARCC score of at least 2). It would therefore appear that the use in such subgroups would have an improved benefit-risk balance and a question on this has been raised. Thirdly, efficacy was only assessed in adults under 50 years of age and therefore an indication for all adults is not appropriate. Lastly, the efficacy data presented are only for signs and symptoms of disease and there were no data presented on the effect of etanercept on disease progression or structural damage.

The safety data presented were consistent with other approved populations and there were no new safety signals. The safety database was, however, of limited size with a maximum exposure duration of 24 weeks. Therefore data to at least 1 year should be presented. For undertaking the benefit-risk assessment the evaluator believes that the risks of etanercept in the nr-AxSpA population would be of a similar significant nature to that already established in other adult populations such as those with AS.

Given the issues discussed above, the evaluator believes the benefits in the proposed broad indication are insufficient to outweigh the significant treatment risks that are already established for etanercept. It is recommended that, due to the lack of data on disease progression, the indication should be limited to treatment of signs and symptoms which would be in line with the wording used for AS. Patients included in the study had active disease with a BASDAI ≥4 and a mean of 6.0 and therefore treatment should be limited to patients with this high level of disease severity. The clinical benefit of treatment in the broad population was marginal therefore tailoring treatment to higher responding subgroups would appear logical.

In summary, the evaluator believes that the efficacy in the broad proposed population, whilst statistically significant, is of marginal clinical benefit and would be outweighed by the significant and serious risks of the treatment. Overall, the benefit-risk balance of Enbrel, given the proposed usage, is unfavourable.

10. First round recommendation regarding authorisation

The evaluator does not recommend that etanercept be authorised for the indication of:

> *Axial spondyloarthritis*
>
> *Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy (see CLINICAL TRIALS).*

The reasons for this are:

- Efficacy was only seen on symptoms and signs of disease and not disease progression.
- The proposed indication covers all adults when data are only available for adults under 50 years of age.
- The indication is too broad for a positive benefit-risk balance to be achieved. Consideration should be given to limiting treatment to populations in which a higher treatment response was found.
- The lack of efficacy and safety data beyond 24 weeks of treatment duration.
- The need for further elucidation on how the proposed population would be identified in clinical practice so that inappropriate patients are not exposed to the risks of treatment.
- Revisions are required on the product information.

11. Clinical questions

11.1. Pharmacokinetics

1. Can the sponsor confirm that the formulation of etanercept registered in Australia is the same as that used in Study B1801031?

11.2. Pharmacodynamics

None

11.3. Efficacy

1. From the inclusion and exclusion criteria for Study B1801031 it can be deduced that the criteria for 'non-radiographic' sacroiliitis would be sacroiliitis on screening X-ray of either Grades 0, 1 or 2 unilaterally or Grades 0 or 1 bilaterally. However if historical X-rays were used, the grading requirement was lower at 0-1 unilaterally or Grade 0 bilaterally. Are these assumptions correct?
2. In B180131 there were 80-82% of subjects who met the inclusion criteria for ASAS based on imaging rather than clinical criteria. It was stated that this was due to the finding of sacroiliitis on MRI. Given that the X-ray findings were as follows for the 225 randomised subjects (Grade 2 unilateral = 80; Grade 1 bilateral = 53; Grade 0 bilateral = 47; Grade 1 unilateral = 45), could the sponsor confirm the criteria used in the trial for 'non-radiographic' axial SpA? Does the sponsor agree that non-radiographic axSpA in the trial could be defined as patients fulfilling the ASAS criteria for axSpA but without X-ray changes consistent with AS?
3. Discuss how non-radiographic axial spondyloarthritis is diagnosed in Australia. Are the ASAS criteria used routinely? Is there an accepted and utilised definition for the subgroup with 'non-radiographic' axSpA? What would be the likelihood of disease misclassification and would there be a risk of treating patients who do not meet the ASAS criteria?
4. There were numerous secondary endpoints discussed in the study report. Why was there no adjustment for multiplicity on analysis of these endpoints? Discuss the implications for not having done this on the reported findings.
5. In B180131 in the open label period, the response in the placebo group who switched to etanercept (placebo/ETN) is higher than in the ETN/ETN group (52% versus 44%). In addition, a rapid response occurred during the first 4 weeks of etanercept treatment that was more than seen in the etanercept group during the first 4 weeks of double-blind treatment. Could the sponsor comment on whether these findings are due to chance or if there may be other explanations?
6. In the evaluator's opinion, the efficacy of etanercept appears limited to patients with elevated hsCRP level and possibly also those with greater degree of inflammatory change on MRI of the SI joints. Discuss efficacy in these groups in further detail and whether the sponsor believes it would be preferable to target the indication to subgroups with a higher treatment response rate.
7. For sites in Russia and the Czech Republic only certain questionnaires were translated (BASDAI, BASFI, Subject Assessment of Disease, total pain and nocturnal back pain assessments) resulting in lower numbers in some analyses on health outcomes. Could the sponsor clarify this issue? How many patients did this involve? Can the sponsor provide assurances that there were no other outcomes which many have been affected by such issues to do with translation or language differences?

11.4. Safety

1. Grade 3 and 4 laboratory test results and liver function tests were reported in the CSR for B1801031. Other laboratory parameters were not reported. Discuss whether there are any other findings of note on clinical chemistry, renal function and haematology in both the double-blind and open label periods of this study.

12. Second round evaluation of clinical data submitted in response to questions

The sponsor submitted responses to the *Clinical questions* and these responses, together with the evaluator's comments, are discussed below.

12.1. Pharmacokinetics

12.1.1. Question 1.

Can the sponsor confirm that the formulation of etanercept registered in Australia is the same as that used in Study B1801031?

12.1.1.1. Sponsor's response:

The formulation of etanercept (50 mg/mL pre-filled syringe) used in Study B1801031 is identical to the 50 mg/mL pre-filled syringe that is currently registered in Australia.

12.1.1.2. Evaluator's comments:

This is acceptable.

12.2. Efficacy

12.2.1. Question 1.

From the inclusion and exclusion criteria for Study B1801031 it can be deduced that the criteria for 'non-radiographic' sacroiliitis would be sacroiliitis on screening X-ray of either grades 0, 1 or 2 unilaterally or grades 0 or1 bilaterally. However if historical X-rays were used, the grading requirement was lower at 0-1 unilaterally or grade 0 bilaterally. Are these assumptions correct?

12.2.1.1. Sponsor's response:

Yes, these assumptions are correct. Historical X-rays were allowed up to a year prior to screening in some countries. By allowing only minimal sacroiliitis, well below the threshold for ankylosing spondylitis (AS), we believe we minimized the possibility that subjects who were enrolled up to a year after their historical X-ray had progressed to AS. At the end of recruitment, it was determined that 18 of 225 subjects had historical X-rays ranging from 1 to 96 days prior to screening. Progression to AS in those who had historical X-rays is considered unlikely.

12.2.1.2. Evaluator's comments:

From this it is assumed that 18/225 patients were included on the basis of historical X-rays and that these historical X-rays were taken no more than 96 days before trial entry at screening. The remainder of subjects (207) would therefore have had X-rays taken during the screening period. As these data could not be located in the clinical study report, the sponsor needs to clarify if this is correct.

12.2.2. Question 2.

In B180131 there were 80-82% of subjects who met the inclusion criteria for ASAS based on imaging rather than clinical criteria. It was stated that this was due to the finding of sacroiliitis on MRI. Given that the X-ray findings were as follows for the 225 randomised subjects (Grade 2 unilateral = 80; Grade 1 bilateral = 53; Grade 0 bilateral=47; Grade 1 unilateral = 45), could the sponsor confirm the criteria used in the trial for 'non-radiographic' axial SpA? Does the sponsor agree that non-radiographic axSpA in the trial could be defined as patients fulfilling the ASAS criteria for axSpA but without X-ray changes consistent with AS?

12.2.2.1. Sponsor's response:

Patients meeting ASAS criteria for axSpA, but not fulfilling the 1984 modified radiographic New York (NY) criteria for ankylosing spondylitis (AS), were eligible for the study. The sponsor agrees that non-radiographic axSpA in the trial could be defined as patients fulfilling the ASAS criteria for axSpA but without X-ray changes consistent with AS.

12.2.2.2. Evaluator's comments:

This issue has now been clarified and is covered in the description of patient population for the pivotal trial (Clinical Trial section of the PI).

12.2.3. Question 3.

Discuss how non-radiographic axial spondyloarthritis is diagnosed in Australia. Are the ASAS criteria used routinely? Is there an accepted and utilised definition for the subgroup with 'non-radiographic' axSpA? What would be the likelihood of disease misclassification and would there be a risk of treating patients who do not meet the ASAS criteria?

12.2.3.1. Sponsor's response:

The sponsor consulted with a group of advisors consisting of seven established local rheumatologists and a radiologist, including most authors of the recently published 'Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA)[15]' to gain greater insight into the diagnosis and management of patients with nr-axSpA in the Australian setting.

In Australia, patients with chronic inflammatory back pain are typically referred to rheumatologists by general practitioners, sports physicians, physiotherapists and chiropractors. Rheumatologists routinely diagnose nr-axSpA based on components of the ASAS criteria. The expert Advisory Board concluded that the ASAS criteria are currently the best available criteria for diagnosing nr-axSpA and that these criteria are appropriate for defining nr-axSpA in the Australian setting.

In the absence of appropriate clinical expertise and objective measures of disease, misclassification of nr-axSpA is possible. In the Australian context however, only rheumatologists make the diagnosis of nr-axSpA and could initiate reimbursed treatment with Enbrel for this indication. Additionally, rheumatologists rely on objective markers such as elevated CRP and/or MRI changes, to support a diagnosis of nr-axSpA based on the ASAS criteria. The risk of disease misclassification or treating patients who do not meet the ASAS criteria would therefore be low in the Australian setting.

12.2.3.2. Evaluator's comments:

Given the complexity in diagnosing the specific population for which etanercept is indicated it would be prudent for its use be limited to rheumatologists with appropriate knowledge of the diagnostic criteria.

12.2.4. Question 4.

There were numerous secondary endpoints discussed in the study report. Why was there no adjustment for multiplicity on analysis of these endpoints? Discuss the implications for not having done this on the reported findings.

12.2.4.1. Sponsor's response:

The study was designed following ICH guideline E9 that recommends controlling for type I error by assigning a primary analysis variable that directly relates to the primary objective of the trial.

[15] Robinson PC, Bird P, Lim I, et al. Consensus statement on the investigation and management of non-radiographic axial spondyloarthritis (nr-axSpA). Int J Rheum Dis 2014;17(5):548-56.

This was done by assigning the ASAS 40 Week 12 comparison between etanercept and placebo as the single primary comparison. All other endpoints and time points in the trial are considered secondary. While it is true that there is a risk of introduction of type I errors by presenting unadjusted p-values for the secondary endpoints, it is not typically done to make multiple comparison adjustments for secondary endpoints. While results with p-values < 0.05 are described as statistically significant for all endpoints for which testing was done, these results should be evaluated as part of the overall strength evidence of the treatment effect and interpreted with caution. In Study B1801031 there was a consistent separation between the etanercept and placebo arms for clinical endpoints in terms of mean differences and response proportions. The sponsor believes that, in addition to the many low p-values, the consistent separation between etanercept and placebo responses strongly support the result shown for the primary endpoint.

12.2.4.2. Evaluator's comments:

The evaluator accepts the reasoning for not adjusting for multiplicity as, firstly, the data from the secondary endpoints demonstrated supportive efficacy evidence through separation between etanercept and placebo together with low p values and secondly, the data are used in a descriptive rather than confirmatory fashion in the PI.

12.2.5. Question 5.

In B180131 in the open label period, the response in the placebo group who switched to etanercept (placebo/ETN) is higher than in the ETN/ETN group (52% versus 44%). In addition, a rapid response occurred during the first 4 weeks of etanercept treatment that was more than seen in the etanercept group during the first 4 weeks of double-blind treatment. Could the sponsor comment on whether these findings are due to chance or if there may be other explanations?

12.2.5.1. Sponsor's response:

For the open-label period, the sponsor did not perform statistical analyses to answer the question as to whether or not the placebo/ETN response was significantly different from the ETN/ETN response. Similarly, no statistical comparison was performed between the first 4 weeks of the double-blind period versus the first 4 weeks of the open-label period. The generally more robust rates of response in the open-label period may be due to the expectation by patients and physicians that a response would occur since they both knew the patients were receiving active drug.

12.2.5.2. Evaluator's comments:

The evaluator accepts that the improved response in the open label period could be explained by the lack of treatment blinding and the impact of this on patient and physician expectations.

12.2.6. Question 6.

In the evaluator's opinion, the efficacy of etanercept appears limited to patients with elevated hsCRP level and possibly also those with greater degree of inflammatory change on MRI of the SI joints. Discuss efficacy in these groups in further detail and whether the sponsor believes it would be preferable to target the indication to subgroups with a higher treatment response rate.

12.2.6.1. Sponsor's response:

The study supporting this indication (B1801031) was not designed to show differences in efficacy between patients who had different baseline levels of inflammation as measured by SIJ MRI or serum hsCRP. Sub analyses showed that there was no significant interaction between hsCRP level (normal versus elevated) and treatment effect. When hsCRP level was analysed as a continuous variable there was a statistically significant relationship between baseline hsCRP levels and treatment effect. For SIJ MRI, there was some suggestion that higher levels of inflammation were associated with a greater treatment effect but this relationship did not reach

statistical significance. Overall there is a suggestion that either elevated baseline hsCRP or evidence of SIJ MRI inflammation is associated with a greater treatment effect.

12.2.6.2. Evaluator's comments:

The sponsor has altered the indication to limit treatment to patients with 'elevated CRP and/or MRI change'. It is appropriate to target treatment to those with higher treatment response rates given the risks associated with the product. The evaluator recommends some rewording of this revised indication to fully capture the fact that patients need objective evidence of inflammatory change.

12.2.7. Question 7.

For sites in Russia and the Czech Republic only certain questionnaires were translated (BASDAI, BASFI, Subject Assessment of Disease, total pain and nocturnal back pain assessments) resulting in lower numbers in some analyses on health outcomes. Could the sponsor clarify this issue? How many patients did this involve? Can the sponsor provide assurances that there were no other outcomes which many have been affected by such issues to do with translation or language differences?

12.2.7.1. Sponsor's response:

Study sites in Russia and Czech Republic were initiated late in the enrolment phase. Due to the length of time involved to translate patient-reported outcomes, the decision was made to only translate key questionnaires. Therefore, only the components of the ASAS 40 (primary endpoint) were translated for these 2 countries. There were a total of 29 subjects in these 2 countries (6 in Russia and 23 in Czech Republic) who were randomized into the study. There were no other study/patient documents affected by this decision.

12.2.7.2. Evaluator's comments:

The evaluator accepts the explanation and, as only small numbers were involved and the impact was on secondary outcomes, agrees that the issue would not have a major impact on the results presented.

12.3. Safety

12.3.1. Question 1.

Grade 3 and 4 laboratory test results and liver function tests were reported in the CSR for B1801031. Other laboratory parameters were not reported. Discuss whether there are any other findings of note on clinical chemistry, renal function and haematology in both the double-blind and open label periods of this study.

12.3.1.1. Sponsor's response:

Please refer to *Laboratory Values Over Time*, of the Week 24 for Study B1801031 for the results of analyses of other laboratory parameters. The conclusions presented in this section are the following: *In general, in the double-blind and open-label periods, there were isolated and transient mean changes observed in some laboratory parameters; however, there were no persistent or clinically meaningful changes observed.*

The incidences of laboratory test abnormalities during the double-blind and open-label periods are summarized in the study report for the double-blind period and the open-label period.

12.3.1.2. Evaluator's comments:

These data have been reviewed and there are no changes evident which alter the safety profile already outlined.

12.4. Indication

Current wording:

Axial spondyloarthritis

Treatment of adults with active non-radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy

12.4.1. Comment:

As data have only shown an effect on signs and symptoms of nr-AxSpA and there are no data on the effect of etanercept on disease progression in this condition, the indication should be limited this fact. Suggested wording is:

Treatment of the signs and symptoms of active

Efficacy data are only available for adults under 50 years of age and so do not support an indication which covers all adults.

In order to ensure a positive benefit-risk balance treatment should only be given to patients with severe active disease.

Consideration should be given to including inadequate response to NSAIDs specifically rather than the term conventional therapy.

Patients with objective signs of inflammation such as elevated CRP, or SI joint MRI SPARCC score of ≥ 2, were the ones who had the more notable positive treatment response. Consideration needs to be given to assessing treatment benefit in a more targeted population (see *Clinical questions Efficacy*).

12.4.1.1. Sponsor's response:

After consideration of the clinical evaluator's comments above, the sponsor has revised the indication as follows:

> *Treatment of adults with active non-radiographic axial spondyloarthritis as indicated by elevated C-reactive protein (CRP) and/or MRI change, who have had an inadequate response to NSAIDs.*

Pfizer acknowledges the recommendation regarding assessing treatment benefit in a more targeted population and has revised the indication accordingly.

Pfizer agrees with the above recommendation to replace 'conventional therapy' with 'NSAIDs' in the indication and has revised the PI accordingly.

Whilst etanercept treatment was associated with rapid and significant improvements in the signs and symptoms associated with nr-AxSpA, treatment outcomes also included significant improvement in physical function and systemic and skeletal inflammation as indicated by the significant decreases in the BASFI, hsCRP, and MRI scores compared to placebo. Furthermore, this MRI evidence of a decrease in inflammation at the disease sites was analysed using published quantitative and statistical methods. Together, these findings clearly demonstrate that Enbrel modifies the underlying inflammatory process in addition to improving the signs and symptoms of nr-AxSpA. Therefore, singular inclusion of 'signs and symptoms' in the indication does not entirely reflect the evidence in the Clinical Trials section of the PI and Pfizer does not agree with adding 'signs and symptoms' to the indication.

Pfizer does not agree with limiting treatment to adults < 50 years of age in the indication. The sponsor would like to clarify that the age cut off of 50 years was meant as a cut off for entry into the trial, and not as a cut off for treatment with drug. The upper age limit of 50 years for entry into the trial was set because the ASAS age criterion for diagnosis of axial spondyloarthritis is 45

years maximum for onset of symptoms.[16] The ASAS criteria, taken with the study eligibility criteria of disease duration < 5 years, resulted in the age limit of 50 years for entry into the study. This is an important measure to ensure that the study captures a true nr-axSpA population as defined by the ASAS criteria. Pfizer believes that the underlying pathological process of the disease does not change after the age of 50 years. Based on the pharmacokinetics of etanercept and adult experience in other indications, no difference is expected in the use of Enbrel to treat nr-AxSpA in patients that are ≥ 50 years compared to patients < 50 years of age. Population pharmacokinetic analyses have shown that there is no effect of diagnosis on the pharmacokinetics of etanercept in adults.[17] Furthermore, the observation that there is no effect of age on etanercept pharmacokinetics in adults with rheumatoid arthritis[18] can reasonably be extrapolated to patients with nr-AxSpA.

Pfizer does not agree with the recommendation to revise the indication to 'severe' active disease, but accepts that including a description in the PI of the level of nr-axSpA disease is useful and appropriate. Pfizer proposes to accept the evaluator's request to revise the Clinical Trials section of the PI to define 'active' disease as a baseline BASDAI score of ≥4, which is more clinically meaningful to physicians, rather than include 'severe' in the indication (please see the revised PI). The BASDAI score is the most accurate descriptor of the level of disease according to the study criteria, rather than 'severe', and addresses the evaluator's rationale of ensuring positive benefit-risk balance for treatment. The BASDAI scale further clarifies '*Scores of 4 or greater suggest suboptimal control of disease, and patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrolment in clinical trials...*'.[19]

12.4.1.2. Evaluator's comments:

Regarding inadequate response prior treatment, the sponsor has agreed to change the words 'conventional therapy' to 'NSAIDs'.

The sponsor has agreed to limit the patient population to those with elevated CRP and/or MRI change. This is acceptable however the evaluator believes that the wording in the EU indication is more specific and appropriate as it states that the treatment needs to be in patients with '*objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence'*. This more specific wording relating to inflammatory changes should be included in the Australian indication.

The evaluator accepts the sponsor's argument not to include the words 'signs and symptoms' in the indication.

The evaluator still believes that treatment should be limited to adults with severe disease as the risk profile of the product is too great for it to be indicated in a mild to moderate level of disease. It is noted in the EU the indication is 'treatment of adults with severe' nr-AxSpA. It is accepted that 'severe' may not be as relevant to rheumatologists as BASDAI score. Therefore, it is recommended to include the BASDAI definition of 'active' (≥ 4) with the indication.

The evaluator accepts the argument for leaving the indication for 'adults' however a statement should be included in the PI (Precautions: Use in the Elderly) that there are no data on the use of etanercept in patients 50 years or older with nr-AxSpA (see Q4 below).

[16] Rudwaleit M, van der Heijde D, Landewe´ R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68(6):777–83.
[17] Zhou H, Buckwalter M, Boni J, et al. Population-based pharmacokinetics of the soluble TNFr etanercept: a clinical study in 43 patients with ankylosing spondylitis compared with post hoc data from patients rheumatoid arthritis. Int J Clin Pharmacol Ther 2004;42(5):267-76.
[18] Lee H, Kimko HC, Rogge M, et al. Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. Clin Pharmacol Ther 2003;73(4):348-65.
[19] BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. www.basdai.com. Accessed 08 September 2014.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of etanercept in the proposed usage are unchanged from those identified in the First round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of etanercept in the proposed usage are unchanged from those identified in the First round evaluation.

13.3. Second round assessment of benefit-risk balance

After the first round evaluation there were a number of issues which led the evaluator to conclude the benefit-risk balance for etanercept was not favourable. The sponsor's response has addressed a number of the concerns which were discussed in the First round benefit-risk balance

All subjects were required to have screening X-rays of the SI joints. Historical X-rays of the SI joints could be used instead but needed to be obtained within 4 months of the screening visit. All X-rays, including historical ones, were sent for central reading. In Germany only, historical X-rays could be obtained with 12 months of screening. If screening X-rays were not evaluable, they were repeated. All MRIs were conducted locally but read by a central reader.

As the sponsor explained in the response (Q1 Efficacy), there were 18 (8%) of the 225 subjects who were included on historical X-rays with a range of up to 96 days prior to screening. From this, it is assumed that 207 patients had their X-rays for inclusion taken during the screening period. As these data could not be located in the clinical study report, the sponsor has been asked to verify if these are correct assumptions. It is noted that the inclusion criteria were more stringent in terms of sacroiliitis changes for these historical X-rays to ensure progression to AS had not occurred in the intervening period.

The study included axial SpA patients (by the ASAS criteria) who were not severe enough to be diagnosed with AS on X-ray (as per the modified NY criteria for AS: sacroiliitis Grade 3-4 unilaterally or Grade ≥ 2 bilaterally[20]). Of the 369 SI joint X-rays read centrally, 71 were found to have AS by the modified NY criteria and excluded (Grade 2 bilateral = 25; Grade 3 bilateral = 12; Grade 4 bilateral = 1; Grade 3 unilateral = 29; Grade 4 unilateral = 4). There were a further 73 subjects excluded from the trial for other reasons. This resulted in 225 subjects randomised (224 treated) with 111 and 113 in the etanercept and placebo groups respectively. There were a further 10 (4.4%) subjects excluded as they were found not to meet the ASAS criteria, leaving the mITT population with 106 and 109 etanercept and placebo treated subjects, respectively. The trial population was also noted to have more males than females (60:40) which is what would be expected in an early AS population.

The evaluator finds that classification of patients in this trial has been thorough and the X-rays were read centrally to ensure consistency. Given these facts, there is no evidence to suggest that the trial has inadvertently included patients with AS or that the results could have been driven by inclusion of the more severe AS population.

[20] Grade 0: Normal. Grade 1: Suspicious changes. Grade 2: Minimal abnormality – small localised areas with erosions or sclerosis, without alteration in the joint width. Grade 3: Unequivocal abnormality – moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis. Grade 4: Severe abnormality – total ankyloses.

The terminology 'non-radiographic' for the subgroup of axial spondyloarthritis is perhaps confusing as it implies there should be no changes on radiology whereas the trial population could have sacroiliitis on screening X-ray of either Grades 0, 1 or 2 unilaterally or Grades 0 or 1 bilaterally (or if historical X-rays were used, the grading requirement was lower at 0-1 unilaterally or Grade 0 bilaterally). This is presumably because only Grade 2 or higher bilaterally, or Grade 3 or higher unilaterally, is regarded as positive evidence of radiographic sacroiliitis. In addition, the ASAS criteria allow for subjects to be classified by 'imaging criteria' of at least one SpA feature and sacroiliitis on MRI. In the submitted study, 80% of subjects met the criteria of MRI changes of sacroiliitis. Another way of thinking of the included trial population is patients fulfilling the ASAS criteria for axial SpA but without X-ray changes consistent with AS.

There are no data available on the effects of etanercept on disease progression or structural damage in nr-AxSpA. The evaluator agrees that there is some evidence of anti-inflammatory effects, so agrees that the indication may remain 'treatment of nr-axSpA'. Nevertheless, it is recommended that a statement be included in the Clinical Trial section of the PI which makes the lack of data on disease progression clear.

Clinical data are only available for adults aged ≤ 50 years while the indication covers all adults. The evaluator accepts that data are available in the older age group for other indications and that a majorly different safety profile in the older nr-axSpA population would not be expected. As such, the evaluator agrees that the indication may remain for treatment of 'adults'. Nevertheless, an appropriate precaution stating this lack of data should be added to the Precautions Use in the Elderly section of the PI. The sponsor has agreed to alter the indication to a subpopulation with elevated CRP or MRI change. The subgroup of patients in the study with elevated hsCRP or ASAS MRI sacroiliitis included 94 and 95 patients in the etanercept and placebo groups, respectively, and excluded 26 (12%) of patients from the mITT population. The response on the primary efficacy endpoint of ASAS 40 in the mITT population was 32.4 versus 15.7%, that is, a difference of 16.4%, which increased to 18.3% in the subgroup with high baseline hsCRP (≥ 3 mg/mL) or positive MRI. The highest response was those with elevated hsCRP (treatment difference of 29.7%) although this subgroup was notably smaller (n = 92). The evaluator contends that this modest change in response rate difference is particularly important in improving the benefit-risk balance of the product as it makes it clear that the product is not to be used in a patient population without these objective inflammatory changes. The proposed indication does, however, need rewording to be more specific in delineating that the patient population need 'objective signs of inflammation'. This change would be in line with the approved European indication.

One of the main issues with etanercept use in the nr-AxSpA population is the lack of efficacy and safety data beyond 24 weeks of treatment duration. At this stage, due to these data limitations and the fact that the treatment may carry considerable risks, it is recommended not to continue therapy beyond 12 weeks in patients who are not responding to treatment. A statement needs to be included in the product information under Dosage and Administration to cover this issue. The wording in the EU label is:

> *Available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.*

The evaluator recommends that a more definitive stand is taken and that the wording state that therapy should not be continued beyond 12 weeks in a patient not responding to treatment.

It is acknowledged that the pivotal Study B1801031 is still ongoing with its 92 week open label extension period. A final report is due in June 2015. These data will further define the long term (104 weeks) efficacy and safety of etanercept in the nr-AxSpA population. A further planned Study B1801381 is listed in the RMP. This study has a primary objective to measure the

proportion of subjects with nr-AxSpA who flare following withdrawal of etanercept once ASAS 40 has been achieved. Secondary objectives include measuring the mean time to flare after withdrawal of etanercept and assessing the efficacy of retreatment in subjects who experience a flare after withdrawal of etanercept. These data will be important in assessing the relapse profile after treatment discontinuation and the safety and efficacy effects of retreatment. The sponsor states the final report for this study will be available in 2019. Data from both these studies will need to be submitted for evaluation when available.

As previously discussed, the appropriate selection of patients with the correct diagnosis in line with the proposed indication may not be straightforward and should be done by specialist rheumatologists versed in the ASAS criteria. This should be taken into account in the risk management plan.

In summary, there were a number of issues after the first round evaluation which have been addressed in the second round evaluation. These include:

- The marginal clinical benefit has been increased to a small extent by limiting to patients with MRI changes and elevated CRP. This change makes it clear that the product must be targeted at patients with inflammatory changes and not used in a broader population. The indication has been altered to reflect this. The product information now makes it clear that there is no evidence on disease progression.
- The safety of the product would be improved by advising that treatment needs to be ceased after 12 weeks if there has been no clinical response.
- The need for long term safety can be addressed by the submission of the data from the open label period of the pivotal trial (data to 104 weeks).
- A proposed study on treatment withdrawal and retreatment should address concerns from lack of data in this area.
- The lack of data in adults over 50 years can be addressed by appropriate precautions and is filled to some extent by safety data from other indications
- Revisions to the product information have largely been addressed and remaining issues are outlined [not in this AusPAR].
- It is recommended, due to the complexity in identifying the indicated population in clinical practice, that treatment be initiated by trained rheumatologists and this be specified in the RMP.

It is accepted that the increase in clinical benefit is small with limiting the indicated population to those with the appropriate inflammatory changes. Nonetheless, when this is taken into account together with the other actions listed above which will address the safety concerns, the evaluator finds that the benefit-risk balance of etanercept becomes favourable. This finding is subject to alteration of the indication and other aspects of the product information in addition to the provision of long term data when available.

14. Second round recommendation regarding authorisation

The evaluator recommends that etanercept be authorised subject to the following:

- Alteration of the indication. A proposed indication is:

  Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation, as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to NSAIDs.*

**Active disease is defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4.*

- Acceptance of the changes to the product information.
- Ensuring the CMI matches the changes proposed in the PI, in particular the revised indication and the fact that it is not recommended to continue treatment beyond 12 weeks in those who have had no response.
- Submission of long term safety and efficacy data from Study B1801031 for evaluation.
- Conduct of Study B1801381 which will assess effects on efficacy and safety of treatment withdrawal and retreatment. Data will need to be submitted for evaluation as soon as available.
- Clarification of the following relating to inclusion of patients from historical X-rays. It is assumed from the data submitted that 18/225 patients were included on the basis of historical X-rays and that these historical X-rays were taken no more than 96 days before trial entry at screening. The remainder of subjects (n=207) would therefore have had X-rays taken during the screening period. As these data could not be located in the clinical study report, could the sponsor clarify if this is correct?
- In order to ensure that patients are correctly identified for treatment according to the specific indication, it is recommended that treatment should only be initiated by appropriately trained rheumatologists.

15. References

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