EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
EMA/CHMP/373893/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enbrel

Procedure no. EMEA/H/C/262/II/167

Marketing authorisation holder (MAH): Pfizer Limited

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

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
CMH	Cochran-Mantel-Haenszel
CRO	Contract research organisation
CSR	Clinical study report
DMARDs	Disease-Modifying Anti-rheumatic Drugs
DVU	Discovertebral units
ESR	Erythrocyte Sedimentation Rate
ETN	Etanercept
EQ-5D	EuroQol EQ-5D Health State Profile
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
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
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
PASS	Patient Acceptable Symptom State
PBO	Placebo
PCS	Physical Component Score
PDCO	Paediatric Committee
PGA	Physician Global Assessment
PIP	Paediatric Investigation plan
RA	Rheumatoid Arthritis
RASSS	Radiographic Ankylosing Spondylitis Spine Score
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
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
WPAI	Work Productivity and Activity Impairment Questionnaire
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 05 November 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Enbrel	Etanercept	See Annex A

The MAH applied for an extension of the indication for the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to conventional therapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH took this opportunity to include minor administrative changes in section 4.2 of the 50 mg SmPC (EU/1/99/126/006-011, 016-021) and in section 2 of the PL (EU/1/99/126/012 and 022).

The variation proposed amendments to the SmPC, and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/241/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/241/2011 was completed.

The PDCO issued an opinion on compliance for the PIP P/241/2011. The statement *as per* article 28(3) of Regulation (EC) No 1901/2006 indicating compliance with this PIP was included in the marketing authorisation as part of variation II/145 approved in July 2012.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Robert James Hemmings

Submission date:	05 November 2013
Start of procedure:	22 November 2013
Rapporteur's preliminary assessment report circulated on:	15 January 2014
Rapporteur's updated assessment report circulated on:	13 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	25 April 2014
Rapporteur's assessment report on the MAH's responses circulated on:	23 May 2014
PRAC Rapporteur's final RMP assessment report circulated on:	13 June 2014
PRAC RMP advice and assessment overview adopted by PRAC:	13 June 2014
CHMP opinion:	26 June 2014

2. Scientific discussion

2.1. Introduction

Enbrel contains the active ingredient etanercept, a fully human protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is comprised of the extracellular domains of two human tumour necrosis factor receptors (TNFR2/p75) attached to the Fc domain of human IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

The pharmacotherapeutic classification of etanercept is tumor necrosis factor alpha (TNF-a) inhibitor (ATC code: L04AB01). The mechanism of action of etanercept is thought to be its competitive inhibition of tumour necrosis factor (TNF) binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (eg. cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Etanercept is approved for the treatment of moderate to severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis (rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, adolescent psoriatic arthritis and adolescent enthesitis-related arthritis) and plaque psoriasis (adult and paediatric).

More specifically, one of the indications of Enbrel is the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. Ankylosing spondylitis (AS) is a well-characterised form of axial Spondyloarthritis (AxSpA). Currently, anti-TNF treatment is available for patients with established AS, defined by the modified New York Criteria,

which includes a radiographic criterion of sacroiliitis (i.e. bilateral grade 2-4 or unilateral grade 3-4). However, the advent of new consensus-based criteria allows earlier identification of patients with AxSpA, before significant X-ray abnormalities develop. The 2009 Assessment in Ankylosing Spondylitis (ASAS) criteria were developed to capture a broader range of AxSpA patients in clinical practice, including those with radiographic AxSpA (radiographic sacroiliitis according to the NY criteria) and without radiographic sacroiliitis (nr-AxSpA). The nr-AxSpA subgroup of AxSpA patients is closely related to and shares many clinical characteristics with the AS population. Patients with nr-AxSpA may suffer significant clinical symptoms, functional disability, and work loss.

Unlike AS, the natural history of nr-AxSpA is not well known as longitudinal studies are lacking; however, available studies indicate that between 23% and 80% of patients with newly diagnosed AxSpA can be expected to be nr-AxSpA patients. If left untreated, nr-AxSpA may progress to AS which can cause permanent structural changes leading to progressive disability severely impacting the quality of life. Because AS is a slowly progressing disease as far as radiographic changes are concerned, definite sacroiliitis on plain radiographs appears relatively late, which is one reason for the long diagnostic delay of 5–10 years in 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.

Limited data exist on the role of anti-tumor necrosis factor (TNF) agents in the treatment nr-AxSpA, including the effect on prevention of anatomical progression in this early disease stage before significant X-ray abnormalities develop. In patients with AS, there is no convincing evidence that TNF inhibitors can prevent progressive structural damage. In clinical trials conducted to date, anti-TNF agents have demonstrated similar efficacy in AxSpA patients with and without radiographic sacroiliitis. Most recently, adalimumab and certolizumab pegol have been approved in the EU for the treatment of adults with nr-AxSpA.

The purpose of this application is to extend the indication of Enbrel to the "*treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to conventional therapy*". This variation is supported by a single study (B1801031) in adult patients presenting with nr-AxSpA. The clinical trial supporting this extension of indication is in line with the Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis (CPMP/EWP/4891/03).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

No environmental risk assessment has been provided in accordance with the CHMP guidance EMEA/CHMP/SWP/4447/00 (01 June 2006) as proteins are exempted from testing because of the chemical structure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of the clinical study

Protocol No. (Country; No. Centers)*	Study Start and Status	Study Design and Objectives	Study Population	Treatment Groups	No. of Subjects	Demographics	Efficacy Endpoints
B1801031 (also known as 0881A3-4725) (ARG, BEL, COL, CZE, FIN, FRA, DEU, HUN, KOR, NLD, RUS, ESP, TWN, GBR; 44 centers)	May 2011 Ongoing (last subject completed week 24 in Feb 2013)	Double-blind, placebo-controlled, two period randomized, multicenter study Primary objective: to compare the efficacy of etanercept against placebo in improving symptoms of early nr-AxSpA at 12 weeks. Secondary objectives: (1) to assess the efficacy and safety of etanercept plus background NSAID over 104 weeks; (2) to compare the effect of etanercept versus placebo on inflammation seen in MRI of the spine at 12 weeks; and (3) to compare the quality of life between those subjects treated with etanercept versus placebo over 12 weeks. Exploratory objective: to evaluate the effect of etanercept plus background NSAID on radiographic and MRI changes for up to 104 weeks.	Diagnosis: Non-radiographic axial spondyloarthritis Inclusion/ Exclusion Criteria: Diagnosis of axial spondyloarthritis (as defined by the ASAS criteria) with a duration of symptoms of >3 months and <5 years at the time of consent, male or female, 18 years or older but less than 50 years at the time of consent, taking a stable dose of an NSAID for at least 14 days before baseline	**Double-blind Period (Weeks 1 through 12):** Etanercept 50 mg SC QW Etanercept placebo SC QW **Open-label Period (Weeks 13 through 104):** Etanercept 50 mg SC QW	Randomized: 225 (111 in etanercept 50 mg group and 114 in placebo group) Received study drug: 224 (111 in etanercept 50 mg group and 113 in placebo group)	Sex: 134 M / 91 F Mean Age (min/max): 31.8 (18/49) years Race: 164 W / 1 B / 49 A / 11 O	The primary endpoint was the proportion of subjects who achieved ASAS 40 at week 12. Secondary endpoints include: ASAS 40 at time points other than 12 weeks, ASAS 20, ASAS 5/6, ASDAS, ASAS partial remission, subject assessment of disease activity, physician global assessment, VAS nocturnal and total back pain over time, BASFI, BASDAI, BASDAI 20, BASDAI 50, BAS-G, BASMI, inflammation as measured by MRI of the spine at week 12, tender and swollen joints, MASES, CRP and ESR, and health outcomes (WPAI, HADS, EQ-5D MFI, SF-36, ASQoL, ASWIS, MOS Sleep, MFI, PASS, and MCII). Exploratory endpoints include: changes in inflammation of the spine and SI joint at 12 weeks, and in the spine and SI joint at 48 weeks and 104 weeks as measured by MRI; and changes in spinal X-ray at 104 weeks as measured by mSASSS and RASSS.

2.3.2. Pharmacokinetics

Etanercept pharmacokinetics have been well characterized in adult subjects with RA, AS, or psoriasis and are similar among all patient populations. Population pharmacokinetic analyses in adults have not identified pharmacokinetic differences that can be linked to specific disease observed in the subjects studied.

Etanercept concentrations were not measured in the double-blind, placebo-controlled randomised study in adult subjects with nr-AxSpA that is included in this variation (study B1801031). The dosage regimen used in this study was 50 mg SC QW, identical to the approved regimen for the treatment of adults with RA, AS, psoriatic arthritis, or psoriasis.

As the pharmacokinetics of etanercept have already been studied in AS, the absence of PK data in this population is considered acceptable by the CHMP. In addition, co-administration of Enbrel with NSAIDs has already been tested in previous trials and no interaction has been observed.

2.3.3. Pharmacodynamics

No new data have been submitted. This is considered acceptable by the CHMP as the mechanism of action of etanercept is expected to be the same as in AS.

2.3.4. Conclusions on clinical pharmacology

No new pharmacological data have been submitted in this application, which is considered acceptable by the CHMP. The dosage regimen used in this study was 50 mg SC QW, identical to the approved regimen for the treatment of adults with RA, AS, psoriatic arthritis, or psoriasis. The mechanism of action of etanercept in severe non-radiographic axial spondyloarthritis is also expected to be the same as in AS.

2.4. Clinical efficacy

2.4.1. Main study

Study B1801031: A Multicentre, 12-Week Double Blind Placebo Controlled Randomized Study of Etanercept on a Background NSAID in the Treatment of Adult Subjects With Non Radiographic Axial spondyloarthritis With a 92-Week Open Label Extension.

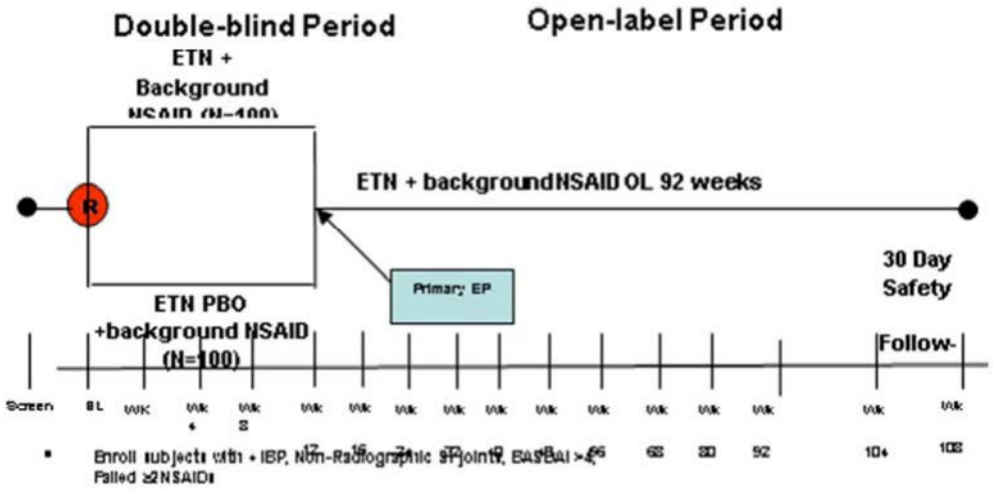
Methods

This was a multicenter, double-blind, placebo-controlled, 2-period randomized study which evaluated the efficacy of etanercept 50 mg weekly vs. placebo in the treatment of subjects with active AxSpA despite optimal NSAID therapy and with non-radiographic sacroiliitis defined as those subjects who did not meet the modified New York (NY) criteria.

The 12-Week double-blind results from the study and the open-label results from Week 12 through Week 24 are presented in the Week 24 clinical study report (CSR) included in this variation. The open-label period of study B1801031 is currently ongoing.

The study design is summarized in Figure 1.

Figure 1: Study Design and Plan



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

Study participants

Main Inclusion criteria

- Female or male 18 years or older but less than 50 years at the time of consent.

- Diagnosis of AxSpA, as defined by the ASAS criteria with duration of symptoms of >3 months and <5 years at the time of consent.
- Active symptoms defined by a BASDAI ≥4 at the Screening Visit.
- 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.
- Stable dose of NSAID for at least 14 days before baseline.
- Negative serum pregnancy test taken at screening, negative urine pregnancy test taken at baseline and negative serum pregnancy test collected at baseline
- Agreement by male subjects who were not surgically sterile and female subjects who were not surgically sterile or post-menopausal to use a highly effective method of birth control for the duration of the study.
- Adequate screening for TB in accordance with local country guideline.

Main exclusion criteria

- Any previous treatment with a TNFα inhibitor, B/T cell inhibitor or other biologic agent or immunosuppressive agent for a condition other than IBD.
- Current or previous treatment within 6 months for IBD with any TNFα inhibitor or any other immunosuppressant.
- Any orthopaedic or medical condition that could cause chronic back pain such as spondylodiscitis, tumour or advance discopathy.
- Evidence of IBD flare or uveitis within 6 months of baseline.
- Radiological sacroiliitis grade 3-4 unilaterally or grade ≥2 bilaterally as defined by the Modified NY Criteria.
- Concurrent treatment with more than 1 NSAID or change in dose within 14 days at baseline.
- DMARDS other than methotrexate, sulfasalazine and hydroxychloroquine within 4 weeks of baseline (Note: Subjects may have been taking only one allowable DMARD at a time).
- Dose of prednisone >10 mg/day (or equivalent) or change in dose within 4 weeks before baseline.
- Intra-articular, intravenous, intramuscular, or SC corticosteroid within 4 weeks before baseline.
- Current or recent (within 2 years) active TB infection; untreated latent TB.

These selection criteria defined a population of patients with a diagnosis of nr-AxSpA (as defined by the Assessment in Ankylosing Spondylitis criteria) and clearly excluded patients with AS. Furthermore, patients had to present with active symptoms including back pain not responding to NSAIDs. The study population was adequately selected although the objective signs of inflammation described in the SmPC indication (elevated CRP and/or MRI evidence) were not a condition for eligibility. A high-sensitivity assay to determine CRP in a central laboratory was chosen in order to ensure the reliability of the diagnosis and investigate the potential correlation of this marker with disease activity and therapeutic effect.

Treatments

Eligible subjects were randomly assigned in a 1:1 ratio to receive either etanercept 50 mg (ETN, pre-filled syringe) subcutaneously (SC) QW plus a stable background NSAID at the optimal tolerated anti-inflammatory dosage as determined by the investigator, or placebo (PBO) SC QW plus background NSAID for 12 weeks (double-blind period).

Permitted concomitant therapy (other than one NSAID)

- short acting analgesics with no anti-inflammatory action (such as paracetamol, or short acting narcotics) except on the day of the study visit
- aspirin at daily doses up to 325 mg if indicated for cardiovascular protection
- oral stable corticosteroid dose (≤10 mg/day of prednisone or equivalent)
- one DMARD (sulfasalazine, hydroxychloroquine, or methotrexate) at stable dose

Etanercept (or placebo) was added to background therapy as administered in clinical practice.

All subjects who completed the 12-week controlled period could enter into the 92-week open-label treatment period with etanercept 50 mg QW plus background NSAID.

Objectives

Primary

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

- To compare the effect of ETN against placebo on inflammation seen in MRI of the spine and on quality of life at 12 weeks when added to a background NSAID at the optimal anti-inflammatory dose
- To assess the efficacy and safety of ETN and background NSAID over 104 weeks

Exploratory

To evaluate the effect of ETN plus background NSAID on radiographic and MRI changes for up to 104 weeks.

Outcomes/endpoints

Primary endpoint

The primary endpoint was the proportion of subjects who achieved ASAS 40 at Week 12. ASAS 40 was derived from the following 4 AS assessments: Subject Assessment of Disease Activity, pain, physical function, and inflammation. If a subject had a missing evaluation for any 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:
    - Subject Assessment of Disease Activity,

- Mean of subject assessment of nocturnal pain and total back pain (note: total back pain was also used for the ASAS calculation in accordance with EMA 2009 guideline),
- Function represented by the Bath Ankylosing Spondylitis Functional Index (BASFI) score,
- Inflammation represented by the mean of the 2 morning stiffness-related BASDAI scores.

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

Secondary endpoints

- Proportion of subjects who achieve ASAS 40 at time points other than 12 weeks;
- Proportion of subjects who achieve ASAS 20;
- Proportion of subjects who achieve ASAS 5/6 (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 high sensitivity C-reactive protein [hsCRP]);
- Changes from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS);
- Proportion of subjects with ASAS partial remission (ASAS partial remission was based on the same 4 domains as the other ASAS endpoints, partial remission was defined as a score of 2 or less [on a scale of 0-10 cm] for each of the 4 domains);
- Time to ASAS partial remission;
- Changes from baseline in Subject Assessment of Disease Activity (Visual Analogue Scale [VAS]);
- Changes from baseline in the VAS Physician Global Assessment;
- Changes from baseline in VAS nocturnal and total back pain over time;
- Changes from baseline in the Bath Ankylosing Spondylitis Functional Index (BASFI) and its components;
- Changes from baseline in the BASDAI and its components;
- Proportion of subjects who achieved BASDAI 20 and BASDAI 50;
- Changes in Bath Ankylosing Spondylitis Patient Global Assessment Score (BAS-G);
- Changes from baseline in spinal mobility as measured by Bath Ankylosing Spondylitis Metrology Index (BASMI) (and its individual components), and occiput-to-wall distance, and chest expansion;
- Changes in inflammation at week 12 as measured by MRI of the spine at week 12;
- Changes from baseline in tender and swollen joint counts (44 count);
- Changes from baseline on dactylitis and enthesitis score (Maastricht Ankylosing Spondylitis Entheses Score [MASES]);
- Changes from baseline in the acute phase reactants hsCRP and erythrocyte sedimentation rate (ESR);
- Health Outcomes Assessments using the following instruments: Work Productivity and Activity Impairment Questionnaire (WPAI), Hospital Anxiety and Depression Scale (HADS), EuroQol EQ-5D Health State Profile (EQ-5D) Multidimensional Fatigue Inventory (MFI), 36-Item Short-Form Health Survey (SF-36), Ankylosing Spondylitis Quality of Life (ASQoL), Ankylosing Spondylitis Work Stability Scale (ASWIS), Medical Outcomes Study (MOS) Sleep, MFI, Patient Acceptable Symptom State (PASS), and Minimum Clinically Important Improvement (MCII).

Exploratory endpoint

Changes from baseline in inflammation of the sacroiliac (SI) joint at 12 weeks as measured by MRI.

X-rays and MRI evaluations (up to week 104) were conducted by a central independent CRO. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and the Radiographic Ankylosing Spondylitis Spinal Score (RASSS) are used to evaluate the radiographic changes of the spine from baseline to Weeks 104. The AS spine MRI score for acute changes (ASspiMRI-a) is used to assess inflammation in the spine and the SPARCC spine and sacroiliac joint (SIJ) scoring method is used to assess the inflammation of the spine and sacroiliac joints from baseline to Weeks 12, 48 and 104.

Sample size

The sample size calculation was based on the original primary endpoint, ASAS 20 response. For the ASAS 20 endpoint, assuming response rates of at least 55% in the ETN plus NSAID group and no more than 30% in the placebo plus NSAID group (based on historical data supplied by ETN studies), 100 subjects per arm would be needed to provide approximately 90% power using 2-sided testing at alpha = 0.05. Based on ASAS 40 data from these studies, plus response data from studies reported in the literature for other TNF-α inhibitors, it was expected that the response rates for each group would be somewhat lower for the ASAS 40 than the ASAS 20, but that the magnitude of the difference between groups would remain in the range of 25%, in which case the planned sample size would provide power at least as great as that for the ASAS 20 endpoint.

Randomisation

Subjects were randomly assigned in a 1:1 ratio to receive either ETN 50 mg subcutaneously (SC) weekly plus a stable background NSAID at optimal anti-inflammatory dosage as determined by the Investigator, or ETN placebo plus background NSAID for 12 weeks. Randomisation was centralised using IVRS (Interactive Voice Response System) and stratified based on positive or negative sacroiliitis on magnetic resonance imaging (MRI).

Blinding (masking)

The study was subject-, investigator- and sponsor-blinded in the double-blind period. Pre-filled syringes of identical appearance containing etanercept or placebo were supplied.

Statistical methods

The primary analyses for this study were done after all subjects had completed the 12 week, double-blind phase of the study and all endpoints through 12 weeks were analysed. An interim analysis for the subsequent open phase of the study was planned after all subjects had completed the Week 24 visit and a database through Week 24 had been finalized. The purpose of this analysis was to summarize 24-week efficacy and safety.

Analysis sets

- Full Analysis Population**:** Defined as all randomized subjects included in the study.
- mITT Population**:** The primary analysis set was a modified intent-to-treat (mITT) population defined as all randomized subjects who took at least one dose of study drug, had at least one on-therapy evaluation and met the ASAS classification criteria for AxSpA. This was the primary population for all efficacy analyses during the double-blind period.

- Per Protocol (PP) Analysis Population**:** The per-protocol population was defined as a subset of the mITT population excluding subjects who had a protocol deviation that was thought to potentially affect efficacy variables. Potential subjects to be excluded from this population were initially identified programmatically and then confirmed by the study clinician prior to unblinding the database.
- Safety Analysis Population**:** The safety analysis set for the double-blind period was defined as all randomized subjects who took at least one dose of study drug during that phase of the study.

Treatment misallocations

- Randomized but not treated: excluded from the efficacy analyses and the safety analyses
- Randomized but took at least one dose of incorrect treatment: reported under randomized treatment group for all efficacy and safety analyses, but omitted from per-protocol analyses.

Handling of Missing Values

Unless otherwise specified, missing items for observations on the individual items of the derived efficacy and health outcome scales were handled as follows. If more than 20% of the items were missing, the total scores for these scales were considered missing. If 20% or fewer items were missing, the average of the available items was multiplied by the total number of items to get a derived total score.

When the last observation carried forward (LOCF) approach was being employed, efficacy assessments were handled in the following manner: if the scheduled assessment was missing, the immediately preceding scheduled assessment was used; baseline data was not carried forward unless otherwise noted. This method was used for primary and secondary endpoints.

As sensitivity analyses for the double-blind period, modelling procedures that included all available data from Weeks 2 through 12 were used.

The missing data were handled using LOCF which is acceptable in this situation where even placebo patients improved during the course of the trial. A variety of other sensitivity analyses have also been provided to allow adequate assessment of the effects of the missing data on the results.

Analysis of primary endpoint

The comparison between 2 treatment groups was performed using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by positive or negative sacroiliitis MRI and geographic region. The value used was the Week 12 visit; for subjects who discontinued before Week 12, the last evaluation after baseline and prior to discontinuation was to be used (LOCF).

As a sensitivity analysis, subjects who discontinued before Week 12 (including subjects who had a Baseline Visit only) were counted as non-responders instead of using an LOCF approach for the missing data.

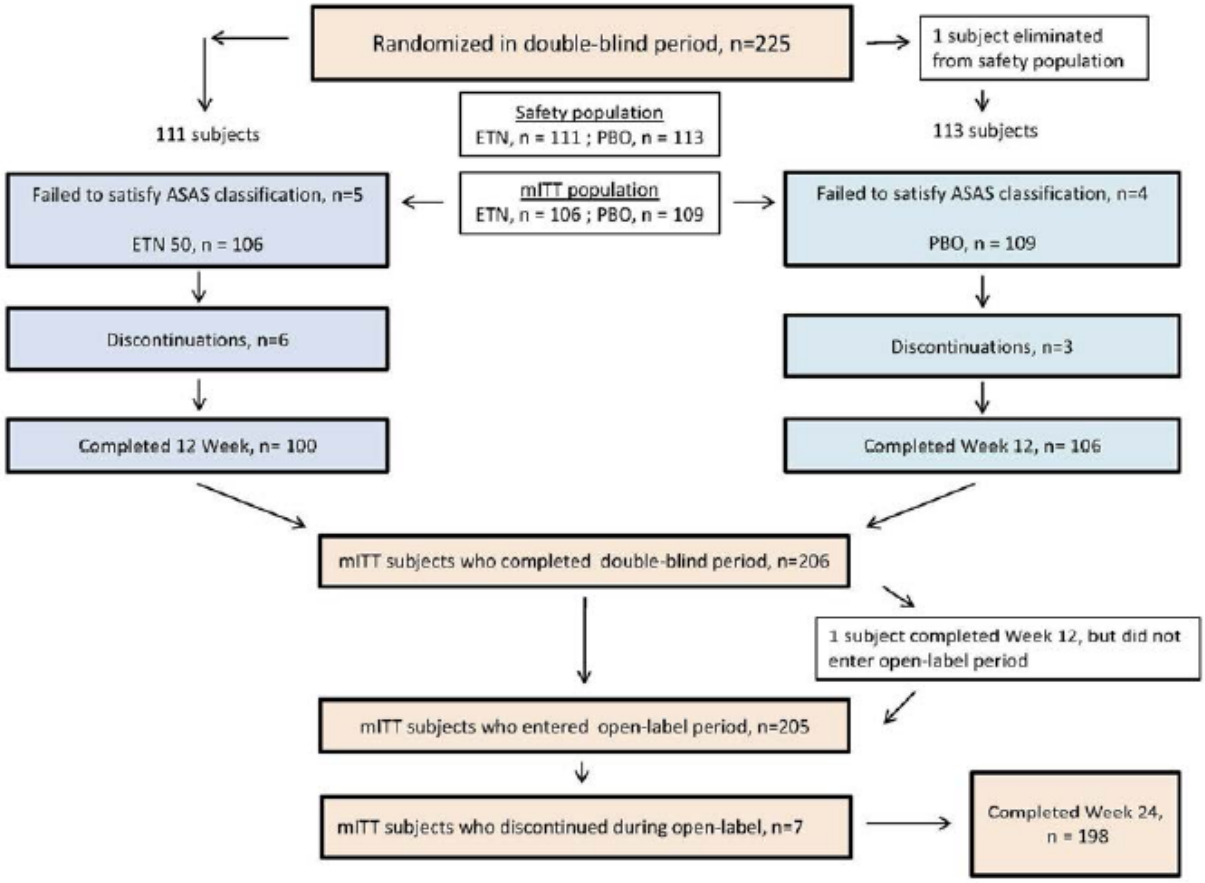
As an additional sensitivity analysis, a generalized estimating equations (GEE) model, using a logit link, a binomial distribution and an auto-regressive correlation structure, with treatment groups, visits and their interaction as fixed factors, was used. The model also included factors of positive or negative sacroiliitis MRI and geographic region.

Subgroup analyses were conducted by key demographic and baseline disease characteristics. In addition a logistic regression model with factors for treatment subgroup and treatment by subgroup interaction was fitted to evaluate consistency of response within the levels of the subgroup.

Results

Participant flow

In total, 383 subjects were screened for the study, of these, 158 subjects were considered screen failures. The remaining 225 subjects (full analysis population) were randomised and 224 subjects received study drug: 111 subjects were randomised to the etanercept 50 mg dose group and 113 subjects were randomized to the placebo group (one subject randomised to placebo did not receive study drug).



Of the 209 subjects who completed the double-blind period, 208 subjects continued into the open-label period of the study (one subject in the placebo group who completed the double-blind period did not enter the open-label period). A total of 200 subjects reached the Week 24 time point: 98 subjects in the ETN/ETN group and 102 in the placebo/ETN group (Table 1).

Table 1 Subject disposition

	ETN (N=111)	Placebo (N=114)	Total (N=225)
Assigned to study treatment	111	114	225
Randomized but not treated	0	1	1
Treated	111	113	224
Discontinued during double-blind period	9	6	15
Does not meet inclusion criteria	3	3	6
No longer willing to participate in study	2	1	3
Protocol violation	1	1	2
AE	3	1	4
Completed the double-blind period	102	107	209
Entered the open-label period	102	106	208
Discontinued during open-label period	4	4	8
Does not meet inclusion criteria	0	1	1
Insufficient clinical response	1	0	1

	ETN (N=111)	Placebo (N=114)	Total (N=225)
Lost to follow-up	0	1	1
No longer willing to participate in study	2	1	3
Protocol violation	1	0	1
AE	0	1	1
Completed 12 weeks of the open-label period a	98	102	200

A high percentage of subjects completed the first phase of the trial, about 93% for the double-blind 12-week period and 89% for the 24-week overall period. The reasons for discontinuation were the same in the active and placebo groups (double-blind period), except for adverse events (3 vs. 1, respectively).

Recruitment

The trial was conducted at 48 centres in 14 countries, with 68% of the randomised patients being from the EU:

- EU (34 centres; 153 patients): Belgium (3; 26 patients), Czech Republic (3; 23 patients), Finland (2; 5 patients), France (4; 13 patients), Germany (5; 18 patients), Hungary (6; 42 patients), Netherlands (2; 12 patients), Spain (4; 9 patients), UK (5; 5 patients)
- Russia (3 centres; 6 patients)
- Korea (3 centres; 20 patients) and Taiwan (3 centres; 29 patients)
- Argentina (2 centres; 3 patients) and Colombia (3 centres; 14 patients)

The first patient was enrolled on 05-05-2011 and the last patient was completed (24-week period) on 19-02-2013.

Conduct of the study

The main amendment, which was implemented before enrolment started, was the change of the primary endpoint from ASAS 20 to ASAS 40. In addition, ASAS 50 and ASAS 70 were deleted.

Baseline data

The baseline demographic and disease characteristics for the full analysis population (225 randomised subjects) are presented in Tables 2 to 4.

In general, the baseline values for the demographic and disease characteristics were similar between the 2 treatment groups. The mean (SD) age for the overall randomised study population was 32 (8) years with a range of 18 to 49 years. The majority of subjects in the study were male (60%) and White (73%). Overall, the mean (SD) duration of disease symptoms was 2.5 (1.8) years with a range of 0.3 to 15.6 years. Approximately 20% of the subjects were taking a DMARD at baseline, and nearly all subjects (99%) were taking an NSAID at baseline (2 subjects in the placebo group were not 100% compliant with taking NSAIDs for the 4 weeks prior to study baseline). The mean (SD) hsCRP value was 6.4 (10.4) mg/L. The mean (SD) values for the patient and physician global assessments of disease activity were 5.7 (2.2) cm and 5.4 (1.9) cm, respectively. The mean (SD) BASDAI total score was 5.96 (1.81).

The patients were well distributed across the treatment groups for demographic and disease characteristics. Overall, 77% had active inflammation on MRI highly suggestive of sacroiliitis associated with SpA; however, only 85% corresponded to the target SmPC indication (patients with elevated CRP and/or MRI evidence of inflammation).

The median hs-CRP was notably lower than the mean presented in Table 3, 2.23 in the total population (range 0.13 – 78.9 mg/L), in line with cohorts published in the literature (e.g. 2.7 mg/L in Poddubnyy, 2010).

Table 2 Demographic characteristics of the FAS Population

	Overall p-Value	ETN (N=111)	Placebo (N=114)	Total (N=225)
Age (years)	0.7102[a]			
Mean (SD)		31.6 (7.8)	32.0 (7.8)	31.8 (7.8)
Gender (%)	0.3419[b]			
Female		41 (36.94)	50 (43.86)	91 (40.44)
Male		70 (63.06)	64 (56.14)	134 (59.56)
Race (%)	0.9849[b]			
White		81 (72.97)	83 (72.81)	164 (72.89)
Black		1 (0.90)	0	1 (0.44)
Asian		24 (21.62)	25 (21.93)	49 (21.78)
Other		5 (4.50)	6 (5.26)	11 (4.89)
Baseline Weight (kg)	0.0823[a]			
Mean (SD)		75.7 (16.1)	72.0 (15.6)	73.9 (15.9)
Baseline Height (cm)	0.1898[a]			
Mean (SD)		172.7 (9.8)	171.0 (8.9)	171.8 (9.4)
Baseline BMI (kg/m^2)	0.1477[a]			
Mean (SD)		25.3 (4.9)	24.5 (4.2)	24.9 (4.6)

a. One-way analysis of variance with treatment as factor.
b. Fisher's Exact Test P-value (2-Tail).

Table 3 Baseline disease characteristics of the FAS Population

	Overall p-Value	ETN (N=111)	Placebo (N=114)	Total (N=225)
Duration of Disease Symptoms (years)	0.8458[Error! Reference source not found.]			
Mean (SD)		2.44 (1.91)	2.49 (1.72)	2.46 (1.82)
hsCRP (mg/L)	0.9088[Error! Reference source not found.]			
N		111	112	223
Mean (SD)		6.49 (10.43)	6.33 (10.35)	6.41 (10.36)
BASDAI Total Score (cm)	0.9901[Error! Reference source not found.]			
N		111	113	224
Mean (SD)		5.96 (1.74)	5.96 (1.88)	5.96 (1.81)
Patient Global Assessment of Disease Activity (cm)[Error! Reference source not found.]	0.8894[Error! Reference source not found.]			
N		111	113	224
Mean (SD)		5.74 (2.28)	5.70 (2.11)	5.72 (2.19)
Physician Global Assessment of Disease Activity (cm)[Error! Reference source not found.]	0.0562[Error! Reference source not found.]			
N		107	109	216
Mean (SD)		5.68 (1.89)	5.18 (1.93)	5.42 (1.92)
Total Back Pain (cm)[Error! Reference source not found.]	0.8961[Error! Reference source not found.]			
N		111	113	224
Mean (SD)		5.42 (2.46)	5.46 (2.34)	5.44 (2.39)
SPARCC MRI SI Score	0.8713[Error! Reference source not found.]			
N		97	106	203
Mean (SD)		7.89 (9.66)	7.67 (10.11)	7.77 (9.87)
Concomitant DMARD Use	1.0000[b]			
Yes		22 (19.82)	22 (19.30)	44 (19.56)
No		89 (80.18)	92 (80.70)	181 (80.44)
Concomitant NSAID Use	0.4979[b]			
Yes		111 (100)	112 (98.25)	223 (99.11)
No		0 (0.00)	2 (1.75)	2 (0.89)
Either Elevated hsCRP or ASAS MRI Sacroiliitis	1.0000[b]			
Yes		94 (84.68)	97 (85.09)	191 (84.89)
No		17 (15.32)	17 (14.91)	34 (15.11)

Table 4 ASAS Classification components for diagnosis of nr-AxSpA (FAS Population)

	Overall p-Value[b]	ETN (N=111)	Placebo (N=114)	Total (N=225)
MRI Sacroiliitis	0.7518			
Positive		87 (78.38)	87 (76.32)	174 (77.33)
Negative		24 (21.62)	27 (23.68)	51 (22.67)
Inflammatory Back Pain	0.5998			
Yes		90 (81.08)	95 (83.33)	185 (82.22)
No		21 (18.92)	18 (15.79)	39 (17.33)
Unknown		0 (0.00)	1 (0.88)	1 (0.44)
Arthritis	0.4245			
Yes		51 (45.95)	59 (51.75)	110 (48.89)
No		60 (54.05)	55 (48.25)	115 (51.11)
Enthesitis	0.6859			
Yes		47 (42.34)	45 (39.47)	92 (40.89)
No		64 (57.66)	69 (60.53)	133 (59.11)
Anterior Uveitis	1.0000			
Yes		9 (8.11)	9 (7.89)	18 (8.00)
No		102 (91.89)	103 (90.35)	205 (91.11)
Unknown		0 (0.00)	2 (1.75)	2 (0.89)
Dactylitis	0.1946			
Yes		5 (4.50)	11 (9.65)	16 (7.11)
No		105 (94.59)	103 (90.35)	208 (92.44)
Unknown		1 (0.90)	0 (0.00)	1 (0.44)
Psoriasis	0.3913			
Yes		14 (12.61)	10 (8.77)	24 (10.67)
No		96 (86.49)	104 (91.23)	200 (88.89)
Unknown		1 (0.90)	0 (0.00)	1 (0.44)
Inflammatory Bowel Disease	1.0000			
Yes		1 (0.90)	1 (0.88)	2 (0.89)
No		110 (99.10)	113 (99.12)	223 (99.11)
Good Prior Response to NSAIDs	0.8652			
N		96	102	198
Yes		22 (19.82)	22 (19.30)	44 (19.56)
No		74 (66.67)	80 (70.18)	154 (68.44)
Family History of SpA	0.3276			
N		93	94	187
Yes		30 (27.03)	23 (20.18)	53 (23.56)
No		61 (54.95)	68 (59.65)	129 (57.33)
Unknown		2 (1.80)	3 (2.63)	5 (2.22)
HLA-B27 Positive	0.1052			
N		109	110	219
Yes		71 (63.96)	83 (72.81)	154 (68.44)
No		38 (34.23)	27 (23.68)	65 (28.89)
Elevated hsCRP (>3 mg/L)	0.7869			
N		111	112	223
Yes		48 (43.24)	46 (40.35)	94 (41.78)
No		63 (56.76)	66 (57.89)	129 (57.33)

Numbers analysed

The analysis sets are presented in Table 5. Ten (10) subjects were excluded from the mITT because they did not meet the ASAS criteria for AxSpA as they were negative for sacroiliitis based on MRI

central reading and were HLA-B27 negative (one of these subjects also did not receive any drug). In addition, 2 subjects included in the mITT population did not provide data for most efficacy analyses, thus resulting in 105 subjects in the ETN group and 108 subjects in the placebo group. An additional 9 subjects were excluded from the PP population, because of treatment deviations (more than 1 DMARD, non-compliance, incorrect treatment) or deviations from eligibility criteria.

Table 5 Analysis sets

	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.

Outcomes and estimation

Primary endpoint

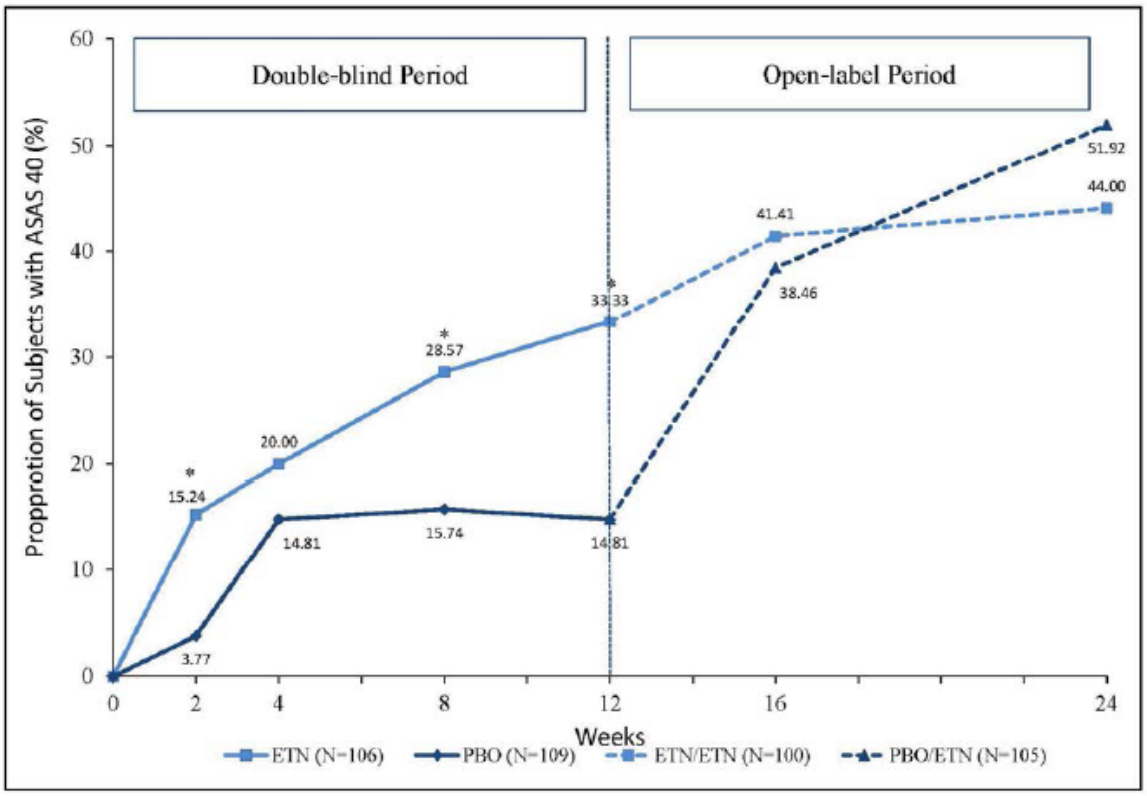
The primary analysis (LOCF - EMA 2005 guideline for back pain) and the analysis using the EMA 2009 guideline are presented in Table 6 and Figure 2. At Week 12, a significantly greater percentage of subjects in the ETN group achieved an ASAS 40 response compared with the placebo group.

Table 6 Proportion of Subjects Who Achieved an ASAS 40 Response at Week 12 (mITT - LOCF)

ASAS 40	ETN n/N (%) (N=105)	Placebo n/N (%) (N=108)	p-Value (CMH)[a]	Difference in Proportions (95% CI)
Week 12 (primary analysis)	34/105 (32.38)	17/108 (15.74)	0.0062	16.64 (5.36, 27.92)
Double-blind Period				
Week 2	16/105 (15.24)	4/106 (3.77)	0.0059	
Week 4	21/105 (20.00)	16/108 (14.81)	0.3786	
Week 8	30/105 (28.57)	17/108 (15.74)	0.0304	
Week 12	35/105 (33.33)	16/108 (14.81)	0.0023	
Open-label Period	**N = 100**	**N = 104**		
Week 16	41/99 (41.41)	40/104 (38.46)	NA	
Week 24	42/100 (42.00)	54/104 (51.92)	NA	

a Cochran-Mantel-Haenszel chi-square test, stratified by MRI and geographic region

Figure 2 Proportion of Subjects Achieving ASAS 40 up to 24 weeks



*p<0.05 (Double-blind period only).

The sensitivity analyses (using EMA 2009 guideline) are presented in Table 7 and showed the same pattern of results.

Table 7 Sensitivity Analyses: Proportion of Subjects Achieving ASAS 40 at Week 12

Time Point	ETN n/N (%)	Placebo n/N (%)	p-Value	Difference in Proportions % (95% CI)
Per-Protocol Population, LOCF	N=101	N=103	a	
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 Imputation	N=106	N=109	a	
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	a	
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)
mITT Population, GEE analysis summary	N=104	N=106	b	
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

a. Cochran-Mantel-Haenszel chi-square test, stratified by MRI and geographic region
b. Model includes positive/negative sacroiliitis status, geographic region, treatment, visit and treatment by visit interaction.

Key secondary endpoints

ASAS 20 (mITT, LOCF)

A significantly greater percentage of subjects in the ETN group achieved an ASAS 20 response compared with the placebo group at Weeks 2 (30.5% [32/105] vs. 16.0% [17/106]; p = 0.019) and 12 (52.4% [55/105] vs. 36.1% [39/108]; p = 0.019). Similar to what was observed for ASAS 40 response, at the end of the open-label period, both treatment groups achieved comparable ASAS 20 responses (65 - 71%).

ASAS 5/6 (mITT, LOCF)

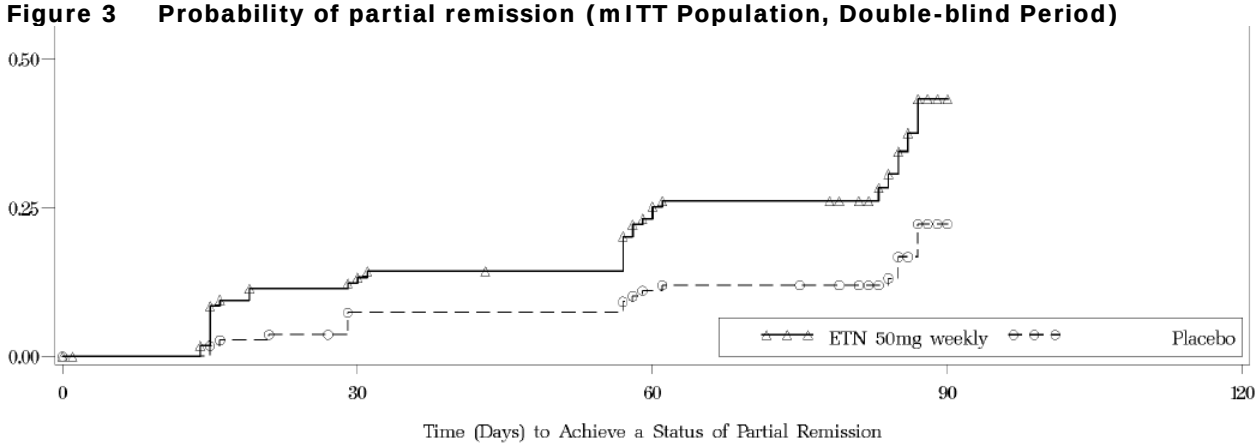
The proportion of subjects in the ETN and placebo groups with at least a 20% improvement in 5 of 6 criteria in ASAS showed a similar pattern as ASAS 40 response. A statistically significant improvement in ASAS 5/6 was observed in favor of the ETN group beginning at the Week 2 time point (15.7% [16/102] vs. 2.9% [3/105]; p = 0.002) and continued through to the last evaluation of the double-blind period (33.0% [34/103] vs. 10.4% [11/106]; p < 0.0001). The proportion continued to increase

during the open-label period in the ETN/ETN group (40.2% [39/97] at Week 24) and in the PBO/ETN group (41.7% [43/103] at Week 24).

ASAS partial remission (mITT, LOCF)

The proportion of subjects in the ETN and placebo groups who achieved a partial remission in ASAS score showed a similar pattern as ASAS 40 response; at week 12, it was 24.8% (26/105) and 11.9% (13/109), respectively (p = 0.02). The Kaplan-Meier estimate of the probability of partial remission at Week 12 was 43.3% in the ETN group and 22.3% in the PBO group (log rank test p = 0.002) (Figure 3).

Figure 3 Probability of partial remission (mITT Population, Double-blind Period)



Components of ASAS (mITT, LOCF)

At Week 12, statistically significant differences in the mean changes from baseline were observed between ETN and PBO groups for all ASAS components (Table 8).

Table 8 Changes from baseline in various ASAS components (mITT, LOCF)

Time Point	Treatment	n	Raw Mean [cm] (SD)	Change Within Group Adjusted Mean (SE)[a]	Percent Improvement[b]	Between Group Comparison p-Value[a]
Subject Assessment of Disease Activity (VAS)						
Baseline	ETN	106	5.77 (2.28)			
	Placebo	109	5.78 (2.09)			
Week 12	ETN	105	3.43 (2.59)	-2.06 (0.31)	35.437	0.0102
	Placebo	109	4.24 (2.31)	-1.26 (0.30)	21.848	
Week 24	ETN/ETN	100	2.85 (2.44)	-2.92 (0.28)	50.622	NA
	Placebo/ETN	105	2.57 (2.34)	-3.21 (0.23)	55.506	
Nocturnal Back Pain (VAS)						
Baseline	ETN	106	5.54 (2.58)			
	Placebo	109	5.40 (2.47)			
Week 12	ETN	105	3.11 (2.79)	-1.96 (0.36)	35.324	0.0091
	Placebo	109	4.02 (2.74)	-1.03 (0.34)	19.172	
Week 24	ETN/ETN	100	2.74 (2.53)	-2.79 (0.30)	50.403	NA
	Placebo/ETN	105	2.13 (2.32)	-3.25 (0.26)	60.427	
Total Back Pain						
Baseline	ETN	106	5.51 (2.44)			
	Placebo	109	5.48 (2.35)			
Week 12	ETN	105	3.22 (2.63)	-1.99 (0.32)	35.888	0.0064
	Placebo	109	4.08 (2.57)	-1.12 (0.31)	20.446	
Week 24	ETN/ETN	100	2.75 (2.45)	-2.76 (0.28)	50.049	NA
	Placebo/ETN	105	2.52 (2.54)	-2.92 (0.24)	53.672	
BASFI						
Baseline	ETN	106	4.18 (2.45)			
	Placebo	108	3.87 (2.51)			
Week 12	ETN	105	2.62 (2.28)	-1.41 (0.24)	33.421	0.0164
	Placebo	108	2.99 (2.35)	-0.84 (0.23)	21.601	
Week 24	ETN/ETN	100	2.35 (2.26)	-1.89 (0.22)	44.535	NA
	Placebo/ETN	104	1.98 (1.92)	-1.85 (0.20)	48.313	
Morning Stiffness (BASDAI)						
Baseline	ETN	106	6.52 (2.18)			
	Placebo	109	6.43 (2.18)			
Week 12	ETN	105	3.59 (2.82)	-2.26 (0.34)	34.550	0.0134
	Placebo	109	4.43 (2.58)	-1.43 (0.32)	22.162	
Week 24	ETN/ETN	100	2.78 (2.52)	-3.71 (0.28)	57.135	NA
	Placebo/ETN	105	2.46 (2.49)	-4.00 (0.25)	61.924	

a ANCOVA model used for 'adjusted' values and between group p-values: Change = baseline score + treatment + region + SI status.

b Percent Improvement =100*(adjusted mean change/baseline mean); adjusted mean change from ANCOVA model.

ASDAS hsCRP and hsCRP (mITT, LOCF)

A significantly greater percentage of subjects in the ETN group had ASDAS hsCRP inactive disease (< 1.3) at Weeks 2, 4, 8, and 12 compared with the placebo group (Table 9). Likewise, statistically significant differences in the mean changes from baseline were observed between ETN and PBO groups at all-time points. The mean score further decreased during the open-label period and reached approximately 50% of the baseline score at 24 weeks (from 3 to 1.5).

Table 9 Proportion of Subjects with ASDAS hsCRP Inactive Disease (mITT, LOCF)

Time Point	ETN n/N (%)	Placebo n/N (%)	p-Value[a] (CMH)
Double-blind Period	**N=105**	**N=109**	
Week 2	19/105 (18.10)	7/107 (6.54)	0.0124
Week 4	27/105 (25.71)	8/109 (7.34)	0.0004
Week 8	41/105 (39.05)	22/109 (20.18)	0.0033
Week 12	42/105 (40.00)	19/109 (17.43)	0.0004
Open-label Period	**N=100**	**N=105**	
Week 16	39/100 (39.00)	45/105 (42.86)	NA
Week 24	47/100 (47.00)	61/105 (58.10)	NA

a Cochran-Mantel-Haenszel chi-square test, stratified by positive/negative sacroiliitis (assessed by MRI) and geographic region.

Statistically significant differences in the mean changes from baseline in hsCRP concentrations were observed between ETN and PBO groups at all time points. The mean hsCRP further decreased during the open-label period; at week 24, the mean hsCRP had decreased by about 70% (Table 10).

Table 10 Change from baseline in hsCRP concentration (mg/L) (mITT, LOCF)

Time Point	Treatment	n	Raw Mean [mg/dL] (SD)	Change Within Group Adjusted Mean (SE)[a]	Percent Improvement [b]	Between Group Comparison p-Value[a]
Double-blind Period						
Baseline	ETN	106	6.76 (10.59)			
	Placebo	108	6.43 (10.51)			
Week 2	ETN	105	2.08 (3.87)	-4.49 (0.71)	65.822	<0.0001
	Placebo	107	4.96 (8.59)	-1.46 (0.67)	22.786	
Week 4	ETN	105	2.36 (4.60)	-3.61 (1.16)	52.989	0.0008
	Placebo	108	6.16 (11.67)	0.25 (1.10)	-3.827	
Week 8	ETN	105	2.64 (7.73)	-4.28 (1.26)	62.725	0.0143
	Placebo	108	5.57 (10.53)	-1.23 (1.19)	19.190	
Week 12	ETN	105	2.95 (6.40)	-2.98 (1.09)	43.742	0.0038
	Placebo	108	5.98 (10.80)	0.14 (1.03)	-2.158	
Open-label Period						
Week 16	ETN/ETN	100	2.28 (4.12)	-4.84 (1.07)	67.985	NA
	Placebo/ETN	104	2.52 (5.61)	-3.82 (1.08)	60.227	
Week 24	ETN/ETN	100	2.50 (5.02)	-4.62 (1.10)	64.921	NA
	Placebo/ETN	104	1.78 (2.55)	-4.56 (1.04)	71.964	

a ANCOVA model used for 'adjusted' values and between group p-values: Change = baseline score + treatment + region + SI status.

b Percent Improvement =100*(adjusted mean change/baseline mean); adjusted mean change from ANCOVA model.

BASDAI total score (mITT, LOCF)

Patients in the ETN group had a significantly greater mean change from baseline in BASDAI total score compared with the placebo group beginning at Week 2 and continuing through the last evaluation of the double-blind-period (Table 11). The mean BASDAI total score continued to show an improving trend in the ETN/ETN group over the course of the open-label period. At Week 24, the response corresponded to an improvement in BASDAI total score of about 50%.

Likewise, a significantly greater percentage of subjects in the ETN group were BASDAI 50 responders compared with the placebo group throughout the double-blind period (e.g. at Week 12: 43.8% [46/105] vs. 23.8% [26/109]; p = 0.0029). At week 24, this proportion was 57% (116/205) in the whole population.

Table 11 Change from Baseline in BASDAI Total Score (mITT Population, LOCF)

Time Point	Treatment	n	Raw Mean Score [cm] (SD)	Change Within Group Adjusted Mean (SE)[a]	Percent Improvement [b]	Between Group Comparison p-Value[a]
Double-blind Period						
Baseline	ETN	106	5.96 (1.75)			
	Placebo	109	5.97 (1.88)			
Week 2	ETN	105	4.74 (2.21)	-0.96 (0.23)	16.084	0.0106
	Placebo	108	5.33 (1.90)	-0.39 (0.22)	6.536	
Week 4	ETN	105	4.26 (2.20)	-1.63 (0.24)	27.185	0.0048
	Placebo	109	4.91 (1.95)	-0.97 (0.22)	16.235	
Week 8	ETN	105	3.63 (2.27)	-2.05 (0.26)	34.274	0.0016
	Placebo	109	4.46 (2.20)	-1.24 (0.25)	20.766	
Week 12	ETN	105	3.63 (2.40)	-1.96 (0.28)	32.734	0.0186
	Placebo	109	4.30 (2.24)	-1.31 (0.27)	21.996	
Open-label Period						
Week 16	ETN/ETN	100	3.25 (2.18)	-2.70 (0.21)	45.417	NA
	Placebo/ETN	105	2.99 (2.19)	-2.98 (0.20)	49.935	
Week 24	ETN/ETN	100	3.10 (2.25)	-2.86 (0.22)	47.990	NA
	Placebo/ETN	105	2.71 (2.13)	-3.26 (0.19)	54.544	

a ANCOVA model used for 'adjusted' values and between group p-values: Change = baseline score + treatment + region + SI status.
b Percent Improvement =100*(adjusted mean change/baseline mean); adjusted mean change from ANCOVA model.

Mobility measurements (mITT, LOCF)

There was no statistically significant difference in the BASMI total score between the treatment groups during the double-blind period. At Week 12, the response corresponded to an improvement of 22.7% for the ETN group and 21.3% for the placebo group. The mean change from baseline in the BASMI components (cervical rotation, Tragus-to-wall distance, modified Schober's test, intermalleolar distance, and lateral side flexion) was analysed. With the exception of lateral side flexion at Week 12, there were no statistically significant differences between the treatment groups during the double-blind period.

The mean change from baseline in chest expansion and occiput-to-wall test was also analysed. With the exception of chest expansion at Week 2, there were no statistically significant differences between the treatment groups during the double-blind period.

Imaging endpoints (Week 12, mITT, LOCF)

Spine

Patients in the ETN group had a significantly greater mean change from baseline in the SPARCC-Spine 6 discovertebral units (DVU) Total Score compared with the placebo group (-2.12 [n=95] vs. -1.16 [n=105]; p = 0.041). The response corresponded to an improvement of 45.4% for the ETN group and 33.4% for the placebo group.

Likewise, patients in the ETN group had a significantly greater adjusted mean change from baseline in the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASspiMRI-a) total score compared with the placebo group (-0.73 vs. -0.33; p = 0.013). The response corresponded to an improvement of 40.9% for the ETN group and 25.6% for the placebo group.

SI joint (exploratory endpoint)

Patients in the ETN group had a significantly greater adjusted mean change from baseline in the SPARCC score for the SI joint compared with the placebo group (-3.77 [n=95] vs. -0.84 [n=105]; p< 0.001). The response corresponded to an improvement of 46.9% for the ETN group and 10.9% for the placebo group.

Health outcomes (mITT, observed cases)

At Week 12, a significant difference between ETN and PBO was observed for the following outcomes:

- increase in EQ-5D VAS score (number of patients: 84/92; p = 0.039) – corresponding improvement of 16.3% vs. 5.8%, respectively;
- proportion of patients with EQ-5D total index score improvement ≥0.05 (51/85 vs. 40/93; p = 0.034);
- increase in SF-36 PCS (general physical function) (number of patients: 85/94; p = 0.013) – corresponding improvement of 16.4% vs. 10.2%, respectively;
- proportion of subjects with an SF-36 PCS improvement ≥ 5 (44/85 vs. 33/94; p = 0.035);
- decrease in % impairment while working due to health problems as assessed in WPAI (number of patients: 48/50; p = 0.046);
- decrease in % activity impairment due to health problems as assessed in WPAI (number of patients: 85/92; p = 0.040).

No statistical difference at Week 12 was observed for the following outcomes:

- proportion of subjects with an EQ-5D VAS score > 82;
- proportion of subjects with an SF-36 PCS improvement ≥ 2.5;
- change in EQ-5D Utility score;
- change in SF-36 MCS (mental component summary);
- change in ASQoL score;
- proportion of subjects employed and work time missed as assessed by WPAI.

Other secondary endpoints

Statistically significant differences between ETN and placebo groups were also observed at Week 12 for the VAS Physician Global Assessment, ESR, number of swollen joints, and enthesitis (MASES) score. However, the differences at Week 12 were not significant for the Bath Ankylosing Spondylitis Patient Global Assessment Score and the number of tender joints.

Ancillary analyses

For the primary endpoint, ASAS 40 response at Week 12, efficacy was evaluated in a number of pre-specified subgroups (Table 12). Among all the subgroup analyses, only race and history of uveitis yielded a significant interaction p-value, but the data are difficult to interpret due to the small sample size of non-white subjects and patients with a history of uveitis.

Table 12 Pre-specified Subgroup Analyses of ASAS 40 Response at Week 12 (mITT)

Subgroup	ETN (N=106) n/N (%)	Placebo (N=109) n/N (%)	Interaction p-Value[a]
Sex			
Male	24/68 (35.29)	12/62 (19.35)	0.3845
Female	11/38 (28.95)	4/47 (8.51)	
Race			
White	28/79 (35.44)	9/79 (11.39)	0.0796
Non-white	7/27 (25.93)	7/30 (23.33)	
Age			
<40 years	32/87 (36.78)	15/89 (16.85)	0.8635
≥40 years	3/19 (15.79)	1/20 (5.00)	
Weight			
<70 kg	13/40 (32.50)	3/45 (6.67)	0.1216
≥70 kg	22/66 (33.33)	13/64 (20.31)	
HLA-B27 status			
Positive	28/71 (39.44)	11/83 (13.25)	0.3109
Negative	7/33 (21.21)	3/23 (13.04)	
Baseline hsCRP			
Normal (<3 mg/L)	12/58 (20.69)	8/64 (12.50)	0.2395
High	23/48 (47.92)	8/44 (18.18)	
Concomitant use of DMARD at baseline			
Yes	6/21 (28.57)	2/21 (9.52)	0.7331
No	29/85 (34.12)	14/88 (15.91)	
MRI Sacroiliitis classification at Screening			
Positive	29/87 (33.33)	16/87 (18.39)	0.9245
Negative	6/19 (31.58)	0/22 (0.00)	
Either positive MRI or elevated baseline hsCRP			
Yes	33/94 (35.11)	16/95 (16.84)	0.9453
No	2/12 (16.67)	0/14 (0.00)	
Both positive MRI and elevated baseline hsCRP			
Yes	19/41 (46.34)	8/36 (22.22)	0.8508
No	16/65 (24.62)	8/73 (10.96)	
History of IBD at screening			
Yes	0/1 (0.00)	0/1 (0.00)	0.9951
No	35/105 (33.33)	16/108 (14.81)	
History of Uveitis at screening			
Yes	5/8 (62.50)	0/9 (0.00)	0.0778
No	30/98 (30.61)	16/98 (16.33)	
Unknown	0/0	0/2 (0.00)	
Group of countries			
Asia Pacific	5/23 (21.74)	5/24 (20.83)	0.4298
Europe	29/78 (37.18)	9/77 (11.69)	
Latin America	1/5 (20.00)	2/8 (25.00)	

a Logistic regression model interaction p-value.

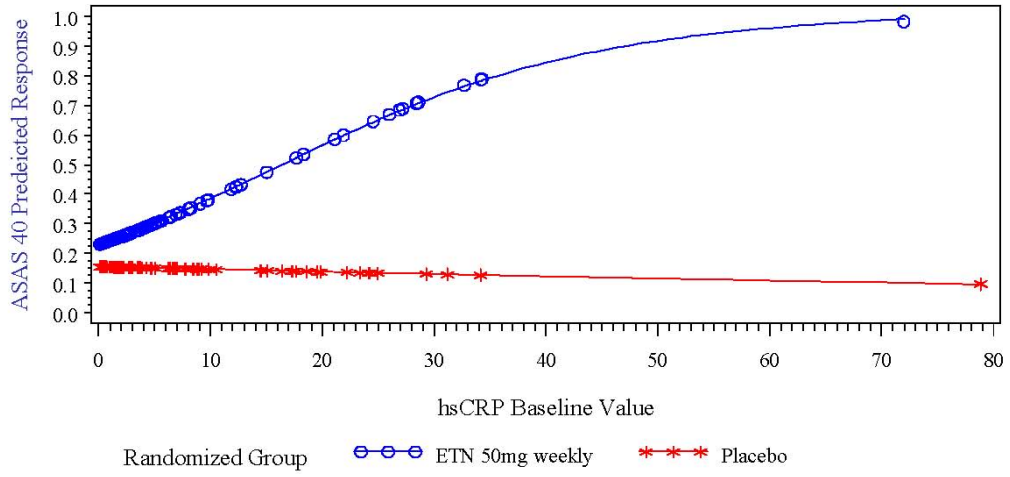
To further understand the effect of various hsCRP and MRI subgroups on ASAS 40 response, additional post-hoc analyses were performed.

Baseline hsCRP

Previous studies in patients with nr-AxSpA have shown that TNF inhibition had a greater effect in subjects with elevated baseline hsCRP than those with normal levels. A pre-specified analysis in the current study suggested this was the case, but did not reach statistical significance. To further evaluate this relationship, an analysis was performed with hsCRP as a continuous variable. The difference

between ETN and placebo response rates increased with increasing hsCRP levels. These data showed a significant relationship between baseline hsCRP levels and placebo-corrected response to etanercept (p =0.0033; Figure 4).

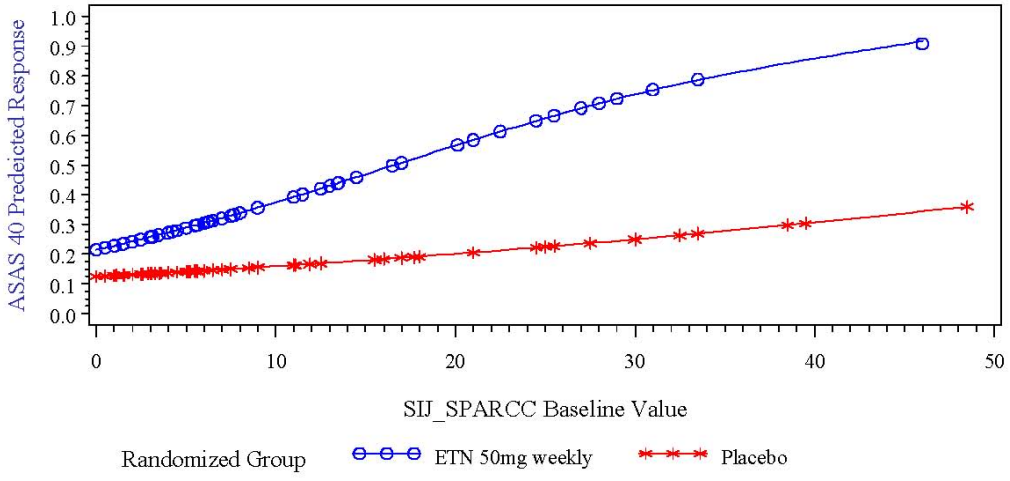
Figure 4 Fitted logistic regression of ASAS40 on baseline hsCRP



Baseline MRI Positivity and Sacroiliac Joint SPARRC Score

As was shown in Table 12, there was no significant subgroup by treatment interaction when the MRI positive subjects were compared to the MRI negative subjects. Due to the relatively small number of subjects in the MRI negative subgroup; these results may not fully inform the effect of MRI status on ASAS 40. In order to further examine the potential relationship between MRI findings and clinical response, SIJ SPARCC scores (<2 versus ≥2) were analyzed. There was no significant interaction between treatment and SIJ SPARCC score <2 versus ≥2 on ASAS 40 response, but the etanercept effect was numerically higher in subjects with SIJ SPARCC scores ≥2 (41.8% vs. 17.9%, respectively). An approach using a continuous analysis using baseline SIJ SPARCC scores as a potential predictor was also evaluated. The difference between etanercept and placebo response rates increased with increasing SPARCC scores which resulted in an interaction p-value that approached statistical significance (interaction p-value=0.1458; Figure 5). The data suggest that etanercept-treated subjects with higher baseline SPARCC scores have higher ASAS 40 response rates.

Figure 5 Fitted logistic regression of ASAS40 on baseline SPARCC SIJ



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of efficacy for trial B1801031

Title: *A Multicentre, 12-Week Double Blind Placebo Controlled Randomized Study of Etanercept on a Background NSAID in the Treatment of Adult Subjects With Non Radiographic Axial spondyloarthritis With a 92-Week Open Label Extension*			
Study identifier	B1801031		
Design	Double-blind placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks NA 12 weeks
Hypothesis	Superiority		
Treatments groups	ETN		Etanercept 50 mg SC weekly, 12 weeks number randomized: 111
	PBO		Placebo SC weekly, 12 weeks number randomized: 114
Endpoints and definitions	Primary endpoint	ASAS 40	% patients who achieve Assessment in Ankylosing Spondylitis (ASAS) 40
	Secondary endpoint	ASAS 20	% patients who achieve ASAS 20
	Secondary endpoint	ASAS 5/6	% patients who achieve ASAS 5/6
	Secondary endpoint	ASAS PR	% patients who achieve ASAS partial remission
	Secondary endpoint	BASDSAI 50	% patients who achieve BASDAI 50
	Secondary endpoint	hsCRP	Change in hs-CRP concentration from BL to Week 12
	Secondary endpoint	SPARCC-Spine MRI	Change in score from BL to Week 12
	Secondary endpoint	SPARCC-SIJ MRI	Change in score from BL to Week 12
	Secondary endpoint	EQ-5D VAS	Change in score from BL to Week 12

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Intent to treat (all randomized subjects who took at least one dose of study drug, had at least one on-therapy evaluation and met the ASAS classification criteria for AxSpA) at Week 12 - LOCF			
Descriptive statistics and estimate variability	Treatment group	ETN	PBO	
	Number of subjects	105	108	
	ASAS 40 (%)	32.4	15.7	
	ASAS 20 (%)	52.4	36.1	
	ASAS 5/6 (%)	33.0	10.4	

	ASAS PR (%)	24.8	11.9	
	BSASDAI 50 (%)	43.8	23.8	
	hsCRP (mg/L) Mean (SD)	-2.98 (1.09)	0.14 (1.03)	
	SPARCC-Spine Mean (SD)	-2.12 (0.49)	-1.16 (0.47)	
	SPARCC-SIJ Mean (SD)	-3.77 (0.66)	-0.84 (0.62)	
	EQ-5D VAS Mean (SD)	9.33 (2.97)	3.26 (2.77)	

Effect estimate per comparison	Primary endpoint ASAS 40	Comparison groups	ETN vs PBO
		Difference in %	16.64
		95% CI	(5.36, 27.92)
		P-value	0.0062
	Secondary endpoint ASAS 20	Comparison groups	ETN vs PBO
		Difference in %	16.27
		95% CI	(3.10, 29.43)
		P-value	0.0195
	Secondary endpoint ASAS 5/6	Comparison groups	ETN vs PBO
		Difference in %	22.63
		95% CI	(11.85, 33.41)
		P-value	< 0.0001
	Secondary endpoint ASAS PR	Comparison groups	ETN vs PBO
		Difference in %	12.84
		95% CI	(2.58, 23.09)
		P-value	0.0209
	Secondary endpoint BASDAI 50	Comparison groups	ETN vs PBO
		Difference in %	19.96
		95% CI	(7.54, 32.37)
		P-value	0.0029
	Secondary endpoint hsCRP	Comparison groups	ETN vs PBO
		Adjusted difference of mean	-3.12
		95% CI	(-5.23, -1.02)
		P-value	0.0038
	Secondary endpoint SPARCC-Spine	Comparison groups	ETN vs PBO
		Adjusted difference of mean	-0.96
		95% CI	(-1.88, -0.04)
		P-value	0.0414
	Secondary endpoint SPARCC-SIJ	Comparison groups	ETN vs PBO
		Adjusted difference of mean	-2.93
		95% CI	(-4.16, -1.70)
		P-value	< 0.001
	Secondary	Comparison groups	ETN vs PBO

	endpoint EQ-5D VAS	Adjusted difference of mean	6.07
		95% CI	(0.30, 11.84)
		P-value	0.0394

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study supporting this extension of indication to the treatment of nr-AxSpA is a double-blind placebo-controlled trial of 12-week duration, followed by an additional 12-week open-label treatment period where all patients received etanercept.

Particular attention was paid to the selection of the patients based on adherence to the 2009 ASAS classification criteria for axial spondyloarthritis with careful exclusion of patients with ankylosing spondylitis; this was confirmed by central X-rays and MRI reading and the use of high sensitivity CRP by central determination. Also the requirement of a BASDAI score ≥ 4 ensured that only patients with moderate to severe disease were enrolled.

Etanercept was added to background therapy as administered in clinical practice. Back pain had to have failed to respond to at least two NSAIDs and treatment with an NSAID at a stable dose was to be continued throughout the study; the combination to one DMARD at a stable dose was also authorised. Etanercept dosing was the same as recommended in AS (50 mg sc weekly).

Adequate efficacy outcomes have been used in line with the 2009 CHMP guideline for treatment of AS. The primary endpoint is ASAS 40 and a wide range of secondary endpoints include ASAS 20, ASAS 5/6, ASAS partial remission, BASDAI, BASFI, BASMI, hsCRP and ESR, various quality of life instruments, and MRI imaging of the spine and sacroiliac joints.

The trial was conducted in 48 centres, mainly in Europe (EU and Russia) and Asia with a few additional patients from Latin America. GCP compliance issues were found in one centre in Taiwan and the data of this centre have been excluded in one of the sensitivity analyses. Statistical methods are acceptable by the CHMP.

The exclusion from the mITT population of the 10 patients (4%) that did not meet the disease definition is acceptable. Baseline characteristics in this population were similar to those in the FAS. Of note, in the mITT population, 88% patients corresponded to the target SmPC indication (patients with elevated CRP and/or MRI evidence of inflammation).

An additional sensitivity analysis was performed in the All treated population (n=224). Only two patients were excluded from this analysis (one in each arm) due to lack of post-baseline data. Since the number is so small and equally balanced between treatments, it is not a concerning issue.

Efficacy data and additional analyses

From a total of 383 subjects screened, 225 were randomised. Most completed the trial and compliance to therapy was high. The patient population is representative of the target population as described in the SmPC; most patients had MRI signs of sacroiliitis (77%) and 85% had either elevated hsCRP or ASAS MRI sacroiliitis.

The single pivotal trial met its primary endpoint with a high level of significance and the results are robust to the method of analysis and the choice of analysis population, as shown by essentially the same results in all the sensitivity analyses performed. About one third of the patients responded to

etanercept after 12 weeks (32.4%), twice as much as those responding to placebo (15.8%) and the response rate increased further over the subsequent 12 weeks during the open-label treatment phase.

The results of the primary endpoint are supported by the results of all key secondary endpoints (usually with high level of significance) except for mobility measurements, for which the duration of observation may be too short. The reduction in active inflammatory lesions (bone marrow oedema) detected at MRI, which appeared statistically different from placebo in both the spine and sacroiliac joints, is particularly relevant and provides objective evidence of anti-inflammatory effects at the lesion site. These results are consistent with those of the ESTHER trial, which compared the effects of etanercept and sulfasalazine in early axial spondyloarthritis on MRI activity (Song, 2011).

In addition, a number of quality of life instruments were able to differentiate etanercept from placebo after 12 weeks of treatment, including BASFI, the EQ-5D VAS score, the SF-36 physical component, and even some items of the Work Productivity and Activity Impairment Questionnaire.

Etanercept was consistently superior to placebo in all patient subgroups, either statistically or at least numerically, except in non-white subpopulation and outside Europe. This is likely to be a chance finding as suggested by the MAH given the small number of patients. Previous studies have shown similar efficacy of etanercept in Asian AS patients.

Importantly, the effect of etanercept appeared more pronounced when inflammatory signs were initially more marked (as reflected by CRP or MRI). In the target population of patients with positive MRI or elevated hs-CRP (as defined in the SmPC), an ASAS 40 response was achieved in 35% (33/94) of the patients treated with etanercept vs. 17% (16/95) of the placebo-treated patients ($p = 0.0048$).

Finally, it is noteworthy that further improvement in the secondary endpoints was observed up to 24 weeks, acknowledging that this may be overestimated due to the open-label nature of the trial design after the first 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period (as described in the product information).

The open-label period of study B1801031 is currently ongoing and its results will be submitted by the MAH to show maintenance of efficacy (as described in the RMP). Furthermore, the need for continuous therapy to maintain clinical response or remission over time is currently unknown. As anti-TNFs have not been shown to prevent progression of structural damage while they are not devoid of serious risks on the long-term, treatment interruption in stable condition is justified. Given that AxSpA is a disease with fluctuating symptomatology and patients with non-radiological disease are likely to start anti-TNF treatment early in life, the possibility of treatment interruptions is especially relevant. An investigator-sponsored trial conducted by German rheumatologists in 76 subjects with early AxSpA, of which half had nr-AxSpA, has shown that about 70% of subjects in remission after 48 weeks of treatment with etanercept relapsed within 24 weeks on average. When retreated, the subjects responded to re-treatment, although full remission was not achieved in all cases (ESTHER trial, *Song IH et al, 2011, 2012, and 2013*). Furthermore, these results appear consistent with those observed in larger trials conducted by the MAH in patients with psoriasis or rheumatoid arthritis.

However, given the small size of the ESTHER trial, the MAH will to conduct a single-arm trial (study B1801381) in a larger sample of nr-AxSpA patients to refine the description of the relapse profile after treatment discontinuation and evaluate the effects of re-treatment (as described in the RMP).

During the procedure the MAH agreed amend the wording of the indication from:" Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to conventional therapy" to "Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs" as this is consistent with the clinical trial supporting this extension of indication..

2.4.3. Conclusions on the clinical efficacy

A well-designed trial has been conducted to support this extension of indication and its results provide convincing evidence of the effects of etanercept on the symptoms and signs of inflammation, including MRI changes, associated with the disease as well as of its short-term benefit to the quality of life of the target patient population. Information on the benefit/risk profile of etanercept in the long-term (2-year treatment) will be provided by the ongoing B1801031 trial (as described in the RMP). In addition, the effects of treatment withdrawal and re-treatment after relapse will be further evaluated in study B1801381 (as described in the RMP).

2.5. Clinical safety

2.5.1. Introduction

Etanercept has been marketed since November 1998 and has been well tolerated with a favourable risk/benefit profile under recommended conditions for use.

The most commonly reported adverse reactions of Enbrel are injection site reactions, allergic reactions, and infections like all TNF antagonists as they affect the immune system. Serious infections, including opportunistic infections and reactivation of tuberculosis or hepatitis B virus infection have been reported. These therapies also imply a potential risk of cancer and of autoimmune reactions. Acute uveitis, Crohn's disease, sarcoidosis, lupus, pancytopenia, demyelinating events have been reported.

Supportive safety data are provided by the information collected in Study B1801031. Immunogenicity data were not collected in this study.

Patient exposure

The safety population consists of 224 subjects who received at least one dose of study medication; 111 subjects received etanercept and 113 received placebo. During the 12-week double-blind period, the median exposure to etanercept was 85 days with a range of 1 to 95 days, and the median exposure to placebo was 85 days with a range of 8 to 100 days. Total exposure during the double-blind period was 24.10 subject-years for the ETN group and 25.29 subject-years for the placebo group.

During the open-label period of the study, there were 102 subjects in the ETN/ETN group and 106 subjects in the placebo/ETN group. Between Weeks 12 to 24 of the open-label period, the median duration of etanercept treatment was 78 days with a range of 15 to 92 days for the ETN/ETN group, and 78 days with a range of 8 to 90 days for the placebo/ETN group. Total exposure to etanercept during the open-label period was 23.10 subject-years for the ETN/ETN group and 24.05 subject-years for the placebo/ETN group.

Adverse events

A tabulated summary of treatment-emergent adverse events (TEAEs) is provided in Table 14.

During the double-blind period (through Week 12), TEAEs were reported in 63 (56.8%) subjects in the ETN group and 51 (45.1%) subjects in the placebo group. In general, the numbers and types of AEs were similar between the 2 treatment groups, with the exception of injection site disorders. Three (3) events were reported with an incidence of ≥5% in either treatment group: injection site erythema, injection site reaction, and nasopharyngitis (Table 15).

During the open-label period (between Week 12 and Week 24), TEAEs were reported by 35 (34.3%) subjects in the ETN/ETN group and by 53 (50.0%) subjects in the placebo/ETN group (Table 15). The

subjects who switched from placebo to etanercept had a higher rate of injection site disorders compared to the subjects who received etanercept in both treatment periods. No events were reported with an incidence of ≥5% in either treatment group (Table 16).

Table 14 Summary of TEAEs throughout the study

Double-blind Period		
	ETN (N=111) n (%)	**PBO (N=113) n (%)**
Subjects with adverse events (non-infectious and infectious events)	63 (56.8)	51 (45.1)
Subjects with Investigator-identified infections	11 (9.9)	10 (8.8)
Subjects with serious adverse events	2 (1.8)	2 (1.8)
Subjects with serious Investigator-identified infections	0 (0.0)	1 (0.9)
Subjects discontinued due to adverse events	3 (2.7)	1 (0.9)
Open-label Period		
	ETN/ETN (N=102) n (%)	**PBO/ETN (N=106) n (%)**
Subjects with adverse events (non-infectious and infectious events)	35 (34.3)	53 (50.0)
Subjects with Investigator-identified infections	12 (11.8)	13 (12.3)
Subjects with serious adverse events	0 (0.0)	1 (0.9)
Subjects with serious Investigator-identified infections	0 (0.0)	0 (0.0)
Subjects discontinued due to adverse events	0 (0.0)	1 (0.9)

Table 15 Incidence of TEAEs Reported in ≥1% of Subjects - Double-blind Period

MedDRA System Organ Class[Error! Reference source not found.] 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)

Table 16 Incidence of TEAEs Reported in ≥1% of Subjects – Open-label Period

MedDRA System Organ Class[Error! Reference source not found.] 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)

MedDRA System Organ Class[Error! Reference source not found.] MedDRA Preferred Term	ETN/ETN (N=102) n (%)	Placebo/ETN (N=106) n (%)
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)

During the double-blind period, the incidence of TEAEs was higher in etanercept-treated patients than in placebo-treated patients due to injection site reactions and skin reactions. Although nasopharyngitis was more frequent in the ETN group, upper respiratory tract infections and bronchitis were more frequent in the PBO group. Overall, no difference in the occurrence of infections was found over this short period. During the open-label treatment period, TEAEs were more frequent in the group of patients initially treated with placebo as expected. Overall, the occurrence of infections appeared the same as in the first 12 weeks of treatment.

Serious adverse event/deaths/other significant events

No deaths occurred through Week 24 of the study and the SAEs reported are summarised in Table 17.

Table 17 Serious Adverse Events through Week 24

1. Subject ID	2. Treatment Group	3. Event Onset/ Stop Day[a]	4. MedDRA Preferred Term	5. Severity/ Outcome	6. Action Taken
Double-blind Period (Through Week 12)					
10171002	ETN	36/>43	Spondyloarthropathy	Severe/Still present	Permanently discontinued study
10281005	ETN	67/77	Cholelithiasis	Moderate/ Resolved	Temporarily discontinued study drug
10311003	Placebo	54/118	Uveitis	Moderate/ Resolved	None
		38/53	Anal abscess	Severe/ Resolved	Permanently discontinued study
10611003	Placebo	38/39	Wound[b]	Moderate/ Resolved	None
Open-label Period (Between Week 12 and Week 24)					
10141006	Placebo/ETN	170/176	Contusion	Mild/Resolved	None
		170/176	Ligament sprain	Mild/Resolved	None
		170/176	Ligament sprain	Mild/Resolved	None

a Day relative to start of study treatment. First day of study treatment = Day 1.
b Due to injury (laceration).

SAEs occurred with equal frequency in the two treatment groups and appeared disease-related. There was no serious infection except for an anal abscess in the PBO group, a likely complication of an underlying lesion.

Adverse events of special interest generally identified for close clinical monitoring in subjects receiving therapy with TNF inhibitors include malignancy, lymphoma, opportunistic infections, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression, autoimmune disorders, IBD, and liver function abnormalities.

There were no cases of malignancy, lymphoma, opportunistic infection, tuberculosis, demyelinating disease, blood dyscrasias related to bone marrow suppression, or IBD that occurred during the first 24 weeks of study B1801031. Acute anterior uveitis flare was reported in 3 patients (1 on PBO, 2 on ETN during the open-label period).

After the Week 24 data cut-off for study B1801031, one opportunistic infection (herpes zoster, involving 2 dermatomes – during the 6th month of therapy) and one event of demyelinating disease (multiple sclerosis – diagnosed 9 months after starting ETN) were reported.

Laboratory findings

During the double-blind period, 5 subjects (2.23%) had a Common Terminology Criteria for Adverse Events v4.0 [CTCAE] Grade 3 or 4 laboratory test result, all related to liver tests (ALT, AST, bilirubin): 3 in the ETN group and 2 in the PBO group. One subject experienced both an ALT and an AST test result of >5 X ULN, which corresponded to an AE of hepatitis. A total of 4 subjects (2 in each group) had elevated bilirubin. Of the 4 subjects with elevated bilirubin, two experienced transient increases in bilirubin, one had a history of Gilbert's syndrome, and one had a history of hepatic steatosis.

Overall, 5 subjects (3 ETN/2 PBO) had increases in AST greater than 2 X ULN and 10 subjects (7 ETN/ 3 PBO) had increases in ALT greater than 2 X ULN. Of these subjects, 3 subjects (two in the ETN group and one in the PBO group) had an increase in ALT/AST >3 X ULN. Of these 3 subjects, one reported an AE of hepatitis (and discontinued ETN treatment), one reported an AE of abnormal hepatic function

(ALT/AST normalized while receiving ETN), and the third had a history of hepatic steatosis. An additional ALT elevation, mild and transient, was reported as an AE in the placebo group.

During the open-label period, 9 subjects (4.33%) had a CTCAE Grade 3 or 4 laboratory test result:

- decreased total neutrophils, which returned to normal at the next visit (2)
- one new case of transient elevated bilirubin and 3 remaining cases continuing from the double-blind period
- transient abnormal potassium level (2)
- ALT increase (1).

Overall, 1 subject had increases in AST greater than 2 X ULN and 6 subjects had increases in ALT greater than 2 X ULN. Of these subjects, one subject in the placebo/ETN group had an increase in ALT greater than 3 X ULN which was associated with an AE of liver function abnormality; ETN was temporarily stopped and re-introduced after AE resolution. An additional ALT elevation, mild and transient was reported as an AE.

No subject was identified as meeting Hy's Law criteria based on abnormal liver function test results during the trial.

In conclusion, elevations of ALT/AST, usually transient, were slightly more frequent under etanercept treatment than placebo. They were not associated with high bilirubin levels or clinical correlates. One case was reported as hepatitis, the patient discontinued ETN treatment, and ALT (but not AST) normalised within a month. Of note, all five subjects who had increased levels of ALT/AST reported as an AE were located in Asia.

Discontinuation due to adverse events

Five (5) patients discontinued treatment due to AE as listed in Table 18.

Table 18 Safety-Related Discontinuations through Week 24

7. Subject ID	8. Treatment Group	9. Event Onset/ Stop Day[a]	10. MedDRA Preferred Term	11. Severity/ Outcome	12. AE
Double-blind Period (Through Week 12)					
10021007	ETN	57/138	Hepatitis	Moderate/Resolved	No
10171002	ETN	36/>43	Spondyloarthropathy	Severe/Still present	Yes
10611006	ETN	2/>16	Asthenia	Moderate/Still present	No
10311003	Placebo	38/53	Anal abscess	Severe/Resolved	Yes
Open-label Period (Between Week 12 and Week 24)					
10171006	Placebo/ETN	104/152	Bronchitis	Moderate/Resolved	No

a Day relative to start of study treatment. First day of study treatment = Day 1.

Discontinuation due to AE occurred slightly more frequently in the ETN group and the AEs may have been treatment-related.

Post marketing experience

A review of the MAH global safety database was conducted to identify reports of AxSpA as an indication for etanercept treatment. The search included medically confirmed cases reported all time through 02 February 2013, which contained the MedDRA version 16.0 Preferred Term Spondylitis as an indication.

The search identified a total of 125 cases fitting the search criteria. The cases were individually reviewed to determine relevant cases reporting AxSpA as an indication.

Of the 125 cases, 121 either reported non-specific spondyloarthritis, peripheral AxSpA, or AS. The remaining four relevant reports involved three males and one female. The patients ranged in age from 21 to 54 years (mean 37.25 years, median 37 years). The reported events include lack of effect (2), uveitis (1), herpes zoster (1), increased alanine aminotransferase (ALT) (1), increased aspartate aminotransferase (AST) (1), hepatic steatosis (1), and Sjogren's syndrome (1). Herpes zoster, increased ALT, increased AST and uveitis are known adverse events associated with etanercept while hepatic steatosis and Sjogren's syndrome are not listed adverse events in the etanercept CDS.

On review, the patient reporting abnormal liver enzymes, in which ALT had a four times increase after two months of etanercept treatment and "marginal increase" of AST after four months of etanercept treatment, was found to have hepatic steatosis. Etanercept and concomitant drug, diclofenac, were withdrawn and the patient was recovering from the increased liver enzymes. Outcome of hepatic steatosis was not known at the time of the report.

Uveitis occurred in a patient with a pre-existing chronic uveitis. This case also reported lack of effect, however, information on inefficacy was unclear on review; etanercept treatment was continuing at the time of the report.

In another case, a patient experienced Sjogren's syndrome after 2 months of etanercept 50 mg subcutaneously of unknown frequency and recovered with treatment. Etanercept was discontinued 1 month later because it was not effective to treat the patient's AxSpA.

In the last case, herpes zoster developed after 1 month of etanercept treatment. Etanercept was discontinued and the patient recovered with treatment.

2.5.2. Discussion on clinical safety

Safety data have been collected up to 24 weeks in the supporting trial.

During the double-blind period, the incidence of TEAEs was higher in etanercept-treated patients than in placebo-treated patients essentially due to injection site reactions and skin reactions. No difference in the occurrence of infections was found and the incidence of SAEs was similar. Liver enzymes (ALT/AST) abnormalities were slightly more frequent, but usually transient.

No new safety concern emerged during the open-label treatment period. No adverse events of special interest were reported except for acute anterior uveitis flares (a feature of SpA), and one case each of herpes zoster and multiple sclerosis (after the Week 24 data cut-off). This emphasises the need to restrict the duration of treatment in patients that are not responding to therapy (as described in the product information).

2.5.3. Conclusions on clinical safety

The safety profile of etanercept in this indication is expected to be similar to its known safety profile in AS. This is indeed the case as shown by the results of the first 24 weeks of treatment. No new safety signal has been identified in this evaluation. No change to the safety sections of the SmPC has been proposed by the MAH, which is acceptable. However, as a clinical response is usually achieved within 12 weeks, a warning has been added in section 4.2 about the need to reconsider continuing therapy in a patient not responding within this time period.

The MAH agreed to conduct a study in nr-AxSpA patients to evaluate the duration of remission after withdrawal of therapy as well as safety of treatment after disease flare (as described in the RMP). The

information obtained from the proposed study B1801381 will be complemented by the results from the current ongoing study B1801031, which will provide an assessment of the long-term safety associated with continuous etanercept treatment (up to 104 weeks) in this population (as described in the RMP).

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 02 February 2014.

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 5.1 the PRAC considers by consensus that the risk management system for etanercept (Enbrel) in the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to conventional therapy is acceptable.

Following the PRAC meeting in June 2014, the MAH submitted a revised Risk Management Plan version 5.2 in order to update the PhV Plan with the most recent changes in the milestones of some of the studies. This advice is based on the following content of the Risk Management Plan:

Safety concerns

The MAH identified the following safety concerns in the RMP:

Table 1: Summary of Safety Concerns

Important identified risks-all indications	Malignancy (including lymphoma and leukemia) Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection) Lupus-like reactions Sarcoidosis and/or granulomas Injection site reactions Allergic reactions Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome) Systemic vasculitis (including ANCA positive vasculitis) Macrophage activation syndrome Central demyelinating disorders Peripheral demyelinating events (CIDP and GBS) Aplastic anemia and pancytopenia Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)
Important identified risks-specific indications	Change in morphology and/or severity of psoriasis in adult and pediatric populations Worsening of CHF in adult subjects Inflammatory bowel disease in JIA subjects

Important potential risks-all indications	Autoimmune renal disease Pemphigus/pemphigoid Amyotrophic lateral sclerosis Myasthenia gravis Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Liver failure Hepatic cirrhosis and fibrosis Severe hypertensive reactions Adverse pregnancy outcomes Potential for medication error (pre-filled pen) Potential for male infertility Weight Gain
Important potential risks – specific indications	Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects
Missing information-all indications	Use in hepatic and renal impaired subjects Use in different ethnic origins Use in pregnant women

Abbreviations: ANCA= antineutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barre Syndrome; JIA=juvenile idiopathic arthritis; TB=tuberculosis.

The PRAC agreed.

Pharmacovigilance plans

Table 2: Ongoing and planned studies in the PhV development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
BSRBR Category 3	A large prospective observational study that obtains data from routine clinical practice and whose objective is to evaluate any excess risk in the occurrence of various adverse events after allowing for confounding factors particularly of disease severity and concomitant rheumatic disease therapy.	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Aplastic anemia and pancytopenia; Worsening of CHF; PML; Acute ischemic CV events; Use in pregnant women	Started	December 2014
RABBIT Category 3	A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with TNF-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs.	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Peripheral demyelinating events; Aplastic anemia and pancytopenia; Worsening of CHF; PML; Acute ischemic CV events; Use in pregnant women	Started	Approximately 2017 (cohort 2)
ARTIS Category 3	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected adverse events in RA, JIA, and other rheumatic	Malignancy; Serious and opportunistic infections; Systemic vasculitis; Central demyelinating disorders; Aplastic	Started	November 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	disease patients treated with etanercept.	anemia and pancytopenia; Interstitial lung disease; Autoimmune hepatitis; Worsening of CHF; Myasthenia gravis; PML; Acute ischemic CV events		
BADBIR Category 3	A long-term prospective, observational, cohort study whose objectives are to ascertain the safety and efficacy of biologic agents compared to non-biologics agents in the treatment of adult psoriasis	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Aplastic anemia and pancytopenia; PML; Adverse pregnancy outcomes; Use in pregnant women	Started	Approximately 2019
German JIA Category 3	A prospective observational cohort study whose aim to describe the long-term safety, effectiveness, and cost of etanercept treatment in patients with polyarticular JIA in comparison to those treated with a conventional DMARD therapy (MTX).	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; PML	Started	May 2016
BSPAR Category 3	A prospective, observational, cohort study whose objectives are to evaluate the long-term safety and effectiveness of etanercept, as well as to monitor the growth and development of children with JIA compared to those children with JIA who are prescribed MTX	Malignancy; Serious and opportunistic infections; Central demyelinating disorders	Started	Approximately 2016
20050111 (Amgen) Category 3	A multicenter, interventional, non-randomized, open-label, extension study for subjects who participated in study 20030211. The primary objective is to evaluate subject incidence of adverse events, including infectious episodes, serious adverse events, and serious infectious episodes.	Malignancy; Serious and opportunistic infections; Lupus-like reactions; Sarcoidosis and/or granulomas; ISRs; Allergic reactions; Severe cutaneous adverse reactions; Systemic vasculitis; MAS; Central demyelinating disorders; Peripheral demyelinating events; Aplastic anemia and pancytopenia; Interstitial lung disease; Autoimmune hepatitis; Liver events in patients with viral hepatitis; Change in morphology and/or	Started	May 2018 or Sooner (6 months after the completion date)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
		severity of psoriasis; Autoimmune renal disease; Pemphigus/ pemphigoid; Amyotrophic lateral sclerosis; Myasthenia gravis; Encephalitis/ leukoencephalo-myelits; PML; Liver failure; Hepatic cirrhosis and fibrosis; Severe hypertensive reactions; Adverse pregnancy outcomes; Growth and development in juvenile subjects; Use in different ethnic origins; Use in pregnant women		
B1801023 Category 3	An open-label extension study to assess the long-term safety of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitisrelated arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014)	Malignancy; Serious and Opportunistic infections; Sarcoidosis and/or granulomas; ISRs; Allergic reactions; Severe cutaneous adverse reactions; Systemic vasculitis; MAS; Central demyelina-ting disorders; Peripheral demyelinating events; Aplastic anemia and pancytopenia; Interstitial lung disease; Autoimmune hepatitis; Inflammatory bowel disease in JIA; Autoimmune renal disease; Amyotrophic lateral sclerosis; Myasthenia gravis; Encephalitis/ Leukoencephalo-myelitis; PML; Liver failure; Hepatic cirrhosis and fibrosis; Severe hypertensive reactions; Adverse pregnancy outcomes; Male infertility; Weight gain; Impaired growth and development in juvenile subjects; Use in pregnant women	Started	Approximately 2021

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
PURPOSE (0881X1-4654) Category 3	A long-term, prospective, observational cohort study of the safety and effectiveness of etanercept in the treatment of paediatric psoriasis patients in a naturalistic setting: a Post-Authorisation Safety Study (PASS)	Malignancy; Serious and opportunistic infections	Started	Approximately 2019
OTIS (Amgen) Category 3	OTIS is a prospective, observational, exposure cohort study of pregnancy outcome in women with RA, JIA, AS, PsA, or psoriasis who are exposed to etanercept in the first trimester of pregnancy, and is designed to evaluate the possible teratogenic effect of etanercept when used in the first trimester of pregnancy with respect to major structural birth defects of newborns.	Adverse pregnancy outcomes; Use in pregnant women	Started	December 2014
20040210 (Amgen) Category 3	A prospective, multicenter, surveillance study of adult patients with chronic plaque psoriasis, who will be treated with commercial etanercept. The primary objective is to assess the incidence rates of serious adverse events, including all malignancies and serious infections. The longterm safety of etanercept will be evaluated.	Malignancy; Serious and opportunistic infections; Lupus-like reactions; Sarcoidosis and/or granulomas; ISRs; Allergic reactions; Severe cutaneous adverse reactions; Systemic vasculitis; MAS; Central demyelinating disorders; Peripheral demyelinating events; Aplastic anemia and pancytopenia; Interstitial lung disease; Autoimmune hepatitis; Liver events in patients with viral hepatitis; Change in morphology and/or severity of psoriasis; Worsening of CHF; Autoimmune renal disease; Pemphigus/ pemphigoid; Amyotrophic lateral sclerosis; Myasthenia gravis; Encephalitis/ Leukoencephalo-myelitis; PML; Liver failure; Hepatic	Started	Approximately 2014

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
		cirrhosis and fibrosis; Severe hypertensive reactions; Adverse pregnancy outcomes; Acute ischemic CV events; Use in different ethnic origins; Use in pregnant women		
B1801130 (088Y1-4689) Category 3	The Post-marketing Use-results Surveillance is to be performed in subjects with polyarticular JIA who are treated with Enbrel, for the purpose of assessing the following endpoints in daily medical practice: (1) Condition of onset of AEs; (2) Factors considered affecting safety; (3) Efficacy data. The assessment of the condition of onset, etc. of AEs is to be performed focusing on the following event: Infections (including varicella)	Serious and opportunistic infections	Started	Final Report November 2014
STORK (Amgen) Category 3	A retrospective cohort study using a large administrative claims database, affiliated with OptumInsight, to examine pregnancy and birth outcomes among women with cIA or PsO who were treated with etanercept, women with cIA or PsO who were not treated with etanercept or any anti-TNF during pregnancy, and a cohort of unexposed women without cIA or PsO. The study will identify women with potential pregnancies recognized in the claims from January 1995 through June 2012 and link mothers and their infants with their enrollment, pharmacy claims, and medical claims data. It will also relate exposures to pregnancy and birth outcomes allowing examination of the possible effects of maternal exposures.	Adverse pregnancy outcomes; Use in pregnant women	Started	February 2015
Epstein-Barr virus testing Category 3	Results from EBV tests as well as lymphoma histology from individual case summary reports will be presented in the PSUR as they become available. The MAH will report EBV results from registries in the PSUR as they become available.	Malignancy	Started	Not applicable; results presented annually in PSUR as they become available

Abbreviations: AEs=adverse events; ARTIS=Anti-Rheumatic Therapy in Sweden; AS=ankylosing spondylitis; BADBIR=British Association of Dermatologists Biological Interventions Register; BSPAR=British Society for Paediatric and Adolescent Rheumatology; BSRBR=British Society of Rheumatology Biologics Register; CHF=congestive heart failure; cIA=chronic inflammatory arthritis; CV=cardiovascular; DMARD=disease modifying anti-rheumatic drug; EBV=Epstein-Barr virus; ISR=injection site reaction; JIA=juvenile idiopathic arthritis; MAH=Marketing Authorisation Holder; MAS=macrophage activation syndrome; MTX=methotrexate; OTIS=Organization of Teratology Information Services; PML=progressive multifocal; leukoencephalopathy; PsA=psoriatic arthritis; PsO=psoriasis; PSUR=periodic safety update report; RA=rheumatoid arthritis; RABBIT=German Adult Register of Biologics Users; TNF=tumor necrosis factor.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important Identified Risks – All Indications		
Malignancy (including lymphoma and leukemia)	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.	None proposed
Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)	SmPC section 4.3 Contraindications SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: The possibility exists for TNF-antagonists to affect host defenses against infection.	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections.
Lupus-like reactions	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Biological-derived proteins can induce an unwanted immune response that is triggered by more than one single factor.	None proposed
Sarcoidosis and/or granulomas	SmPC section 4.8 Undesirable effects; if indicated additional changes to SmPC will be undertaken. Justification: Sarcoidosis events in placebocontrolled, active-controlled, and open-label trials of Enbrel have been reported. Assessment of potential risk is ongoing.	None proposed
Injection site reactions	SmPC section 4.8 Undesirable effects Justification: Injection site reactions have been reported in patients treated with etanercept.	None proposed
Allergic reactions	SmPC section 4.3 Contraindications SmPC section 4.4 Special warnings and	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	precautions SmPC section 4.8 Undesirable effects Justification: Allergic reactions have been associated with etanercept usage.	
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)	SmPC section 4.8 Undesirable effects Justification: Cases of severe cutaneous adverse reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.	None proposed
Systemic vasculitis (including ANCA positive vasculitis)	SmPC section 4.8 Undesirable effects Justification: Uncommonly, cases of systemic vasculitis including ANCA positive vasculitis have been reported.	None proposed
Macrophage activation syndrome	SmPC section 4.8 Undesirable effects Justification: Cases of macrophage activation syndrome have been reported.	None proposed
Central demyelinating disorders	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Demyelinating events have occurred in patients treated with etanercept.	None proposed
Peripheral demyelinating events (CIDP and GBS)	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects; if indicated additional changes to SmPC will be undertaken. Justification: Very rare reports of peripheral demyelinating polyneuropathies (including GBS) have been occurred in patients treated with etanercept.	None proposed
Aplastic anemia and pancytopenia	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects Justification: Rare cases of pancytopenia and very rare cases of aplastic anemia, with some fatal outcomes, have been reported.	None proposed
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	SmPC section 4.8 Undesirable effects Justification: Uncommonly, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported.	None proposed
Autoimmune hepatitis	SmPC section 4.8 Undesirable effects Justification: Rarely, autoimmune hepatitis has been reported	None proposed
Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)	SmPC section 4.4 Special warnings and precautions; if indicated, additional changes to SmPC will be undertaken. Justification: Reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus who are receiving TNF antagonists including Enbrel has been reported. There have been reports of worsening of hepatitis C in patients receiving Enbrel. Assessment of potential risk is ongoing	None proposed
Important Identified Risks – Specific Indications		
Change in morphology and/or severity of psoriasis in adult and	SmPC section 4.8 Undesirable effects Justification: Uncommonly, psoriasis including new onset and pustular, primarily	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
pediatric populations	involving palms and soles has been reported.	
Worsening of congestive heart failure in adult subjects	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects; if indicated; additional changes to SmPC will be undertaken. Justification: There have been postmarketing reports of worsening of CHF with and without identifiable precipitating factors in patients taking Enbrel. Assessment of potential risk is ongoing.	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to congestive heart failure.
Inflammatory bowel disease in JIA subjects	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects. Justification: Assessment of potential risk is ongoing.	None proposed
Important Potential Risks – All Indications		
Autoimmune renal disease	MAH reviewed topic, available evidence did not support inclusion of this safety concern as an adverse drug reaction. Justification: Assessment of potential risk is ongoing.	None proposed
Pemphigus/pemphigoid	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Amyotrophic lateral sclerosis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Myasthenia gravis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Encephalitis/ leukoencephalomyelitis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Progressive multifocal leukoencephalopathy	MAH reviewed topic, available evidence insufficient at this time to support inclusion of this safety concern as an adverse drug reaction. Justification: Assessment of potential risk is ongoing.	None proposed
Liver failure	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Hepatic cirrhosis and fibrosis	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Severe hypertensive reactions	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Adverse pregnancy outcomes	SmPC section 4.6 Fertility, pregnancy and lactation; if indicated, additional changes to SmPC will be undertaken. Justification: Preclinical data about peri-	None proposed.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available. Assessment of potential risk is ongoing.	
Potential for medication errors (pre-filled pen)	Clear Package Leaflet Instructions for use of the pre-filled pen (PFP). Justification: There have been reports of medication errors in patients treated with the etanercept pre-filled pen.	Educational materials Training is given to patients, care givers and healthcare professionals (HCPs) in the appropriate use of the PFP. The experiences from providing training to patients in the US, where a similar Enbrel PFP was introduced for more than two years prior to launch of the PFP in the EU, have been utilised. Based on experience from the US, EU post launch experience and market research studies, numerous enhancements have been made to the HCP and patient training materials and resources including: • Market research in the form of a “use study” was conducted with European rheumatology and dermatology patients in order to identify improvements in the instructions for use. Furthermore, readability testing of the PFP Package Leaflet was satisfactorily completed in 2007 and further readability testing is currently being conducted. The outcome of this latest round of testing will be used to determine the need for updates to the instructions for use section of the leaflet. In addition, a highly visual teaching guide was developed to facilitate HCP training of patients in the clinician’s office. This teaching guide has been made available to support clinicians in their training of patients. • Availability of a needle free demonstration device. This device allows patients to practice injections prior to using the actual PFP. These devices have been made available to clinicians for training purposes in the clinician’s

Safety concern	Routine risk minimization measures	Additional risk minimization measures
		office. • Availability of instructional materials in both print and DVD formats. HCPs have been provided with print and DVD instructional materials to share with patients to demonstrate the proper use of the PFP. At the discretion of the local affiliate, a toll-free telephone number and website for assistance may also be made available.
Potential for male infertility	SmPC section 4.6 Fertility, pregnancy and lactation; if indicated, additional changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Weight Gain	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed
Important Potential Risks –Specific Indications		
Impaired growth and development in juvenile subjects	If indicated, changes to SmPC will be undertaken. Justification: Assessment of potential risk is ongoing.	None proposed.
Acute ischemic CV events in adult subjects	SmPC section 4.8: Undesirable effect; if indicated, additional changes to SmPC will be undertaken. Justification: Serious adverse events of acute ischemic CV events have been reported in clinical trials. Assessment of potential risk is ongoing.	None proposed
Missing Information – All Indications		
Use in hepatic and renal impaired subjects	SmPC section 4.2 Posology and administration SmPC section 4.4 Special warnings and precautions; if indicated, additional changes to SmPC will be undertaken. Justification: Clinical experience in these populations is limited. Assessment of potential risk is ongoing.	None proposed
Use in different ethnic origins	If indicated, changes to SmPC will be undertaken. Justification: There is limited experience in some ethnic origins. Assessment of potential risk is ongoing.	None proposed
Use in pregnant women	SmPC section 4.6 Pregnancy and lactation; If indicated, additional changes to SmPC will be undertaken. Justification: There are no studies with etanercept in pregnant women. Assessment of potential risk is ongoing.	None proposed.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated (**addition,** ~~deletion~~). The Package Leaflet has been updated accordingly.

4.1 Therapeutic indications

[…]

Axial spondyloarthritis

Ankylosing spondylitis **(AS)**

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Non-radiographic axial spondyloarthritis

Treatment of adults with severe 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 nonsteroidal anti-inflammatory drugs (NSAIDs).

4.2 Posology and method of administration

Enbrel 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 treated with Enbrel should be given the Patient Alert Card.

Posology

[…]

Psoriatic arthritis, ~~and~~ ankylosing spondylitis and **non radiographic axial spondyloarthritis**

The recommended dose is 25 mg Enbrel administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, 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.

5.1 Pharmacodynamic properties

Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, **one study in adults with non-radiographic axial spondyloarthritis**, four studies in adults with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psoriasis.

[…]

Adult patients with non-radiographic axial spondyloarthritis

The efficacy of Enbrel in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received Enbrel 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at week 12. The double-blind period was followed by an open-label period during which all patients receive Enbrel 50 mg weekly for up to an additional 92 weeks.

Compared to placebo, treatment with Enbrel resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

Double-Blind Clinical Responses at Week 12	Placebo N=106 to 109*	Enbrel N=103 to 105*
ASAS** 40	15.7	32.4[b]
ASAS 20	36.1	52.4[c]
ASAS 5/6	10.4	33.0[a]
ASAS partial remission	11.9	24.8[c]
BASDAI***50	23.9	43.8[b]

*Some patients did not provide complete data for each endpoint

**ASAS=Assessments in Spondyloarthritis International Society

***Bath Ankylosing Spondylitis Disease Activity Index

a: p<0.001, b:<0.01 and c:<0.05, respectively between Enbrel and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint as measured by MRI for patients receiving Enbrel. Adjusted mean change from baseline was 3.8 for Enbrel treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001).

Enbrel showed statistically significantly greater improvement from baseline to week 12 compared to placebo in most health-related quality of life and physical function assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received Enbrel were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

The package leaflet has been updated accordingly.

In addition, the MAH took this opportunity to include minor administrative changes in section 4.2 of the 50 mg SmPC (EU/1/99/126/006-011, 016-021) and in section 2 of the PL (EU/1/99/126/012 and 022) which were reviewed and accepted by the CHMP.

Furthermore, Annex II has been clarified with a reference to the existing healthcare professional educational material and the Patient Alert Card.

No user consultation with target patient groups on the package leaflet (PL) has been performed. As the Enbrel PLs have undergone recent user consultations and the changes proposed in this variation are deemed not to be substantial, further readability testing is not considered to be required.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In a well-designed trial where patients were carefully selected to meet the ASAS criteria of nr-AxSpA, etanercept showed convincing evidence of significant anti-inflammatory effects when compared to placebo in a population of patients with severe active disease not adequately responding to NSAIDs. The results of the primary endpoint are supported by the results of all key secondary endpoints, except for mobility measurements, and include:

- ASAS 40 (Week 12 - primary endpoint): % difference = 16.6% (95% CI = 5.4, 27.9); p = 0.006
- ASAS 20 (Week 12): % difference = 16.3% (95% CI = 3.1, 29.4); p = 0.02
- BASDAI 50 (Week 12): % difference = 20.0% (95% CI = 7.5, 32.4); p = 0.003

The reduction in active inflammatory lesions (bone marrow oedema) detected at MRI appeared statistically different from placebo in both the spine and sacroiliac joints:

- SPARCC spine (Week 12): adjusted difference of mean = -0.96 (95% CI = -1.88, -0.04); p = 0.04
- SPARCC SIJ (Week 12): adjusted difference of mean = -2.93 (95% CI = -4.16, -1.70); p < 0.001

These data are particularly relevant and provide objective evidence of anti-inflammatory effects at the lesion site. It is consistent with the results of the ESTHER trial, which compared the effects of etanercept and sulfasalazine in early axial spondyloarthritis on MRI activity (Song, 2011).

In addition, a number of quality of life instruments were able to differentiate etanercept from placebo after 12 weeks of treatment, including BASFI, the EQ-5D VAS score, the SF-36 physical component, and even some items of the Work Productivity and Activity Impairment Questionnaire.

Etanercept was consistently superior to placebo in most patient subgroups, either statistically or at least numerically. Importantly, the effect of etanercept appeared more pronounced when inflammatory signs were initially more marked (as reflected by CRP or MRI), which corresponds to the target population of patients as defined in the SmPC.

Uncertainty in the knowledge about the beneficial effects

The need for continuous therapy to maintain clinical response or remission over time is currently unknown. As anti-TNFs have not been shown to prevent progression of structural damage while they are not devoid of serious risks on the long-term, treatment interruption in stable condition is justified.

Given that AxSpA is a disease with fluctuating symptomatology and patients with non-radiological disease are likely to start anti-TNF treatment early in life, the possibility of treatment interruptions is especially relevant.

Continued therapy should be carefully reconsidered in a patient not responding within 12 weeks of treatment (as described in the product information).

The remaining uncertainty about the optimal conditions of use in the long-term has been addressed in the RMP with two studies, the ongoing B1801031 and a study B1801381 to be conducted in a larger sample of nr-AxSpA patients to refine the description of the relapse profile after treatment discontinuation and evaluate the effects of re-treatment.

Risks

Unfavourable effects

During the double-blind period, the incidence of TEAEs was higher in etanercept-treated patients than in placebo-treated patients essentially due to injection site reactions and skin reactions. No difference in the occurrence of infections was found and the incidence of SAEs was similar. Liver enzymes (ALT/AST) abnormalities were slightly more frequent, but usually transient.

Uncertainty in the knowledge about the unfavourable effects

No new safety concern emerged during this trial over a 24-week period. The safety profile of etanercept in the target population is consistent with its known safety profile in AS. No additional uncertainty in the current knowledge of the risks of etanercept has been identified. The MAH agreed to conduct a study in nr-AxSpA patients to evaluate the duration of remission after withdrawal of therapy as well as safety of treatment after disease flare (as described in the RMP). The information obtained from the proposed study B1801381 will be complemented by the results from the current ongoing study B1801031, which will provide an assessment of the long-term safety associated with continuous etanercept treatment (up to 104 weeks) in this population (as described in the RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The beneficial effects of etanercept in the target population have been demonstrated with a range of standard composite scores used in AS, which assess the main symptoms of the disease (in particular back pain and morning stiffness), functional limitation, and disease activity. These have been supported by significant reduction in systemic and local signs of inflammation. A positive impact of the treatment on the patient quality of life and work has also been shown. These changes are clinically relevant. They represent at Week 12 an improvement from baseline of about 35% with respect to symptoms and functional limitation as evaluated by the patient and about 45% with respect to objective inflammatory signs (CRP, MRI).

The unfavourable effects of etanercept are well known given the extensive experience accumulated over 15 years and for most manageable. For a majority of patients, the safety profile of etanercept is acceptable with generally self-limiting injection site reactions.

Continued therapy should be carefully reconsidered in a patient not responding within 12 weeks of treatment (as described in the product information). The remaining uncertainty about the optimal conditions of use in the long-term has been addressed in the RMP with two studies, the ongoing

B1801031 and a new trial (B1801381) to be conducted in a larger sample of nr-AxSpA patients to refine the description of the relapse profile after treatment discontinuation and evaluate the effects of re-treatment.

Benefit-risk balance

If left untreated, a sizeable proportion of patients with sacroiliac inflammation on MRI but who lack radiographic findings are expected to progress to the more debilitating state of AS although 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.

NSAIDs are currently recommended as first-line therapy in patients with AxSpA, including those with nr-AxSpA. Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine are sometimes used but have demonstrated minimal efficacy in treating AxSpA. Thus, there is a medical need for patients with nr-AxSpA whose disease is not responsive to NSAIDs. Two anti-TNF monoclonal antibodies, adalimumab and certolizumab pegol, have been approved in the EU for the treatment of adults with nr-AxSpA.

Currently, most studies of anti-TNFs have failed to show an impact on structural progression in AS. Therefore, early therapeutic intervention may potentially impact the natural history of the disease progression by reducing early inflammation, as this may be the forerunner of irreversible bony ankylosis.

The benefit provided by symptomatic improvement and its positive impact on quality of life and work, in addition to the potential of delaying or preventing progression to debilitating AS, is considered to exceed the rare serious risks of etanercept.

Discussion on the Benefit-Risk Balance

The benefit-risk balance of etanercept in the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence, who have had an inadequate response to NSAIDs, is considered positive.

4. Recommendations

☒ The application for the treatment of non-radiographic axial spondyloarthritis is approvable since other concerns have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) accepted		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

Extension of Indication to include the treatment of adults with severe 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 nonsteroidal anti-inflammatory drugs (NSAIDs). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance.

In addition, the MAH took this opportunity to include minor administrative changes in section 4.2 of the SmPC of the 50 mg formulation.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State comprising of information provided to all healthcare professionals expected to prescribe the product on the correct and safe use of the pre-filled pen and a Patient Alert Card which is to be given to patients using Enbrel.

The healthcare professional's educational material should contain the following key elements:
- Teaching guide to facilitate training of the patients in the safe use of the pre-filled pen
- A needle-free demonstration device
- Instructional materials to share with patients

The Patient's Alert Card should contain the following key elements for patients treated with Enbrel:
- The risk of opportunistic infections and tuberculosis (TB)
- The risk of Congestive Heart Failure (CHF)