21 June 2012

EMA/CHMP/220041/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Humira

adalimumab

Procedure No.: EMEA/H/C/000481/II/0085

Note

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

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1. Scientific discussion

1.1. Introduction

About the product

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically and with high affinity to the soluble and transmembrane forms of TNF-α and inhibits the binding of TNF-α with its receptors. Adalimumab is approved for the treatment of inflammatory diseases including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (Ps), ulcerative colitis (UC) and Crohn's disease (CD).

Problem statement

Spondyloarthritidis is a group of diseases that share common clinical, radiographic, and genetic features. This includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic or inflammatory bowel disease (IBD)-related arthritis and undifferentiated spondyloarthritis (SpA). Because there is an overlap of features among these diseases, there is some variability in the way physicians may interpret and apply these diagnoses in clinical practice. An alternative way of categorizing SpA patients would be to define them by their primary clinical manifestation – axial or peripheral SpA. The Assessments in Spondyloarthritis International Society (ASAS) Working Group has proposed and validated new classification criteria for patients with axial SpA and for those with peripheral SpA.[1,2] This new set of criteria incorporates the use of magnetic resonance imaging (MRI) for visualizing sacroiliitis in addition to traditional x-rays.

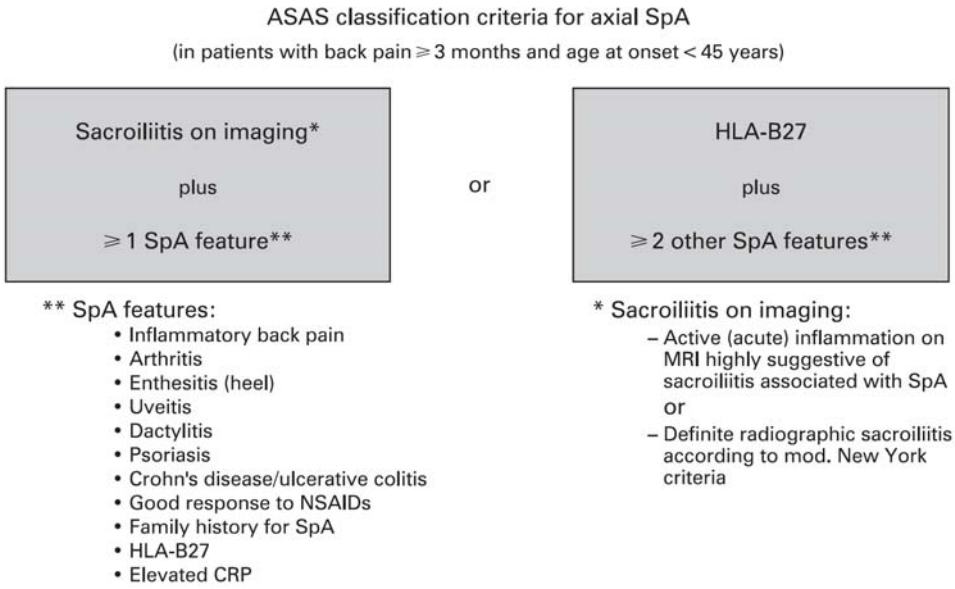


Figure 1 Proposed classification criteria for axial SpA

(Rudwaleit et al, Ann Rheum Dis Mar 2009, 68)

[1] Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis (Part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.

[2] Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.

There is a medical need in patients with axial SpA who have disease features similar to patients with AS, but who do not fulfill the modified New York criteria for AS by virtue of not having evidence of structural damage in the form of radiographic sacroiliitis. Patients with non-radiographic axial SpA (nr-axSpA) can present with disease features and a level of disease activity similar to those observed in patients with AS.

While non-steroidal anti-inflammatory drugs (NSAIDs) are effective in treating the signs and symptoms of axial SpA in some patients, traditional anti rheumatic therapies such as methotrexate or sulfasalazine are not effective for the axial component of SpA and the use of systemic corticosteroids is not supported by evidence. When NSAIDs fail to provide adequate control of the disease, patients with non-radiographic axial SpA do not have alternative treatments available. However, such patients may continue to experience signs and symptoms similar to AS patients but without alternative treatment.

Scope of the variation

In this submission the MAH applied for a new therapeutic indication for the treatment of adults with severe axial spondyloarthritis, including ankylosing spondylitis who have had an inadequate response to conventional therapy or are intolerant to NSAIDs. Sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated accordingly as well as Annex II and IIIB. Some editorial changes have also been made throughout the SmPC.

The initially applied wording for the extension of indication reads as follows (additions and ~~deletion~~ to the existing approved AS indication):

Axial spondyloarthritis including Ankylosing spondylitis

Humira is indicated for the treatment of adults with severe axial spondyloarthritis, including ~~active~~ ankylosing spondylitis who have had an inadequate response to conventional therapy or are intolerant to NSAIDs.

The following variation application is made in this submission:

Clinical:

Variation requested		**Type**
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/141/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/141/2011 was not yet completed as some measures were deferred.

Development programme

A clinical program was developed by the MAH to study the efficacy and safety of adalimumab in patients with axial SpA who do not fulfil the modified New York criteria for AS. This development program consists in a currently ongoing, single pivotal Phase 3 clinical study (Study M10-791) aiming to demonstrate the efficacy and safety of adalimumab 40 mg given subcutaneously (SC) every other

week (eow) versus placebo in adult subjects with axial SpA diagnosed according to the published criteria of the ASAS working group.

The pivotal randomized, double-blind, placebo-controlled design of study M10-791 was chosen to demonstrate the efficacy of adalimumab in subjects with active axial SpA not fulfilling the modified New York criteria for AS who had an inadequate response or intolerance to 1 or more NSAIDs, or had a contraindication for NSAIDs. Study M10-791 includes a 12-week, double-blind (DB), placebo-controlled period and a 92-week open-label (OL) treatment period.

The 40 mg adalimumab dose was chosen in accordance with the AS and PsA dosage recommendations in the EU SmPC. Moreover, the adalimumab clinical trial safety database across multiple disease indications is also largely comprised of data recorded with the 40 mg eow dose, which is also the approved maintenance dose for adult patients across all other indications.

Compliance with scientific advice

The applicant did not seek scientific advice at the CHMP.

Compliance with CHMP guideline

There is no specific guideline for the development of medicinal products for the treatment of non-radiographic axial spondyloarthritis. Reference was made to the CHMP 2009 Guideline on Clinical Investigation for Medicinal Products for the treatment of AS (CPMP/EWP/4891/03).

Although ASAS20 is commonly used in placebo-controlled trials in AS for some products (e.g. NSAIDs), ASAS40 was chosen as the primary endpoint also considering that a more stringent efficacy improvement may be required in certain circumstances, particularly in the case of products belonging to therapeutic classes different from NSAIDs.

Overall the study M10-791 was in line with the EMA guideline (CPMP/EWP/4891/03) and in particular with respect to study design, main efficacy endpoint and secondary endpoints.

General comments on compliance with GMP, GLP, GCP

The clinical trial submitted in support of this variation was performed in accordance with GCP as claimed by the applicant. 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.

1.2. Clinical aspects

1.2.1. Clinical pharmacology

Pharmacokinetics (PK) data were not collected in Study M10-791 as the PK of adalimumab have been previously established (as described in section 5.2 of the approved SmPC).

Since non-radiographic axial SpA, AS, and PsA all belong to the spondyloarthritides group of diseases, the 40 mg adalimumab dose was chosen in accordance with the approved AS and PsA dosage recommendations in the EU SmPC. No new clinical pharmacology data are being submitted as part of this application.

The approach taken in order to select the dose is considered appropriate by the CHMP.

1.2.2. Clinical efficacy

1.2.2.1. Main pivotal study

Study M10-791

Study M10-791 is a multicenter study evaluating the efficacy and safety of the human anti-TNF monoclonal antibody adalimumab in subjects with axial spondyloarthritis.

Methods

Study M10-791 includes a 12-week double-blind (DB), placebo-controlled phase followed by a 92-week open-label (OL) phase.

Subjects were randomized in a 1:1 ratio to receive either adalimumab 40 mg SC eow or matching placebo for 12 weeks during the DB period. Following the DB period, at Week 12 all subjects entered the OL arm of the study in which they received adalimumab 40 mg SC eow for up to an additional 92 weeks (all subjects on placebo were started on adalimumab and subjects already on adalimumab continued during the 92 weeks of the OL period).

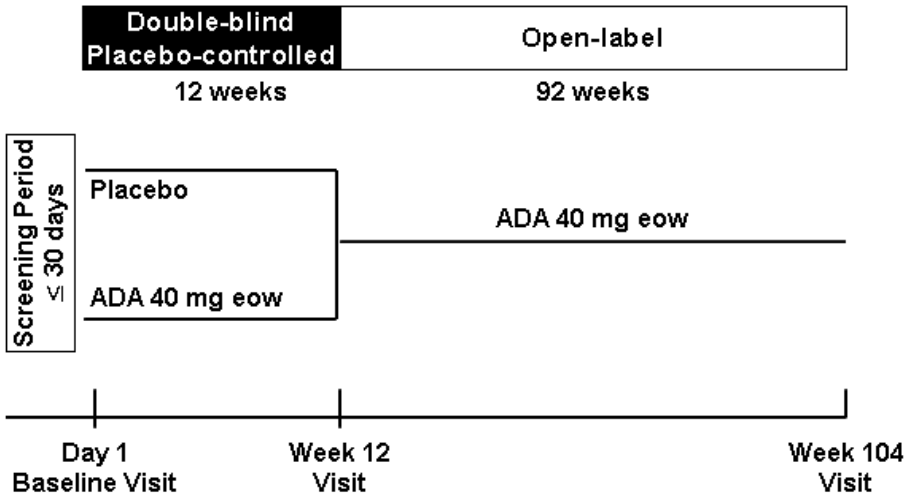


Figure 2 Study design schematic

Subjects were to visit the study site at weeks 2, 4, 8, and 12 during the DB period, and at Weeks 16, 20, 24, 28, 36, 44, 52, 60, 68, 80, 92, and 104 during the OL period. If, during the course of study drug administration, the subject prematurely discontinued study drug use, the procedures outlined for the termination visit were to be completed within 2 weeks of the last dose of study drug, and preferably prior to the initiation of another therapy.

MRI of the spine and sacroiliac (SI) joints was performed at screening and on Weeks 12, 52 and 104.

Study Participants

Main inclusion criteria:

1. Subject was ≥18 years of age.
2. Subject must have had an inadequate response to NSAIDs, intolerance to ≥1 NSAID, or had a contraindication for NSAIDs as defined by the investigator.
3. Subject must have had chronic back pain (of at least 3 months duration) with onset at age <45 years.

4. MRI evidence of active inflammatory lesions of sacroiliac joints (past or present) with definite bone marrow edema/osteitis, suggestive of sacroiliitis associated with SpA plus ≥1 of the clinical criteria listed below:

   OR

   Positive human leukocyte antigen-B27 (HLA-B27) plus ≥2 of the clinical criteria listed below other than HLA-B27 positivity:

   - Inflammatory back pain defined as the presence at screening of at least 4 out of the following 5 parameters: 1) age at onset <40 yrs, 2) insidious onset, 3) improvement with exercise, 4) no improvement with rest, 5) night pain with improvement upon getting up;
   - Arthritis (past or present);
   - Heel enthesitis (past or present);
   - Anterior uveitis confirmed by an ophthalmologist (past or present);
   - Dactylitis (past or present);
   - CD or ulcerative colitis (past or present);
   - Good prior response to an NSAID – back pain was not present anymore or much better 24 to 48 hours after a full dose of an NSAID;
   - Family history of SpA;
   - Positive HLA-B27;
   - Elevated C-reactive protein (CRP).

5. Subjects must have Baseline disease activity as defined by having a Total Back Pain VAS score ≥ 40 mm and BASDAI ≥ 4 at both the Screening and Baseline visits.

Main exclusion criteria:

1. Past or present diagnosis of AS, psoriasis, psoriatic arthritis, or history of inflammatory arthritis other than axial SpA (e.g., rheumatoid arthritis, gout, lupus, or polyarticular or systemic juvenile idiopathic arthritis).
2. Prior exposure to any biologic therapy with a potential therapeutic impact on SpA, including anti-TNF therapy.
3. Use of second-line antirheumatic therapy, except MTX, SSZ, hydroxychloroquine, or azathioprine, within 28 days prior to Baseline.
4. Subject had been treated with intra-articular joint injection(s) or spinal/paraspinal injection(s) of corticosteroids in the preceding 28 days prior to the Baseline visit
5. Subject with extra-articular manifestations (e.g. IBD, uveitis, etc.) that were not clinically stable for at least 30 days prior to study entry.

<u>Allowed concomitant medication</u>

Subjects could continue on stable doses of MTX, SSZ, hydroxychloroquine, azathioprine, prednisone, and/or NSAIDs provided the stability requirements were met:

DMARDs: Subject was to be on stable dose of MTX (≤25 mg per week) and/or SSZ (≤3 g per day), and/or hydroxychloroquine (≤400 mg per day) for 28 days prior to the Baseline visit.

Azathioprine: Subject was to be on stable dose (≤150 mg/day) for 28 days prior to the Baseline visit and without another concomitant immunosuppressive drug at study entry.

Oral corticosteroids: Subject was to be on stable dose of prednisone (≤10 mg per/day), or oral corticosteroid equivalents, for at least 14 days prior to the Baseline visit.

NSAID: Subject was to be on stable doses of NSAIDs and/or analgesics for 14 days prior to the Baseline visit.

Prohibited Concomitant Medication

Cyclosporine or other second line anti-rheumatic therapy (except MTX, SSZ, hydroxychloroquine, or azathioprine) within 28 days prior to the Baseline visit was prohibited.

Opioid analgesics (other than tramadol) within 14 days prior to Baseline visit were prohibited.

Only one intra-articular corticosteroid injection for a peripheral joint was to be allowed during the first 24 weeks of the study. After Week 24, intra-articular corticosteroid injections were to be allowed at the investigator's discretion. Once a joint was injected it was to be considered not evaluable/assessable during the 28 days following injection. No spinal, para-spinal, or sacroiliac joint injections were to be allowed during the first 24 weeks of the study.

Treatments

Study drug was to be provided as a sterile SC injection solution in 1-ml pre-filled syringes containing either adalimumab 40 mg/0.8 mL or matching placebo for adalimumab. Study drug was to be self-administered SC eow at approximately the same time of day. The day of the first dose of study drug was designated as Day 1.

Objectives

The objective of the study was to evaluate the efficacy and safety of adalimumab 40 mg given eow subcutaneously compared to placebo for 12 weeks followed by OL safety and efficacy assessments in subjects with active axial SpA not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to 1 or more NSAIDs, or had a contraindication for NSAIDs.

Outcomes/endpoints

The primary efficacy variable for this study was the proportion of subjects who achieved ASAS40 response at the Week 12 visit. A subject was to be categorized as an ASAS40 responder at the Week 12 visit if the subject achieved:

Improvement of ≥40% and absolute improvement of ≥20 units (on a scale of 0 to 100) from Baseline in ≥3 of the following 4 domains with no deterioration at all in the potential remaining domain:

- Patient's Global Assessment – Represented by the Patient's Global Assessment of Disease Activity VAS score (0 to 100 scale)
- Pain – Represented by the total back pain VAS score (0 to 100 scale)
- Function – Represented by the BASFI score (10 VAS scales on functional items, like putting on socks, bending for a pen, doing a full day’s activities (0 to 100 scale). Mean of the ten scores is calculated.)

- Inflammation – Represented by the mean of the 2 morning stiffness-related BASDAI VAS scores (i.e. the average of items 5 and 6 of the BASDAI, severity and duration of morning stiffness.)

The ranked secondary efficacy variables that were to be analyzed at Week 12 included:

1. ASAS20 response (improvement of ≥20% and absolute improvement of ≥10 units from Baseline in ≥3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain [defined as a worsening of ≥20% and a net worsening of ≥10 units])
2. BASDAI 50 (50% improvement from Baseline in BASDAI. 6 VAS-scales scoring fatigue, spinal pain, peripheral arthritis, enthesitis, intensity and duration of morning stiffness. The mean of the 2 last items is calculated, and added to the mean of questions 1-4. The result is divided by 5.)
3. Mean change in SF-36v2 physical component
4. ASAS partial remission (absolute score of <20 units for each of the 4 domains identified above in ASAS40)
5. ASAS5/6 response (20% improvement in 5 out of the following 6 domains: BASFI, total back pain, PTGA-Disease Activity, inflammation [represented by questions 5 and 6 of the BASDAI], lateral lumbar flexion from BASMI, and acute phase reactant [pooled CRP])
6. Mean change in HAQ-S
7. Mean change in hs-CRP
8. Mean change in SPARCC MRI score for sacroiliac joints
9. Mean change in SPARCC MRI score for the spine

Other variables that were to be analyzed at various timepoints included:

- ASAS50 response (improvement of ≥50% and absolute improvement of ≥20 units from Baseline in ≥3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain [defined as a worsening of ≥20% and a net worsening of ≥10 units])
- ASAS70 response (improvement of ≥70% and absolute improvement of ≥30 units from Baseline in ≥3 of the 4 domains identified above in ASAS40, with no deterioration in the remaining domain [defined as a worsening of ≥20% and a net worsening of ≥10 units])
- AS disease activity score (ASDAS) (a composite score of BASDAI questions 2, 3, and 6; PTGA-Disease Activity; and pooled CRP)
- Swollen joint index (66 joints)
- Tender joint index (68 joints)
- BASDAI
- Inflammation (mean of BASDAI questions 5 and 6)
- $BASMI_{lin}$ (the results from 5 mobility assessments are transformed into values form 0-10 with the aid of a linear function sheet.)
- Chest expansion
- MASES (Maastricht Ankylosing Spondylitis enthesitis Score, 13 sites are scored as 0 or 1)
- Plantar fascia enthesitis

- Dactylitis
- Physician's Global Assessment of Disease Activity (VAS)
- Nocturnal pain VAS
- Total back pain VAS
- Patient's Global Assessment of Disease Activity (VAS)
- Patient's Global Assessment of Pain (VAS)
- Short Form-36v2 Health Survey questionnaire
- WPAI-SHP
- PASS
- MOS Sleep Scale
- EQ-5D
- BASFI
- Levels of biomarkers (serum MMP-3, urine CTX-II, and VEGFA)

Sample size

The study was powered to detect differences in ASAS40 response rates at Week 12 in SpA subjects with axial disease. Assuming an expected ASAS40 response rate of 15% in the placebo group and 35% in the adalimumab group, a total sample size of 194 subjects (that is, 97 placebo and 97 adalimumab subjects) will provide approximately 90% statistical power to detect the difference between the two treatment groups. This sample size calculation assumed a 1:1 randomization ratio, and was based on a 2-sided chi-square test with a significance level of 0.05.

Randomisation

Subjects were to be randomized in a 1:1 ratio to receive either adalimumab or matching placebo for 12 weeks. At the Week 12 visit all subjects were then to receive OL adalimumab to be administered through Week 104.

Blinding

The MAH, the investigator, study site personnel, and the subject were to remain blinded to each subject's treatment throughout the 12-week blinded period of the study. An Interactive voice response system was to provide access to blinded subject treatment information in the case of medical emergency. Subjects could be unblinded after the database lock on the blinded portion of the study.

Statistical methods

Analyses of the endpoints described above were conducted on the following analysis sets:

- Intent-to-Treat Population (ITT)

  The ITT population was defined as all randomized subjects who received at least 1 dose of blinded study drug. However, as a result of investigator noncompliance, the MAH determined that 7

subjects enrolled at a specific site should be excluded from the efficacy analyses. Therefore, no analyses were conducted using the ITT population except as a sensitivity analysis for the primary endpoint and ranked secondary endpoints.

- Full Analysis Set (FAS)

  All efficacy analyses were conducted on the FAS, which is a subset of the ITT population that excludes the 7 subjects. Efficacy analyses on the FAS were conducted according to subjects' assigned treatment groups.

- Per Protocol Population (PPP)

  In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary efficacy variable was conducted on the PPP, which consists of all FAS subjects who completed the DB portion of the study and did not meet any major protocol violation during the DB portion. The exclusion of subjects was determined via classification prior to interim database lock for data pertaining to the DB period.

- Open-Label (OL) population

  The OL population was comprised of all randomized subjects who completed Week 12 and had at least 1 dose of OL study drug. This population is a subset of the FAS. No PPP is defined for the OL population.

- Any Adalimumab Set

  The Any Adalimumab set includes all randomized subjects who received at least 1 dose of adalimumab any time during the study, with the exception of the 7 subjects. This population is a subset of the FAS and was analyzed to evaluate the efficacy of adalimumab over time.

The primary efficacy endpoint was the proportion of responders according to ASAS40 response criteria at Week 12, and the response rate observed in the group randomized to adalimumab 40 mg eow was to be compared to that in the placebo group. The null hypothesis associated with this comparison states that there is no difference in response rates between the adalimumab and placebo groups; the alternative hypothesis is that the response rates are different. The response rates were tested using a two-sided Pearson's chi-square test with $\alpha = 0.05$. Subjects with missing ASAS40 response at Week 12 were to be treated as non-responders according to the NRI method.

The ranked secondary efficacy endpoints were tested in hierarchical order. The first secondary endpoint was tested at $\alpha = 0.05$; if the null hypothesis was rejected, next hypothesis in sequence was tested at $\alpha = 0.05$; this process was to continue until the null hypothesis for a particular endpoint was accepted.

Discrete variables were summarized using count and percentages and were compared between adalimumab and placebo groups using Pearson's chi-square or Fisher's exact test (if ≥25% of the cells have expected counts less than 5). Continuous efficacy variables were to be summarized by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum) at Week 12. Change from Baseline at Week 12 in the continuous variables was to be compared between adalimumab and placebo groups using an analysis of covariance method adjusting for the Baseline score. This was to be done for both observed and LOCF imputed values.

The OL data (beyond Week 12) were summarized descriptively.

Safety analyses were to be carried out using the safety population, which include all subjects that received at least 1 dose of study medication. Treatment-emergent, and pre- and post-treatment AEs were to be summarized and reported.

Results

Participant flow and number analysed

Study M10-791 is currently ongoing. This submission includes interim data collected from the study through 02 February 2011. As of this cut-off date, all active subjects have completed the 12-week DB phase and at least 12 weeks of OL treatment (i.e. data through Week 24 are available for all active subjects) and treatment was ongoing in the study as of the data cut-off. Additionally, longer-term OL data are included for those subjects who enrolled earlier in the study, with some subjects having approximately 1 year of adalimumab exposure.

A total of 192 subjects with active axial SpA were enrolled at 37 study sites. All 192 subjects were randomized; however, the MAH identified an investigator noncompliance with protocol requirements at an investigative site. As a result of this finding, the 7 subjects enrolled at this site were excluded from the efficacy analyses conducted on 185 subjects in the Full Analysis Set (FAS), but were included in the safety analysis. As of the data cut-off date (02 February 2011), 154 subjects were ongoing in the study (Figure 3).

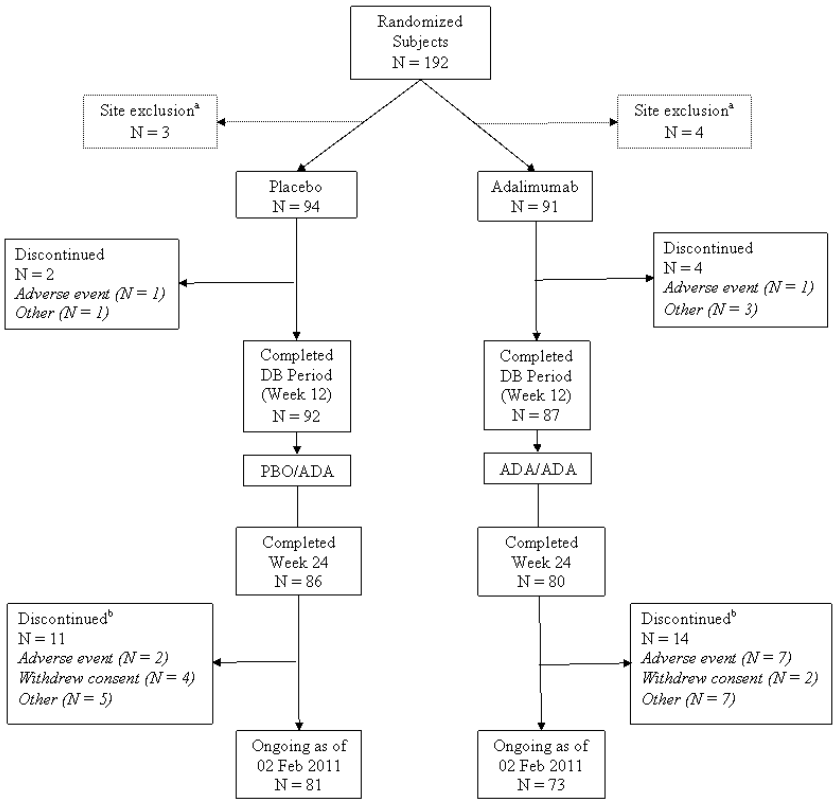
Table 1 Disposition of subjects (Full Analysis Set)

	Number (%) of Subjects by Randomization Group		
Subject Status	**Placebo N = 94**	**Adalimumab N = 91**	**Combined N = 185**
Completed Week 12 (DB Period)	92 (97.9)	87 (95.6)	179 (96.8)
Completed Week 24 (OL Period)	86 (93.5)	80 (92.0)	166 (92.7)
Ongoing as of 02 February 2011	81 (86.2)	73 (80.2)	154 (83.2)
Discontinued at any time during study[a]	13 (13.8)	18 (19.8)	31 (16.8)
Reasons for discontinuation[b]			
Adverse event	3 (3.2)	8 (8.8)	11 (5.9)
Withdrew consent	4 (4.3)	2 (2.3)	6 (3.4)
Lost to follow-up	0	0	0
Other[c]	6 (6.4)	10 (11.0)	16 (8.6)

a. Includes discontinuations after the Week 24 visit.
b. Subjects could have discontinued for more than 1 reason.
c. Reasons for discontinuation recorded as "other" included lack of efficacy, pregnancy, investigator decision, and inclusion/exclusion criteria violation.

The most common reason for discontinuation was "other" (8.6% of all randomised patients), which included lack of efficacy, protocol violation, investigator's decision and pregnancy; followed by adverse events (5.9 %).

The flow of subjects from randomization through the cut-off date of 02 February 2011 is outlined in Figure 3.



a. Investigator site that was excluded for noncompliance with the protocol.
b. All discontinuations during the OL Period (before and after Week 24). All reasons for discontinuation are shown; subjects may have given more than 1 reason for discontinuation
Note: Reasons for discontinuation recorded as "other" included lack of efficacy, pregnancy, investigator decision, and inclusion/exclusion criteria violation.

Figure 3 Subject flow diagram (Full Analysis Set)

Major protocol deviations, as defined according to ICH guidelines, that occurred in the FAS during the DB Period and the OL Period through the data cutoff date included entry criteria violations and the use of excluded concomitant treatment (Table 2). The FAS does not include the 7 subjects who were excluded from a site. Major protocol deviations which may have impacted primary efficacy analysis were accounted for by exclusion of the pertinent subjects from the PPP and did not impact the interpretation of efficacy based on the primary endpoint for the study.

Table 2 Protocol deviations during study (Full Analysis Set)

	Number (%) of Subjects by Randomization Group		
Deviation Category[a]	**Placebo N = 94**	**Adalimumab N = 91**	**Combined N = 185**
Inclusion/exclusion criteria deviations	13 (13.8)	12 (13.2)	25 (13.5)
Developed withdrawal criteria but was not withdrawn	0	0	0
Received wrong treatment or incorrect dose	0	0	0
Received excluded concomitant treatment	3 (3.2)	1 (1.1)	4 (2.2)

a. Subjects with multiple protocol deviations are counted once in each deviation category.

Conduct of the study

The original protocol had 4 amendments. Eighty-three subjects were enrolled under the original protocol, one subject was enrolled under Amendment 1, 73 were enrolled under Amendment 2, 35

subjects were enrolled under Amendment 3, and no subjects were enrolled under Amendment 4. Amendment 1 included updates made for general consistency throughout the protocol; modifications made to the inclusion/exclusion criteria for clarity and added direction for the sites; clarifications of procedures added for direction to the sites. Amendment 2 included the correction to the SAE process and minor typographical errors. Amendment 3 included clarification of acceptable time frames for evaluations at screening of the ASAS criteria; correction and clarification to concomitant medication acceptability; additional clarification that the Week 12 MRI should be completed prior to Week 12 open-label dose. Amendment 4 included the addition of a confirmatory HLA-B27 test if the result is initially reported as equivocal.

Statistical Changes

In Amendment 1, $BASMI_2$ was changed to linear BASMI. $BASMI_2$ was added to the non-ranked secondary endpoints in addition to the linear BASMI for comparison to earlier study data. The summarization of the anterior uveitis assessment and HCRU were also added to the non-ranked secondary endpoints in Protocol Amendment 1 to reflect changes in the eCRF during the study. No changes to the planned statistical analyses were made with Protocol Amendments 2 through 4.

Changes from last Amendment to final statistical analysis plan: the MAH identified an investigator noncompliance with protocol requirements at an investigative site. As a result, all 7 subjects enrolled at this site were excluded from the efficacy analyses. The FAS was therefore defined in the SAP as the subset of the ITT population excluding subjects from the site of this investigator. All efficacy analyses were conducted on the FAS with the ITT population only used for sensitivity analysis. The analysis of categorical and continuous data was incorrectly stated in the final SAP. Treatment group homogeneity for categorical demographic data (sex, race, ethnicity, and age categories) was to be assessed using a one-way ANOVA model using treatment as the independent factor. For continuous demographic data (age and baseline weight), treatment group homogeneity was to be evaluated using the appropriate chi-square method.

Baseline data

Demographic and baseline characteristics

The majority of subjects in the Full Analysis Set were female, white, and <40 years old. No statistically significant differences were observed between treatment groups.

Axial SpA medical history

Subjects reported having had symptoms of axial SpA for a mean of approximately 10 years, but the majority (70.3%) had been diagnosed with axial SpA for ≤ 3 years prior to Baseline.

Approximately one-half of the subjects in each arm met the ASAS axial SpA criteria-defined evidence of sacroilitis on MRI (Table 3). The majority of subjects were HLA-B27-positive. Almost all subjects (97% in each arm) had back pain that was inflammatory in nature as defined in the ASAS axial SpA criteria. Less than one-half of the subjects had a history of elevated CRP.

The majority of subjects had no history of anterior uveitis or of inflammatory bowel disease (Crohn's disease or ulcerative colitis). None of the subjects reported a history of psoriasis (this would have been a protocol violation as subjects with psoriasis were excluded from the study).

Table 3 Axial spondyloarthritis-related medical history (Full Analysis Set)

	Number (%) Subjects		
Axial SpA Medical History Characteristica	**Placebo N = 94**	**Adalimumab N = 91**	**Combined N = 185**
Active inflammatory lesions on MRI of sacroiliac joint[b]			
Yes	43 (45.7)	46 (50.5)	89 (48.1)
No	51 (54.3)	45 (49.5)	96 (51.9)
Positive HLA-B27			
Yes	67 (71.3)	72 (79.1)	139 (75.1)
No	27 (28.7)	19 (20.9)	46 (24.9)
Inflammatory back pain[c]			
Yes	91 (96.8)	88 (96.7)	179 (96.8)
No	3 (3.2)	3 (3.3)	6 (3.2)
Arthritis (past or present)			
Yes	49 (52.1)	32 (35.2)	81 (43.8)
No	45 (47.9)	59 (64.8)	104 (56.2)
Dactylitis (past or present)			
Yes	10 (10.6)	10 (11.0)	20 (10.8)
No	84 (89.4)	81 (89.0)	165 (89.2)
Heel enthesitis (past or present)[d]			
Yes	38 (40.4)	36 (39.6)	74 (40.0)
No	56 (59.6)	55 (60.4)	111 (60.0)
Anterior uveitis confirmed by ophthalmologist (past or present)			
Yes	10 (10.6)	12 (13.2)	22 (11.9)
No	84 (89.4)	79 (86.8)	163 (88.1)
IBD (CD or UC) (past or present)			
Yes	6 (6.4)	4 (4.4)	10 (5.4)
No	88 (93.6)	87 (95.6)	175 (94.6)
Good prior response to NSAIDs[e]			
Yes	70 (74.5)	64 (70.3)	134 (72.4)
No	24 (25.5)	27 (29.7)	51 (27.6)
Family history of SpA[f,g]			
Yes	23 (24.7)	28 (30.8)	51 (27.7)
No	70 (75.3)	63 (69.2)	133 (72.3)
Missing	1	0	1
Elevated CRP[h]			
Yes	36 (38.3)	36 (39.6)	72 (38.9)
No	58 (61.7)	55 (60.4)	113 (61.1)

CD = Crohn's disease; CRP = C-reactive protein; HLA-B27 = Human Leukocyte Antigen-B27; IBD = inflammatory bowel disease; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; SpA = spondyloarthritis; UC = ulcerative colitis

a. Based on the reported axial SpA medical history page of the CRF.
b. MRI showing definite bone marrow edema/osteitis suggestive of sacroiliitis associated with SpA.
c. Inflammatory back pain had to meet 4 of the following 5 parameters: 1) Age at onset < 40 yrs; 2) Insidious onset; 3) Improvement with exercise; 4) No improvement with rest; 5) Night pain with improvement upon getting up.
d. Past or present spontaneous pain or tenderness at examination of the site of insertion of the Achilles tendon or plantar fascia at the calcaneus.
e. Back pain not present or much better 24 to 48 hours after full dose of NSAID.
f. Presence of AS, psoriasis, acute uveitis, reactive arthritis, or IBD among first- or second-degree relatives.
g. Percentages calculated based on nonmissing values.
h. CRP concentration above upper limit of normal in the presence of back pain; after exclusion of other causes of elevated CRP.

Baseline disease activity

No statistically significant differences in baseline disease activity were observed between treatment groups. Baseline disease activity was generally similar to what has been reported for the AS population in the ATLAS study (Study M03-607), a global, randomized, controlled trial of adalimumab (van der Heijde 2006). However, Baseline BASFI and $BASMI_2$ scores were noted to be lower than in the ATLAS study, implying better functionality and less spinal mobility restriction among subjects with non-radiographic axial SpA than those with AS. There is evidence of significant baseline disease activity with approximately two-thirds of patients having BASDAI >6 and almost all of the subjects falling under the ASDAS "high" or "very high" disease activity states. Few patients had evidence of peripheral disease as measured by tender and swollen joint counts, dactylitis count, MASES, and presence/absence of plantar fasciitis. Approximately one-third of subjects had abnormal CRP (hs-CRP [high sensitivity] or pooled) at Baseline.

Baseline health-related quality of life

No statistically significant differences in mean Baseline SF-36v2 scores were observed between the treatment groups. Mean SF-36 PCS and MCS summary scores were substantially lower compared with the general population (Kimel 2011).

Twenty-three subjects reported visiting a health care professional (HCP) in relation to their axial SpA between the Screening and Baseline visits (Table 4).

Table 4 Baseline Health Care Resource Utilization (Full Analysis Set)

HCRU Question	Placebo N = 94	Adalimumab N = 91	Combined N = 185	*P* value
Medical visit for axial SpA since screening				
Yes	11 (16.9)	12 (20.0)	23 (18.4)	0.657[a]
Health care professional	11 (100)	12 (100)	23 (100)	
Emergency department	0	0	0	
Hospitalization	0	0	0	
No	54 (83.1)	48 (80.0)	102 (81.6)	
Missing	29	31	60	
Number of visits to HCP				
Mean ± SD	5.27 ± 4.901	5.25 ± 4.712	5.26 ± 4.693	0.991[b]
Median (min–max)	3.00 (1.0 – 15.0)	4.00 (1.0 – 15.0)	3.00 (1.0 – 15.0)	

HCP = health care professional; HCRU = Health Care Utilization Questionnaire; SD = standard deviation
a. P value to compare adalimumab versus placebo was based on chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected counts < 5) using nonmissing values.
b. *P* value to compare adalimumab versus placebo was based on one-way ANOVA.
Note: Baseline is defined as the last nonmissing value prior to the first dose of study drug.

No statistically significant differences in mean Baseline HAQ-S scores were observed between the treatment groups (Table 5). The majority of subjects reported moderate to complete impairment in function when asked to what extent they were able to carry out everyday physical activities.

Table 5 Baseline Health Assessment Questionnaire modified for the spondyloarthropathies (HAQ-S) Scores (Full Analysis Set)

HAQ-S Question	Placebo N = 94	Adalimumab N = 91	Combined N = 185	*P* value
HAQ-S score				
n	94	91	185	
Mean ± SD	1.05 ± 0.569	0.99 ± 0.550	1.02 ± 0.559	0.482[a]
Median (min – max)	1.00 (0 – 2.9)	0.89 (0.1 – 2.4)	1.00 (0 – 2.9)	
Pain in the past week				
n	93	91	184	
Mean ± SD	71.82 ± 17.804	70.84 ± 17.339	71.33 ± 17.534	0.705[a]
Median (min – max)	75.00 (0 – 100.0)	72.00 (10.0 – 100.0)	75.00 (0 – 100.0)	
Overall health in the past week				
n	93	91	184	
Mean ± SD	56.42 ± 22.900	57.69 ± 19.864	57.05 ± 21.403	0.688[a]
Median (min – max)	50.00 (0 – 97)	60.00 (0 – 100.0)	55.00 (0 – 100.0)	
Stiffness in the past week[b]				
n	94	89	183	
Mean ± SD	65.34 ± 19.252	65.05 ± 18.945	65.20 ± 19.051	0.918[a]
Median (min − max)	67.00 (0 – 100.0)	63.81 (0 – 100.0)	65.71 (0 – 100.0)	
Overall physical activity (n [%])				
Completely	13 (14.1)	17 (18.9)	30 (16.5)	0.534[c]
Mostly	30 (32.6)	32 (35.6)	62 (34.1)	
Moderately	41 (44.6)	31 (34.4)	72 (39.6)	
A little	8 (8.7)	10 (11.1)	18 (9.9)	
Not at all	0	0	0	
Missing	2	1	3	

SD = standard deviation; HAQ-S= Health Assessment Questionnaire Modified for the Spondyloarthropathies
a. *P* value to compare adalimumab versus placebo was based on one-way ANOVA.
b. Values adjusted to account for a revision to the CRF that changed the length of the VAS line from 105 mm to the correct length of 100 mm. Data based on the earlier version were adjusted by the following formula to change to the common scale: (0.96) * value.
c. *P* value to compare adalimumab versus placebo was based on chi-square test (or Fisher's exact test if ≥ 25% of the cells had expected counts < 5) using nonmissing values.
Note: Baseline is defined as the last nonmissing value prior to the first dose of study drug.

Use of Concomitant Medication

Approximately one-fifth of subjects reported concomitant DMARD use during the study, most of whom used 1 concomitant DMARD, sulfasalazine and methotrexate being the most frequently used (Table 6). The majority of subjects reported concomitant NSAID use.

Table 6 Summary of concomitant DMARD, NSAID, and systemic corticosteroid use (Full Analysis Set)

	Number (%) of Subjects		
Concomitant Medication	Placebo N = 94	Adalimumab N = 91	Combined N = 185
Concomitant DMARD use	16 (17.0)	19 (20.9)	35 (18.9)
Number of concomitant DMARDs			
0	78 (83.0)	72 (79.1)	150 (81.1)
1	14 (14.9)	18 (19.8)	32 (17.3)
2	2 (2.1)	1 (1.1)	3 (1.6)
3 or more	0	0	0
Concomitant DMARDs by generic name[a]			
Azathioprine	3 (3.2)	0	3 (1.6)
Hydroxychloroquine	1 (1.1)	1 (1.1)	2 (1.1)
Methotrexate	3 (3.2)	7 (7.7)	10 (5.4)
Sulfasalazine	11 (11.7)	12 (13.2)	23 (12.4)
Concomitant NSAID use	76 (80.9)	74 (81.3)	150 (81.1)
Concomitant systemic corticosteroid use[b]	14 (14.9)	18 (19.8)	32 (17.3)

DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal anti-inflammatory drug
a. Generic name based on WHODrug Q1__2010.
b. Systemic corticosteroids include oral, injected and rectal preparations and do not include non-systemic preparations (opthalmologicals, dermatologicals, and inhalants).
Note: Concomitant medication defined as having a start date concurrent with or after first study drug dose through 14 days after the last study drug dose.

Outcomes and estimation

Primary endpoint

A statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS40 responses at Week 12 compared with placebo. Sensitivity analyses were performed on the ITT population to assess the impact of omitting the 7 subjects from the non-compliant site from the efficacy analyses, and on the PPP to assess the impact of major protocol violations. Both sensitivity analyses resulted in statistically significant outcomes in favor of adalimumab.

Table 7 ASAS40 Response at Week 12 (NRI)

Analysis Set	n/N[a] (%) of Subjects		*P* value[b]
	Placebo	Adalimumab	
Primary Analysis			
FAS	14/94 (14.9)	33/91 (36.3)	< 0.001
Sensitivity Analyses			
ITT population	14/97 (14.4)	33/95 (34.7)	0.001
PPP	11/78 (14.1)	28/78 (35.9)	0.002

FAS = Full Analysis Set; ITT = Intent-to-Treat; PPP = Per Protocol Population
a. N for each analysis set.
b. *P* value to compare adalimumab 40 mg eow to placebo was based on chi-square test (or on Fisher's exact test if ≥ 20% of the cells have expected cell count < 5).
Note: NRI (non-responder imputation): missing response was imputed as non-response.

Secondary endpoints

The Week 12 (end of DB period) analysis shows that there was a statistically significant difference in favor of adalimumab 40 mg eow versus placebo for all 9 ranked secondary efficacy endpoints.

Table 8 Summary of results of ranked secondary efficacy endpoints (Full Analysis Set; NRI, LOCF, and observed cases)

	Placebo N = 94		Adalimumab N = 91		
Ranked Endpoint	**n[a]**	**Result**	**n[a]**	**Result**	***P* value**
1. ASAS 20 response (n [%])	94	29 (30.9)	91	47 (51.6)	0.004[b]
2. BASDAI50 response (n [%])	94	14 (14.9)	91	32 (35.2)	0.001[b]
3. SF-36v2 physical component (mean change from Baseline ± SD)	93	2.0 ± 7.04	91	5.5 ± 8.98	0.001[d]
4. ASAS partial remission (n [%])	94	5 (5.3)	91	15 (16.5)	0.014[b]
5. ASAS5/6 response (n [%])	94	6 (6.4)	91	28 (30.8)	< 0.001[b]
6. HAQ-S total score (mean change from Baseline ± SD)	94	–0.1 ± 0.42	91	–0.3 ± 0.49	0.027[c]
7. hs-CRP (mg/L) (mean change from Baseline ± SD)	73	–0.3 ± 6.39	70	–4.7 ± 12.32	< 0.001[c]
8. SPARCC MRI score for sacroiliac joints (mean change from Baseline ± SD)	84	–0.6 ± 6.19	84	–3.2 ± 8.34	0.003[d]
9. SPARCC MRI score for the spine (mean change from Baseline ± SD)	83	–0.2 ± 3.32	85	–1.8 ± 4.51	0.001[d]

ASAS = Assessments in Spondyloarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; HAQ-S = Health Assessment Questionnaire modified for the Spondyloarthropathies; hs-CRP = high-sensitivity C-reactive protein; SPARCC = Spondyloarthritis Research Consortium of Canada; MRI = magnetic resonance imaging; eow = every other week
a. For each endpoint, n = number of subjects with nonmissing value.
b. *P* value for categorical variables (NRI imputation for missing values) was based on 2-sided chi-square test (or Fisher exact test).
c. *P* value for continuous variables (LOCF imputation for missing values) was based on an ANCOVA model adjusting for Baseline value with treatment as a factor.
d. *P* value for continuous variables (as observed; no LOCF imputation for missing values) was based on an ANCOVA model adjusting for Baseline value with treatment as a factor.
Notes: NRI (non-responder imputation): missing response was imputed as non-response.
LOCF (last observation carried forward): missing response was imputed with last non-missing value.

A pre-planned sensitivity analysis to assess the impact of omitting the 7 subjects from the non-compliant site from the efficacy analyses was performed for the ranked secondary endpoints using the ITT population. In this sensitivity analysis, the first 5 ranked endpoints met the criteria for statistical significance, but ranked endpoint No. 6 (mean change from Baseline in HAQ-S total score) missed statistical significance (p = 0.096). Although, the hierarchical testing was interrupted with item 6 not meeting the requirements, the remaining ranked endpoints met the criteria for statistical significance in favour of the adalimumab treatment group (p value ranged from <0.001 to 0.003 compared with placebo).

Supportive secondary endpoints

Supportive efficacy endpoints assessed using observed cases (OC) at Weeks 12 and 24 demonstrated the effect of adalimumab on multiple components of active axial SpA. Many of these endpoints achieved statistical significance in favor of adalimumab at Week 12, with results being sustained or improving further at Week 24 (Table 9). As of the data cut-off, improvements continued to be observed through Week 52.

Table 9 Summary of supportive secondary efficacy endpoints at Weeks 12 and 24 (Observed Cases)

	% of Subjects *OR* Mean[b] *OR* Mean Change from Baseline					
	Week 12 (FAS)			Week 24 (OL Population)		
Endpoint[a]	Placebo	Adalimumab	*P* value	PBO/ADA	ADA/ADA	Combined
Reduction of Signs and Symptoms Variables						
ASAS50	9.9%	31.8%	<0.001	49.4%	43.9%	46.8%
ASAS70	4.4%	15.9%	0.010	27.0%	30.5%	28.7%
PTGA-Disease Activity	−9.7	−22.5	<0.001	−31.6	−34.6	−33.0
Total back pain	−11.5	−23.8	<0.001	−34.0	−35.2	−34.5
BASFI	−6.7	−11.2	0.060	−19.5	−18.3	−18.9
Inflammation[c]	−1.2	−2.3	0.001	−3.5	−3.6	−3.6
BASDAI total score	−1.1	−2.0	0.005	−3.0	−3.2	−3.1
ASDAS clinically important improvement	14.1%	40.5%	<0.001	64.0%	64.9%	64.4%
ASDAS major improvement	3.5%	20.2%	<0.001	27.9%	22.1%	25.2%
ASDAS disease activity state						
Inactive	4.5%	25.0%	<0.001	29.2%	42.0%	35.3%
Moderate	17.0%	22.7%	0.345	28.1%	19.8%	24.1%
High	43.2%	46.6%	0.649	32.6%	35.8%	34.1%
Very high	35.2%	5.7%	<0.001	10.1%	2.5%	6.5%
ASDAS score	−0.4	−1.1	<0.001	−1.4	−1.5	−1.5
MASES	−0.8	−0.6	0.962	−1.9	−1.9	−1.9
Plantar fascia enthesitis	16.1%	19.8%	0.519	14.3%	13.8%	14.0%
PGA	−13.4	−21.7	0.024	−32.0	−34.8	−33.3
PTGA-Pain	−10.1	−22.1	<0.001	−33.6	−33.4	−33.5
Tender joint count	−0.6	−1.0	0.730	−1.8	−2.2	−2.0
Swollen joint count	−0.2	−0.3	0.754	−0.4	−0.7	−0.5
Dactylitis count	−0.054	−0.044	0.492	−0.077	−0.151	−0.113
Nocturnal pain	−8.5	−24.9	<0.001	−32.4	−36.0	−34.1
Metrology Variables						
$BASMI_{lin}$	−0.1	0.0	0.263	−0.2	−0.1	−0.2
$BASMI_2$	0.1	−0.0	0.573	−0.3	−0.2	−0.3
Chest expansion	0.3	0.3	0.585	0.4	0.1	0.2
Health-Related Quality of Life Variables						
WPAI-SHP Domains						
Absenteeism	2.3	−7.2	0.005	−4.5	−6.4	−5.5
Presenteeism	−5.8	−12.3	0.070	−19.4	−17.3	−18.3
Overall Work Impairment	−5.7	−12.1	0.122	−20.8	−18.5	−19.6
Activity Impairment	−3.6	−14.9	0.002	−18.7	−22.7	−20.6
PASS	16.5%	28.4%	0.056	39.3%	37.8%	38.6%
MOS Sleep Scale Domains						
Sleep disturbance	−4.3	−7.2	0.185	−11.4	−11.6	−11.5
Daytime Somnolence	−1.7	−4.8	0.346	−7.5	−8.2	−7.8

Endpoint[a]	% of Subjects *OR* Mean[b] *OR* Mean Change from Baseline					
	Week 12 (FAS)			Week 24 (OL Population)		
	Placebo	Adalimumab	*P* value	PBO/ADA	ADA/ADA	Combined
Perceived sleep adequacy	5.8	4.8	0.934	17.8	8.0	13.0
Awaken short of breath or with headache	−2.8	2.2	0.134	−4.6	0.2	−2.2
Snoring	−1.1	0.4	0.808	−1.6	0.2	−0.7
Sleep quantity	−0.3	0.3	0.004	0.0	1.1	0.6
Sleep problem index 6	−4.0	−4.3	0.728	−11.9	−7.8	−9.9
Sleep problem index 9	−4.2	−5.2	0.59	−11.4	−8.9	−10.2
EQ-5D (UK version)	0.0	0.10	0.037	0.17	0.20	0.18
EQ-5D (US version)	0.0	0.10	0.038	0.12	0.13	0.12
HCRU: Medical visit for axial SpA since last study visit	14.1%	13.3%	0.657	13.5%	11.0%	12.3%
HCRU: Number of visits to HCPb	7.67	7.18	--	6.5	7.1	6.7
Biomarkers						
MMP-3	−2.6	−4.8	0.282	−5.4	−5.3	−5.3
CTX-II	−111.52	−90.70	0.686	47.4	−26.1	9.9
$VEGF_A$	−57.7	−70.7	0.449	−135.9	−117.0	−126.5

ASAS = Assessments in Spondyloarthritis International Society response criteria; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; $BASMI_2$ = Bath Ankylosing Spondylitis Metrology Index-2; $BASMI_{lin}$ = linear Bath Ankylosing Spondylitis Metrology Index; CTX-II = type II collagen C- telopeptide; EQ-5D = European Quality of Life – 5 Dimensions questionnaire; FAS = full analysis set; HCRU = Health Care Resource Utilization survey; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MMP-3 = matrix metalloproteinase-3; OL = open-label; PASS = Patient Acceptable Symptom State; PGA = physician's global assessment of disease activity; PTGA = patient's global assessment; $VEGF_A$ = vascular endothelial growth factor-A; WPAI-SHP = Work Productivity and Activity Impairment – Specific Health Problem Questionnaire

a. Endpoints not included in the long-term efficacy analysis are listed.
b. Mean values are reported for HCRU: number of visits to HCP only; all other endpoints are reported as % of subjects or mean change from Baseline.
c. Mean of BASDAI Questions 5 and 6.

Comparison of results in subpopulations

Subgroup analyses were performed to evaluate the impact of Baseline conditions on efficacy (ASAS40 response at Week 12). A logistic model with treatment and a prespecified subgroup in the model was performed to assess the treatment and subgroup interaction. If the interaction term was significant ($P \leq 0.10$), then treatment effect needed to be assessed for components of the subgroup. The only significant interaction terms were for the age category and pooled CRP subgroups (Table 10)

Within the age category subgroup, a statistically significant treatment effect in favor of adalimumab was observed among subjects <40 years old ($P<0.001$) but not for subjects 40 to 65 years old ($P=0.616$); only 2 subjects in the adalimumab group and no subjects in the placebo group were >65 years old, thus treatment effect could not be assessed in this age category. Within the pooled CRP subgroup, a statistically significant treatment effect in favor of adalimumab was observed among subjects with abnormal pooled CRP ($P<0.001$) but not among subjects with normal pooled CRP ($P=0.199$).

These results should be considered with caution because of the limited number of patients.

There were 3 logistic models that did not converge (race, concomitant use of NSAIDs at Baseline, and presence of IBD at Screening) due to insufficient data.

Non-significant results of the interaction analyses imply that subjects who received adalimumab had better clinical responses compared to placebo regardless of subgroup category. The finding that there are overall better clinical responses with adalimumab compared to placebo in all of the subgroups investigated suggests a treatment benefit with adalimumab for active axial SpA patients regardless of the specific Baseline characteristics evaluated.

Table 10 Subgroup Analysis of ASAS40 Response at Week 12 (NRI) (Full Analysis Set)

Subgroup	n/N (%) of Subjects[a] Placebo N = 94	Adalimumab N = 91	Interaction *P* value[b]
Sex			0.346
Male	8/40 (20.0)	23/44 (52.3)	
Female	6/54 (11.1)	10/47 (21.3)	
Race			N.C.
White	14/91 (15.4)	33/91 (36.3)	
Non-white	0/3	0/0	
Age category			0.051[c]
< 40 years	7/52 (13.5)	26/56 (46.4)	
40 to 65 years	7/42 (16.7)	7/33 (21.2)	
> 65 years	0/0	0/2	
Weight			0.858
< 70 kg	5/35 (14.3)	12/36 (33.3)	
> 70 kg	9/59 (15.3)	21/55 (38.2)	
Baseline pooled CRP status			0.027
Normal	10/57 (17.5)	17/62 (27.4)	
Abnormal	4/37 (10.8)	16/29 (55.2)	
Baseline hs-CRP status			0.111
Normal	9/46 (19.6)	12/49 (24.5)	
Abnormal	4/27 (14.8)	10/21 (47.6)	
HLA-B27 status			0.342[d]
Positive	10/64 (15.6)	29/71 (40.8)	
Negative	3/22 (13.6)	3/16 (18.8)	
Equivocal	1/8 (12.5)	1/4 (25.0)	
Concomitant use of DMARDs at Baseline[e]			0.827
Yes	3/16 (18.8)	8/17 (47.1)	
No	11/78 (14.1)	25/74 (33.8)	
Concomitant use of NSAIDs at Baseline[e]			N.C.
Yes	14/73 (19.2)	28/72 (38.9)	
No	0/21	5/19 (26.3)	
MRI results at Screening			0.649
Positive	7/43 (16.3)	16/46 (34.8)	
Negative	7/51 (13.7)	17/45 (37.8)	
History of IBD at Screening[f]			N.C.
Yes	0/6	3/4 (75.0)	
No	14/88 (15.9)	30/87 (34.5)	
History of uveitis at Screening[f]			0.813
Yes	2/10 (20.0)	6/12 (50.0)	
No	12/84 (14.3)	27/79 (34.2)	

DMARD = disease-modifying anti-rheumatic drug; HLA-B27 = human leukocyte antigen-B27; IBD = inflammatory bowel disease; MRI = magnetic resonance imaging; N.C. = not calculated; NRI = non-responder imputation; NSAID = nonsteroidal anti-inflammatory drug

a. For each subgroup, N = number of subjects within the subgroup.
b. Logistic regression model interaction *P* value.
c. Age group category for logistic regression combines age categories of 40 to 65 years and > 65 years.
d. HLA-B27 categories for logistic regression were positive and negative.
e. Concomitant DMARD/NSAIDs at Baseline had start date before first dose of study drug and were ongoing or had stop date after first dose of study drug.
f. As confirmed by a physician.

Note Missing responses were imputed as non-response.

Persistence of Efficacy and/or Tolerance Effects

Evaluation of the primary and 9 ranked secondary endpoints at Week 12 and up to 52 weeks of treatment with adalimumab demonstrates the persistence of response throughout the study as of the data cutoff date (02 February 2011). The primary and all ranked secondary endpoints achieved statistical significance in favour of adalimumab at Week 12; assessments that were conducted at later time points indicated continued improvements with further adalimumab treatment.

1.2.2.2. Discussion on clinical efficacy

Study M10-791

The clinical development program for adalimumab in subjects with severe nr-axSpA included a single pivotal Phase 3 study, Study M10-791. This was a placebo-controlled, double-blinded, randomized study in subjects with active axial SpA who had an inadequate response or intolerance to 1 or more NSAIDs, or a contraindication for NSAIDs. Study M10-791 was ongoing at the time of submission of this application. A data cut-off of 02 February 2011 was used for this submission. As of the data cut-off date, 154 subjects were ongoing in the study and 166 patients completed week 24 (80 ADA/ADA arm and 86 PBO/ADA arm). Data from this study form the basis for all efficacy data to support the claimed indication.

Design and conduct of clinical studies

The design of Study M10-791, aimed to improve clinical signs and symptoms of active axial SpA, reflects the recommendation of the guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis (CPMP/EWP/489/03). The objective of the study was to evaluate the efficacy and safety of SC adalimumab 40 mg given eow compared to placebo for 12 weeks followed by OL safety and efficacy assessments in subjects with active axial SpA not fulfilling the modified New York criteria for AS who had an inadequate response to, or intolerance to 1 or more NSAIDs, or had a contraindication for NSAIDs. The primary efficacy variable was the proportion of subjects who achieved ASAS40 response at the Week 12 visit. ASAS response is a composite variable assessing four domains: Patient's Global Assessment of Disease Activity (represented by the Patient's Global Assessment of Disease Activity VAS score), Pain (represented by the total back pain VAS score), Function (represented by the BASFI score) and Inflammation (represented by the mean of the 2 morning stiffness-related BASDAI VAS scores). It is an established outcome measure for AS, but is not validated for spondyloarthritis. There is no regulatory guideline describing the endpoints for evaluating treatments of axial spondyloarthritis,however, the CHMP considered justified to use ASAS response as AS is the most representative type of axial SpA (CPMP/EWP/4891/03).

The primary endpoint ASAS40 at week 12, a composite efficacy endpoint requiring a relative improvement of ≥40% and absolute improvement of ≥20 units (on a scale of 0 to 100) from Baseline in ≥3 of these 4 domains, without worsening in the remaining domains, is considered a stringent tool to evaluate adalimumab efficacy. The specified 9 ranked secondary endpoints at Week 12 aimed to assess inflammation, spinal mobility, symptoms of pain, discomfort, stiffness and fatigue, patient's global status are in line with the guideline. The choice of the mean change in SPARCC MRI score for the sacroiliac joints, as MRI scoring system for grading inflammation is considered acceptable as results obtained with this score are reproducible and reliable.

Concerning the inclusion and exclusion criteria the CHMP considered that they were reasonable in relation to the proposed axial spondyloarthritis classification criteria and the well known safety profile of adalimumab. During the procedure, the MAH clarified that the inadequate response to NSAIDs, in terms of doses and treatment duration, was not univocally defined but based on investigator's expert discretion as for local standard of care and that the same definition was previously used in other adalimumab clinical trials i.e. in M03-607 which is the pivotal study for AS indication. Almost all patients have been treated with at least one NSAID and more than one third (36.3%) took 2 NSAIDs before study entry. Patient's distribution according to the number of NSAIDs prior to baseline is considered well balanced between adalimumab group and placebo. The reported mean and median duration of NSAID use is in line with the natural history of axial SpA. The results indicated that the duration of prior NSAID use (≥ versus < median duration of 20.5 months) did not affect the likelihood of achieving Week 12 ASAS40 response.

In the inclusion criterion: "MRI evidence of active inflammatory lesions of sacroiliac joints (past or present) with definite bone marrow oedema/osteitis", the MAH clarified that the protocol did not specify the allowed interval between a "past" positive MRI and Baseline visit. However, of the 89 subjects who were reported to have "MRI evidence of active inflammatory lesions of SI joints," only 9 were based on "past" MRI findings. Six had past MRI within 12 months or less prior to the Baseline visit, while 3 had past MRI anywhere from 3 to 5 years prior to the Baseline visit. For completeness a revised subgroup analysis excluding the 3 patients was submitted. The week 12 ASAS40 response was similar to that in the previous analysis. Based on the non-significant interaction *P* value, past or present MRI evidence of sacroiliitis does not influence Week 12 ASAS40 results.

Generally, the main inclusion criteria were consistent with the ASAS criteria for axial spondyloarthritis, with the modification that psoriasis was excluded as criterion and that established AS i.e. radiographic signs of inflammation of the SI joints was not allowed. The ASAS criteria for Axial SpA include both AS and psoriatic arthritis but these conditions, for which the MAH already hold a marketing authorization were contraindications for entering the study to avoid a bias.

The demographic characteristics of enrolled patients were well balanced between the placebo and adalimumab groups. As current evidence suggests that obesity is associated with a lower response to various biologic agents in RA and spondyloarthritides, the MAH provided information on the subjects Body Mass Index (BMI). Mean BMI at Baseline was similar between adalimumab and placebo groups. Approximately 45% of the subjects in the study had normal BMI.

Baseline patients' characteristics were also well balanced and representative of the studied population. Patients had axial SpA symptoms for a mean of approximately 10 years before enrolment. This time period is similar to that reported in the ATLAS study, the pivotal registration study for the indication of adalimumab in AS.

Almost all subjects (97% in each arm) had back pain that was inflammatory in nature as defined in the ASAS axial SpA criteria. Less than 40% of the subjects had a history of elevated CRP. The majority of subjects had no history of anterior uveitis or of inflammatory bowel disease (Crohn's disease or ulcerative colitis). In half of the enrolled patients (45.7% placebo and 50.5% adalimumab) past or present evidence of active inflammatory lesions on MRI of sacroiliac joint was documented. The majority of subjects were HLA-B27-positive. As no grading of baseline inflammation has been initially presented, the MAH reported the number of subjects who had the SPARCC MRI score for both sacroiliac joints and for spine unchanged, improved (decreased) or worsened(increased) from baseline to week 12. Overall, at Week 12, more subjects in the adalimumab arm had improvement (any decrease) in their MRI scores for the SI joints and spine. Although similar percentages of patients had worsening (any increase) in the SI joint MRI SPARCC scores, there were more subjects in the placebo arm who had worse spine MRI SPARCC scores compared to the adalimumab group. There were more subjects in the placebo arm that had unchanged MRI scores at Week 12, but almost half of these subjects had scores >0, whereas most of the subjects in the adalimumab arm who had unchanged MRI scores had baseline scores of 0. Among patients (SI joints and spine) who had SPARCC score at week 12 unchanged, the large majority (79% SI joints and 60% spine in adalimumab group) had baseline score equal to zero.

The baseline disease activity status of patients enrolled in the M10-791 study was high in score (ASDAS mean values 3.36 placebo and 3.22 adalimumab) and comparable between placebo and adalimumab arm. The disease activity status was also generally similar to that reported in the ATLAS study, except for functional indices such as the BASFI and the BASMI which were lower in the M10-791 study. The BASFI score, assessed with 0-10 cm VAS, was 5.6 placebo - 5.2 adalimumab mean values in the ATLAS study and 4.8 placebo-4.5 ADA mean values in the M10-791 study. The baseline $BASMI_2$ based on 0-2 scale for each of the 5 clinical measurements, was 4.2 placebo - 3.8 adalimumab mean

values in the ATLAS study and 1.8 placebo - 1.8 adalimumab mean values in the M10-791 study. This difference implies a better functionality and spinal mobility of patients diagnosed with nr-axSpA (M10-791 study) compared with AS patients (ATLAS study) which reflect the common clinical presentation of the two forms of spondyloarthritis.

Efficacy data and additional analysis

A statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS40 responses at Week 12 compared with placebo (36.3% vs 14.9%; p<0.001). Sensitivity analyses were performed on the ITT population to assess the impact of omitting the 7 subjects from the non-compliant site from the efficacy analyses, and on the PPP to assess the impact of major protocol violations. Both sensitivity analyses resulted in statistically significant outcomes in favor of adalimumab (ITT: 14.4 vs 34.7; p<0.001 and PPP: 14.1 vs 35.9; p<0.002). These results, both in the primary analysis and in all sensitivity analyses, show a significant and robust clinical benefit of adalimumab treatment in axial SpA at 12 week.

Seven (7) patients were excluded from the efficacy analysis, after their site was closed due to compliance issues. In addition, a total of 25 subjects did not meet entry criteria but still received study medication. Seven (7) of these do not appear to have met the proposed axial spondyloarthritis criteria. For another 4 patients, concomitant medication issues were reported. From a GCP standpoint, a total of 29 major protocol deviations is a high number in relation to the total number of subjects enrolled. However, as they are evenly distributed between the 2 groups they have not affected the overall results.

The Week 12 data analysis shows that there was a statistically significant difference in favour of adalimumab 40 mg eow versus placebo for all 9 ranked secondary efficacy endpoints. As expected, a higher percentage of patients (30.9% placebo and 51.6% adalimumab) reached the ASAS20 endpoint as compared to ASAS40. Consistent results were observed in the in SPARCC MRI score with adalimumab-treated patients showing a significant reduction (mean change from baseline±SD) for both sacroiliac joints (-0.6 ±6.19 PBO group and -3.2 ±8.34 adalimumab group, p=0.003) as well as for spine (-0.2±3.32 PBO group and -1.8 ±4.51 ADA group, p=0.001).

Subgroup analyses were performed to evaluate the impact of Baseline conditions on efficacy (ASAS40 response at Week 12). The only significant interaction terms were for the age category and pooled CRP subgroups, where the subgroup with elevated CRP showed a statistically significant treatment effect in favour of adalimumab (*P* <0.001) but not among subjects with normal pooled CRP. Within the age category subgroup, a statistically significant treatment effect in favor of adalimumab was observed among subjects <40 years old (*P* <0.001) but not for subjects 40 to 65 years old (*P* = 0.616).

During the procedure the CHMP questioned the reliability, sensitivity, specificity and predictive value of the ASAS classification criteria for axial spondyloarthritis to define a subgroup with early axial spondylarthritis who could benefit the most from adalimumab treatment. The new criteria allow for identification of patients before the apparition of radiographic changes of the SI joints, which can take several years after the start of symptoms. Nevertheless, as the diagnosis of nr-axSpA does not require the presence of active inflammation as detected by MRI of the SI joints or spine, there is a potential to treat patients with no inflammatory back pain. The problem of delayed AS diagnosis was acknowledged by the CHMP, however, little is known about what proportion of nr-axSpA patients actually develop AS.

The MAH presented further data in order to demonstrate that the ASAS classification criteria for axial spondyloarthritis were sufficiently reliable, sensitive, specific and predictive to define a subgroup with non-radiographic axial spondylarthritis who could benefit from the treatment. The MAH compared the ASAS criteria for axial SpA to other SpA criteria. The ASAS criteria were shown to be superior both

regarding specificity and sensitivity. The MAH clarified that the Positive Predictive Value (PPV) of the proposed ASAS criteria for Axial Spondyloarthritis has been calculated to be 89% in the targeted cohort where the prevalence of disease was 60%. To further address the CHMP's concerns, and consistent with the ASAS recommendation, the MAH proposed to require that nr-axSpA patients who are candidates for adalimumab treatment exhibit objective measures of inflammation by elevated CRP or MRI, in addition to having severe active disease despite treatment with NSAIDs. The CHMP acknowledged that requiring the presence of a positive MRI or elevated CRP improves the specificity of the adalimumab treatment patient population, thereby reducing the likelihood that a patient without nr-axSpA will be treated with adalimumab. In addition, a publication from Rudwaleit et al (Rudwaleit et al, Ann Rheum Dis 2009), where the ASAS criteria for AxSpA are presented, showed that in the presence of positive MRI the PPV raised to 97.5 in the 60% cohort, which constitute a significant improvement.

In addition to improving the specificity of the adalimumab treatment patient population, this modification is supported by the results of the subgroup interaction analyses for Study M10-791. In that study, patients with elevated (abnormal) CRP levels had an approximately 2-fold greater likelihood of clinical response based on the Week 12 ASAS40 response. Patients with a baseline MRI SPARCC SI joint score ≥2 had a numerically higher response rate than those with a score <2, although the P value for the interaction analysis for subgroups based on baseline MRI SPARCC SI joint score was not statistically significant. However, a significant interaction with treatment was observed based on logistic regression between continuous MRI SPARCC SI joint scores at baseline and ASAS40 response at Week 12 (P = 0.046, NRI). Of the patients with a MRI SPARCC SI joint score of < 2 at baseline, 49% had objective evidence of inflammation in the spine on MRI with a baseline MRI SPARCC spine score of ≥ 2. Thus, the same analysis was conducted for subgroups based on baseline SPARCC scores of ≥ 2 for either the SI joint or spine compared to those who had scores < 2 for both SI joint and spine, and a similar trend was noted. The same analysis was also conducted for the target nr-axSpA population (positive MRI defined by a SPARCC score ≥ 2 for either the SI joint or spine, or elevated CRP). The Week 12 ASAS40 response was significantly higher in the ADA group compared to PBO for the proposed candidate nr-axSpA population for adalimumab therapy (PBO = 13.7%, ADA = 40.6%, P < 0.001, NRI), but there was no difference in clinical response between PBO and ADA among patients who did not have a positive MRI or elevated CRP. The interaction analysis did not result in a significant P value, but it should be noted that the patient population that did not have a positive MRI or elevated CRP was quite small (PBO, n = 20; ADA, n = 22). All 9 ranked secondary efficacy endpoints for Study M10-791 also met statistical significance when analyzed for the proposed nr-axSpA population with a positive MRI or elevated CRP at baseline, further supporting the efficacy of adalimumab in this subgroup of nr-axSpA patients.

Taken all this information together, requiring that candidates for adalimumab treatment exhibit objective signs of inflammation by elevated CRP or MRI increases the specificity in identifying the target population and reduces considerably the possibility of treating patients with non inflammatory disease. Also, based on the data presented, this allows identifying a subgroup of patients with non-radiographic axial spondylarthritis who benefit the most from adalimumab treatment. For clarification the CHMP required a change to the indication wording requiring the presence of an elevated CRP and/or a positive MRI in the target population to make clear that patients displaying both signs of inflammation are also covered in the indication. This was accepted by the MAH.

One aim of early treatment of axial spondylarthritis with a biologic could be to reduce the risk for progression to AS, with associated structural damage. No data are available to confirm whether any treatment intervention for nr-axSpA can slow or prevent the progression to AS. Due to the relatively slower radiographic progression in axial SpA compared to other rheumatologic diseases such as RA, and varying degrees by which patients progress, it is not ethical to conduct a controlled clinical trial to

assess the impact of adalimumab treatment on progression of nr-axSpA to AS. Regardless of any potential impact of adalimumab treatment on the long term progression of nr-axSpA, treatment of the signs and symptoms of disease, as shown by the results of study M10-791, is considered clinically relevant.

Long-term efficacy up to Week 52 was assessed through the OL phase of the M10-791 study during which placebo–treated patients were shifted to adalimumab treatment. Results for primary and ranked secondary endpoints (ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, and BASDAI50) for PBL/ADA-treated patients and ADA-ADA treated patients have been separately reported at week 24, 36 and 52. Overall a clinical benefit of adalimumab treatment was observed for all endpoints throughout the 12-52 week period. Patients switched to ADA treatment from PBL achieved ASAS20, ASAS40, ASAS 5/6, ASAS partial remission, and BASDAI50 response by Week 24 (i.e. after 12 weeks of OL adalimumab treatment) at a rate comparable to that seen in patients treated with ADA/ADA patients at both Week 12 and 24. Additional data up to Week 68 became available during the procedure, with all remaining patients having now received at least 52 weeks of treatment with adalimumab in the open-label phase of the study. The observed clinical response rates at Week 12 were, in those patients who maintained in the study, sustained up to Week 68. In these patients, both HAQ-s and SF-35 improved between Week 12 and 52. Overall, the observed clinical response rates were sustained up to Week 68 of the study, supporting the durability of clinical response and benefit of continued adalimumab therapy up to 68 weeks. Within this procedure the MAH extended the duration of Study M10-791 from 2 to 3 years after which supplementary data would become available to further describe adalimumab long term efficacy. As described in the RMP the MAH will submit the final results of Study M10-791 by Q4 2013.

There are current data in the literature[3,4] suggesting that continuous anti-TNF therapy is needed for nr-axSpA patients to maintain clinical response or remission over time. To further validate these observations in a controlled setting, the MAH committed to conduct a post-approval randomized, controlled, remission-withdrawal-retreatment study in nr-axSpA subjects who have had an inadequate response to at least 2 NSAIDs or are intolerant or have a contraindication for NSAIDs. The results of such a study will provide information on how long treatment should be continued in subjects in whom there is no disease activity following treatment for 24 weeks; what proportion of patients treated early in their disease achieve remission and also on the safety and efficacy of re-treatment after disease flare. Active disease for study entry will be defined as BASDAI ≥ 4 on a numerical rating scale, ASDAS ≥2.1, and total back pain ≥4 on a numerical rating scale. The study will have 2 treatment periods. In Period 1, all subjects will receive open-label adalimumab for 24 weeks. Those who achieve ASDAS Inactive Disease (ASDAS <1.3) at Weeks 20 and 24 of open-label adalimumab treatment will be randomized in a blinded manner to continued adalimumab therapy or placebo (withdrawal of therapy) during Period 2. Subjects who flare during Period 2 will be provided rescue therapy with open-label adalimumab. The MAH will provide the results of this study by Q3 2015 as described in the RMP.

1.2.2.3. Additional expert consultation

During the procedure at the CHMP's request an ad-hoc expert group meeting was organized. Amongst the experts there was a consensus that Axial Spondyloarthritis is a clinical entity established in the rheumatology community and that symptom control is an acceptable treatment goal. The responses to the four questions asked to the experts by the CHMP are reproduced below.

[3] Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis. Arthritis Rheum. 2008;58(7):1981-91.

[4] Amtenbrink AL, Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong R, et al. Efficacy of adalimumab in the treatment of patients with axial spondyloarthritis (SPA) and no radiographic sacroiliitis: continuous adalimumab (Humira®) therapy is necessary to prevent relapses after treatment withdrawal. Ann Rheum Dis. 2008;67(Suppl II):373

1. Is the new clinical entity Axial Spondyloarthritis (AxSpA) established enough in the rheumatology community to justify its adding as an indication?

   There was consensus amongst the experts that AxSpA is a clinical entity sufficiently established nowadays in the rheumatology community. Whether this would justify as an indication was subject to debate with a majority of experts in favour of not considering this diagnosis classification as an indication on its own. It was agreed that this entity was recognised as a way of classifying a group of patients but this differed from identifying a group of patients who needed treatment. Therefore, other parameters such as the severity should be taken into account to define a sub-group of patients with AxSpA for whom treatment is indicated. One expert however recognized AxSpA as an established clinical entity as well as an established indication.

2. What would be the aim of anti-TNF treatment in this population? If the aim is symptomatic treatment, what would the appropriate study duration be to define the benefit for such treatment?

   There was a consensus amongst the experts that the aim of anti-TNF treatment in AxSpA is symptom control. The experts also agreed that it is unknown whether such treatment has an impact on the structural damage.

   From a clinician's perspective the aim of symptomatic treatment was deemed valuable even without knowing whether the treatment could slow-down structural damage. The patient representatives stressed that minimising the symptoms (e.g. pain) as much as possible is of particular relevance ("it is the 1st priority for the patients").

   The experts agreed that a 3 month period could be considered as sufficient to define the benefit of symptomatic treatment. It will be important nevertheless to perform a long term follow-up of patients to investigate the impact on disease's progression as well as the long term safety in this patient population. The duration of such follow-up should be > 1 years (2-3 years was mentioned). It was generally agreed that long term follow-up of patients through a registry would be extremely valuable.

   Furthermore, the relapse study proposed by the applicant was considered important.

3. AxSpA includes patients with and without signs of sacroiliitis on MRI. Is there reason to make a distinction regarding treatment strategy between these two groups?

   Based on the applicant's data and results the experts recognised that patients who show objective evidences of inflammation by MRI [MRI (+)] and by CRP [CRP (+)] benefit the most from the anti-TNF treatment compared to MRI (–) and CRP (-) patients. As such MRI constitutes important and helpful criteria to anticipate a clinical response. Nevertheless there was discussion amongst the experts to which extent MRI can be used to decide whether treatment should be initiated or not. It was mentioned that MRI has a sensitivity of ~60% therefore other concomitant criteria must be met for a diagnosis of AxSpA (inflammatory back pain, uveitis, HLA-B27 (+), elevated CRP, etc...) in order to trigger anti-TNF treatment.

   Overall, the majority of experts agreed that MRI was seen as one potential helpful tool to identify a group of patients for treatment, although there might be other diagnostic tools. One expert voiced that the clinical diagnosis of inflammatory back pain needs to be taken into consideration.

   Discussing the complexity, as an example MRI (+) patients treated by NSAIDs could become MRI (-) although not responding anymore to NSAIDs and might benefit from anti-TNF treatment.

Also it was pointed out that some patients can be without signs of sacroiliitis on MRI but display inflammatory signs in the spine on MRI and hence be eligible for the anti-TNF treatment.

4. Are there criteria which are sufficiently precise and validated that can be used to define a subpopulation of the nra AxSpA population who could benefit from anti-TNF treatment?

   The experts agreed that the criterion "patients presenting inflammatory chronic back pain with age of onset <45 years and who have had inadequate response to, or intolerance to NSAIDs together with objective evidence of inflammation by MRI or by CRP" allow to define enough a subgroup of patients who could benefit most from an anti-TNF treatment. These criteria were seen as sufficient to define a subgroup of patients that had been shown to particularly benefit from anti-TNF treatment in the trial that had already been conducted by the applicant.

   The experts agreed that the history of NSAID use was important to consider and that more than one NSAID should be used in appropriate doses before anti-TNF treatment was initiated in this condition. The experts mentioned that further subgroup analysis of this trial might be useful to optimise efficacy possibly by taking into account variables such as the degree of elevation in CRP and the MRI appearances.

1.2.2.4. Conclusion on clinical efficacy

The submission is based on a single pivotal Phase 3 study, Study M10-791, in about 192 adult subjects with nr-axSpA randomized to adalimumab 40mg eow or matching placebo for 12 weeks. Thereafter, all received open label adalimumab. The primary endpoint was the proportion of patients achieving an ASAS40 response at Week 12. The Week 12 analysis showed that a statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS40 responses compared with placebo. Similar results were observed using the Per Protocol Population (35.9% versus 14.1%, P = 0.002). Consistent results were obtained in an ITT sensitivity analysis (ITT: 14.4% vs 34.7%, p<0.001). Significant effects were also demonstrated at week 12 for all ranked secondary efficacy endpoints, including two MRI endpoints (SPARCC MRI score sacroiliac joints, and for the spine, p=0.003 and 0.001, respectively). In addition a number of "supportive secondary endpoints" were assessed with an overall pattern of results favoring active treatment. This is overall considered a robust effect, and of clinical relevance in terms of symptomatic treatment. A clinical benefit of adalimumab treatment was also observed for all endpoints throughout the 12-52 week period. Additional data up to 68 weeks showed that the observed clinical response rates at Week 12 were sustained up to Week 68. As described in the RMP the MAH will submit the final results of Study M10-791 Q4 2013 which will bring additional data to further characterize the long term benefit of adalimumab treatment of nr-axSpA patients.

During the procedure the CHMP questioned reliability, sensitivity, specificity and predictive value of the ASAS classification criteria for axial spondyloarthritis to define a subgroup with early axial spondylarthritis who could benefit the most from adalimumab treatment. As the diagnosis of nr-axSpA does not require the presence of active inflammation as detected by MRI, there is a potential to treat patients with no inflammatory back pain. As the data presented showed that patients with evidence of either inflammation on MRI of either the spine or SI joints, or an elevated CRP, are more likely to achieve better clinical responses to adalimumab, the MAH proposed to require the presence of an elevated CRP or a positive MRI in the target population in addition to having severe active disease despite treatment with NSAIDs. The CHMP agreed with this measure as it helps reducing considerably the possibility of treating patients with non inflammatory disease and thereby identifies a population in whom the benefit/risk balance is positive. For clarification the CHMP required a change to the wording requiring the presence of an elevated CRP and/or a positive MRI in the target population to make clear

that patients displaying both signs of inflammation are also covered in the indication. This was accepted by the MAH.

Overall the CHMP agreed that the original AS indication remains unchanged and is supplemented with the indication in the treatment of patient with axial spondyloarthritis without radiographic evidence of AS but who display objective signs of inflammation by elevated CRP and/or MRI. Both indications are under a common heading of axial spondyloarthritis.

1.2.3 Clinical safety

Safety data were collected in the form of adverse events (AEs), physical examinations, vital signs, and laboratory tests throughout the treatment period and up to 70 days after the last injection of the study drug. Safety data with a cutoff date of 02 February 2011 were assessed. Two datasets were utilized for the analysis of safety:

1. The Safety Analysis Set includes all subjects who had taken at least 1 dose of the study drug (placebo subjects =97; adalimumab subjects =95; total subjects =192). Safety analyses were conducted according to the actual treatment received by subjects, irrespective of treatment group assignment. No subjects were excluded from the safety analyses.
2. The Any Adalimumab Safety Set is comprised of all randomized subjects who received at least 1 dose of adalimumab any time during the study (placebo subjects [in the open-label phase] =95; adalimumab subjects =95; total subjects =190). No subjects were excluded from the safety analyses.

Patient exposure

The majority of subjects (180 of 185 subjects; 97.3%) received at least 76 days of the study treatment during the DB period with a total of 41.6 patient-years (PY) of exposure to the study drug (table 10). Among subjects exposed to adalimumab at any time during the study, a majority (142 of 190 subjects; 74.7%) received at least 175 days of treatment with adalimumab with a total of 131.1 PY of exposure to adalimumab.

Table 11 Extent of exposure to study drug during the double-blind period of the study (Full Analysis Set)

Exposure to Study Drug	Placebo N = 94	Adalimumab N = 91	Combined N = 185
Duration of Treatment (days)			
Mean ± SD	82.7 ± 7.95	81.7 ± 10.34	82.2 ± 9.19
Median	83.0	83.0	83.0
Minimum – maximum	14 – 92	25 – 91	14 – 92
Duration of Exposure (n [%])			
≥ 1 day	94 (100)	91 (100)	185 (100)
≥ 16 days	93 (98.9)	91 (100)	184 (99.5)
≥ 31 days	93 (98.9)	88 (96.7)	181 (97.8)
≥ 46 days	93 (98.9)	88 (96.7)	181 (97.8)
≥ 61 days	92 (97.9)	88 (96.7)	180 (97.3)
≥ 76 days	92 (97.9)	88 (96.7)	180 (97.3)
Total Patient-Years	21.3	20.4	41.6

Note: If a subject discontinued during the DB period of the study, then the duration of exposure was the number of days between the first dose of study drug and the last dose if study drug + 14 days. If a subject continued into the OL period of the study, then the duration of exposure was the number of days between the first dose of study drug and the day prior to the first OL dose.

Adverse events

All AEs discussed are treatment-emergent AEs (TEAEs), unless otherwise noted. TEAEs are defined as AEs that begin either on or after the first dose of the study medication, and up to 70 days after the last

dose of the study medication. The only exception was for those subjects who continued on adalimumab therapy after the end of study participation. These subjects were not required to complete the 70-day follow-up and any new AEs were reported through the mechanism used for all post-marketing adverse experiences.

All AEs were collected, whether solicited or spontaneously reported by the subject. In addition, serious AEs (SAEs) were collected from the time the subject signed the study-specific informed consent. SAEs are defined as AEs that resulted in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, congenital anomaly, spontaneous or elective abortion, an important medical event requiring medical or surgical intervention to prevent serious outcome, and AEs that were life-threatening.

During the DB period of the study, the most frequently reported AE were nasopharyngitis, nausea, and headache in the adalimumab group and nausea and diarrhoea in the placebo group (Table 13). All other AEs were reported by <5% of subjects in either the placebo or adalimumab treatment groups.

Table 12 Summary of adverse events experienced by >=3% of subjects during the double-blind period of the study (Safety Analysis Set)

	Number (%) of Subjects	
MedDRA Preferred Term	**Placebo N = 97**	**Adalimumab N = 95**
Nasopharyngitis	3 (3.1)	11 (11.6)
Nausea	8 (8.2)	7 (7.4)
Headache	3 (3.1)	6 (6.3)
Diarrhea	7 (7.2)	4 (4.2)
Injection site reaction	0	4 (4.2)
Upper respiratory tract infection	4 (4.1)	3 (3.2)
Asthenia	2 (2.1)	3 (3.2)
Rash	2 (2.1)	3 (3.2)
Fatigue	0	3 (3.2)
Injection site erythema	0	3 (3.2)
Pharyngitis	0	3 (3.2)
Gastroenteritis	3 (3.1)	2 (2.1)
Vomiting	3 (3.1)	2 (2.1)
Constipation	3 (3.1)	1 (1.1)
Injection site pain	3 (3.1)	1 (1.1)

Among subjects who received adalimumab at any time during the study, the most frequently reported AE included nasopharyngitis, spondylitis, diarrhoea, headache, nausea, sinusitis, bronchitis, and upper respiratory tract infection (Table13). All other AEs were reported by <5% of subjects treated with adalimumab.

Table 13 Summary of adverse events experienced by >=3% of subjects administered adalimumab at any time throughout the study (Any Adalimumab Safety Set)

	Number (%) of Subjects
MedDRA Preferred Term	**Any Adalimumab N = 190**
Nasopharyngitis	28 (14.7)
Spondylitis[a]	16 (8.4)
Diarrhea	13 (6.8)
Headache	13 (6.8)
Nausea	13 (6.8)
Bronchitis	11 (5.8)
Sinusitis	11 (5.8)
Upper respiratory tract infection	11 (5.8)
Injection site reaction	8 (4.2)
Insomnia	8 (4.2)
Abdominal pain upper	7 (3.7)
Anxiety	6 (3.2)
Asthenia	6 (3.2)
Back pain	6 (3.2)
Fatigue	6 (3.2)
Gastroenteritis	6 (3.2)
Influenza	6 (3.2)
Injection site erythema	6 (3.2)
Pruritus	6 (3.2)
Rhinitis	6 (3.2)

a. Represents worsening or flare of axial SpA (MedDRA lower level term "spondylarthritis" codes to PT "spondylitis"

More subjects in the adalimumab treatment group (32.6%) compared with the placebo group (21.6%) reported AEs that the investigator considered possibly or probably related to study drug (table 15). The frequency of any specific possibly or probably related AEs were similar between treatment groups. However, more subjects in the adalimumab treatment group reported injection site reactions (4.2%) and nasopharyngitis (7.4%) compared with placebo (0 and 1.0%, respectively). Other frequently reported (≥3%) possibly or probably related AEs were injection site erythema, injection site pain, and nausea. All other events were reported by <3% of subjects in either treatment group.

Table 14 Summary of adverse events possibly or probably related to study drug experienced by >1 subject in either treatment group during the double-blind period of the study (Safety Analysis Set)

	Number (%) of Subjects	
MedDRA System Organ Class MedDRA Preferred Term	**Placebo N = 97**	**Adalimumab N = 95**
Any adverse event	21 (21.6)	31 (32.6)
Gastrointestinal disorders		
Diarrhea	2 (2.1)	2 (2.1)
Nausea	3 (3.1)	3 (3.2)
General disorders and administrative site conditions		
Injection site erythema	0	3 (3.2)
Injection site pain	3 (3.1)	1 (1.1)
Injection site reaction	0	4 (4.2)
Pyrexia	0	2 (2.1)
Infections and infestations		
Bronchitis	2 (2.1)	1 (1.1)
Nasopharyngitis	1 (1.0)	7 (7.4)
Oral herpes	0	2 (2.1)
Pharyngitis	0	2 (2.1)
Pharyngitis streptococcal	2 (2.1)	0
Rhinitis	1 (1.0)	2 (2.1)
Tonsillitis	2 (2.1)	1 (1.1)
Upper respiratory tract infection	2 (2.1)	0
Nervous system disorders		
Headache	1 (1.0)	2 (2.1)
Skin and subcutaneous tissue disorders		
Pruritus	1 (1.0)	2 (2.1)

a. Represents worsening or flare of axial SpA (MedDRA lower level term "spondylarthritis" codes to PT "spondylitis").

Among subjects who received adalimumab at any time during the study, the majority of AEs reported were considered possibly or probably related to study drug by the investigator. The most frequently reported possibly or probably related AEs were nasopharyngitis, sinusitis, bronchitis, upper respiratory tract infection, injection site reaction, and injection site erythema. All other events were reported by <3% of subjects.

Table 15 Summary of Adverse Events Possibly or Probably Related to Study Drug Experienced by >1 Subject Administered Adalimumab at Any Time Throughout the Study (Any Adalimumab Safety Set)

MedDRA System Organ Class MedDRA Preferred Term	Number (%) of Subjects Any Adalimumab N = 190
Any adverse event	76 (40.0)
Gastrointestinal disorders	
Aphthous stomatitis	3 (1.6)
Diarrhea	5 (2.6)
Nausea	4 (2.1)
General disorders and administrative site conditions	
Asthenia	2 (1.1)
Fatigue	2 (1.1)
Injection site erythema	6 (3.2)
Injection site pain	2 (1.1)
Injection site pruritus	2 (1.1)
Injections site reaction	8 (4.2)
Pyrexia	3 (1.6)
Infections and infestations	
Bronchitis	7 (3.7)
Cystitis	3 (1.6)
Gastroenteritis	2 (1.1)
Nasopharyngitis	14 (7.4)
Oral herpes	3 (1.6)
Pharyngitis	2 (1.1)
Pneumonia	2 (1.1)
Rhinitis	5 (2.6)
Sinusitis	6 (3.2)
Tonsillitis	2 (1.1)
Upper respiratory tract infection	6 (3.2)
Vaginal infection	3 (1.6)
Vulvovaginal candidiasis	2 (1.1)
Vulvovaginal mycotic infection	2 (1.1)
Musculoskeletal and connective tissue disorders	
Spondylitis[a]	2 (1.1)
Nervous system disorders	
Headache	4 (2.1)
Respiratory, thoracic, and mediastinal disorders	
Oropharyngeal pain	3 (1.6)
Skin and subcutaneous tissue disorders	
Eczema	2 (1.1)
Pruritus	3 (1.6)
Vascular disorders	
Hypertension	2 (1.1)

The majority of AEs reported during the DB period of the study were considered mild or moderate in severity and all severe events were reported by 1 subject each (placebo group: Tooth abscess, limb injury, post-traumatic pain, spondylitis and adalimumab group: fatigue, hepatitis acute, migraine).

Among subjects who received adalimumab at any time during the study, 2 subjects reported severe migraines. All other severe events were reported by 1 subject each (chest pain, fatigue, injection site pain, hepatitis acute, influenza, pneumonia, exostosis, muscle spasms, spondylitis, completed suicide, pruritus).

Serious adverse events/deaths/other significant events

Serious adverse events

Within the DB period of the study and among subjects who received adalimumab at any time during the study, all SAEs were reported by 1 subject each.

Table 16 Summary of treatment-emergent serious adverse events during the double-blind period and any adalimumab treatment throughout the study (Safety Analysis Set)

	Number (%) of Subjects		
	Double-Blind Period		Any
MedDRA System Organ Class MedDRA Preferred Term	Placebo N = 97	Adalimumab N = 95	Adalimumab N = 190
Any serious adverse event	1 (1.0)	3 (3.2)	13 (6.8)
Ear and Labyrinth Disorders			
Vertigo	0	0	1 (0.5)
Eye Disorders			
Oscillopsia	0	0	1 (0.5)
Gastrointestinal Disorders			
Nausea	1 (1.0)	0	0
Vomiting	1 (1.0)	0	0
Constipation	0	0	1 (0.5)
Diarrhea	0	0	1 (0.5)
Stomatitis	0	0	1 (0.5)
General Disorders and Administration Site Conditions			
Chest pain	0	0	1 (0.5)
Chills	1 (1.0)	0	0
Pyrexia	1 (1.0)	0	0
Hepatobiliary Disorders			
Hepatitis acute	0	1 (1.1)	1 (0.5)
Infections and Infestations			
Postoperative wound infection	0	0	1 (0.5)
Sinusitis	0	0	1 (0.5)
Tuberculosis	0	0	1 (0.5)
Nervous System Disorders			
Dizziness	1 (1.0)	0	0
Headache	0	0	1 (0.5)
Psychiatric Disorders			
Completed suicide	0	0	1 (0.5)
Reproductive System and Breast Disorders			
Breast dysplasia	0	1 (1.1)	1 (0.5)
Menorrhagia	0	0	1 (0.5)
Vaginal prolapse	0	0	1 (0.5)
Surgical and Medical Procedures			
Abortion induced	0	1 (1.1)	1 (0.5)

The majority of SAEs were considered not related or probably not related to treatment by the investigator. The number of subjects who experienced a serious event (treatment-emergent adverse events during administration of adalimumab at any time throughout the study were) were 13 (6.8%) of whom 4 (2.1%) had a SAE at least possibly drug-related, as assessed by the investigators. A listing of subjects with possibly or probably related treatment emergent SAEs (regardless of treatment) is provided in Table 17.

Table 17 Listing of treatment-emergent serious adverse events by randomized treatment group (Safety Analysis Set)

Sex/ Race	Onset Study Period	Onset Day[a]	Duration (days)	Preferred Term	Severity	Reason Serious	D/C Due to SAE?	Relationship to Study Drug[b]
Placebo								
M/White	POST	223 (40)	1	Completed suicide	Severe	Death of subject	No	NR
F/White	DB	29	3	Dizziness	Moderate	Hospitalization	No	PN
	DB	29	3	Vomiting	Moderate	Hospitalization	No	PN
	DB	29	3	Nausea	Moderate	Hospitalization	No	PN
	DB	29	3	Pyrexia	Moderate	Hospitalization	No	PN
	DB	29	3	Chills	Moderate	Hospitalization	No	PN
M/White	OL	135	23	Postoperative wound infection	Moderate	Hospitalization	No	PS
F/White	OL	140	132	Menorrhagia	Moderate	Hospitalization	No	NR
F/White	OL	156	36	Diarrhoea	Moderate	Hospitalization	No	PN
	POST	164 (8)	18	Headache	Moderate	Hospitalization	Yes	PN
	POST	164 (8)	18	Vertigo	Moderate	Hospitalization	Yes	PN
	POST	164 (8)	18	Oscillopsia	Moderate	Hospitalization	Yes	PN
Adalimumab								
F/White	OL	114	98	Vaginal prolapse	Moderate	Hospitalization, Medical/surgical intervention	No	NR
M/White	DB	1	50	Hepatitis acute	Severe	Hospitalization	Yes	PN
M/White	OL	279	21	Chest pain	Severe	Hospitalization	No	PN
F/White	DB	61	78	Breast dysplasia	Moderate	Hospitalization, Medical/surgical intervention	No	NR
F/White	POST	131 (3)	6	Stomatitis	Moderate	Hospitalization	Yes	PR
M/White	OL	326	96	Sinusitis	Moderate	Hospitalization	No	PS
M/White	OL	274	> 107	Tuberculosis	Moderate	Hospitalization	Yes	PR
F/White	POST	95 (24)	< 1	Abortion induced	Mild	Elective abortion	No	NR
F/White	OL	139	18	Constipation	Mild	Hospitalization	No	NR

D/C = discontinuation; F = female; M = male; NR = not related; OL = open-label period; PN = probably not related; POST = any time after the last dose of study drug; PR = probably related; PS = possibly related; SAE = serious adverse event
a.Total study days. For events in the POST period, numbers in parentheses indicate number of days after the last dose of study drug. b.As assessed by the Investigator.

Adverse events of special interest were specifically monitored. These events were of special interest because they were considered potential safety issues due to the immunomodulating mechanism of action of adalimumab or due to higher rates of some events in the axial SpA population. The results showed that no cases of opportunistic or parasitic infections, PML, malignancies (including lymphomas, NMSC, melanoma, HSTCL, and leukemia), lupus-like syndrome, demyelinating disease, hematologic events, cutaneous and noncutaneous vasculitis, diverticulitis, intestinal perforation related events, intestinal stricture related events, CV events (including MI, CVA, and CHF), pulmonary embolism, interstitial lung disease, medication error related events, Stevens-Johnson syndrome, erythema multiforme-related events, pancreatitis, sarcoidosis, RPLS, or ALS were reported during the study.

Deaths

A male with a history of heavy alcohol use and anxiety who received placebo during the DB period of the study experienced intermittent headaches beginning on Day 2, sinusitis on Day 24 that ended on Day 32, abdominal bloating on Day 59, and diarrhoea on Day 84. All of these events were not serious and considered possibly related to study drug by the investigator. The subject continued into the OL period of the study and withdrew consent for lack of efficacy. The subject committed suicide on Day

223 (40 days after the last dose of adalimumab). The investigator assessed this event as not related to study drug.

Events of special interest

Infections and serious infections

Infections were reported by 45.8% of subjects during any adalimumab exposure throughout the study. The most frequently reported infections were nasopharyngitis, sinusitis, bronchitis, and upper respiratory tract infection; all other infections were reported by <5% of subjects each

Table 18 Summary of Treatment-Emergent Infections Experienced by >2 Subjects in Any Treatment Group by Double-Blind Period and Any Adalimumab Treatment Throughout the Study (Safety Analysis Set; Any Adalimumab Safety Set)

	Number (%) of Subjects		
	Double-Blind Period		
MedDRA System Organ Class MedDRA Preferred Term	Placebo N = 97	Adalimumab N = 95	Any Adalimumab N = 190
Any infection	28 (28.9)	28 (29.5)	87 (45.8)
Nasopharyngitis	3 (3.1)	11 (11.6)	28 (14.7)
Sinusitis	2 (2.1)	1 (1.1)	11 (5.8)
Bronchitis	2 (2.1)	1 (1.1)	11 (5.8)
Upper respiratory tract infection	4 (4.1)	3 (3.2)	11 (5.8)
Gastroenteritis	3 (3.1)	2 (2.1)	6 (3.2)
Rhinitis	2 (2.1)	2 (2.1)	6 (3.2)
Influenza	0	2 (2.1)	6 (3.2)
Pharyngitis	0	3 (3.2)	5 (2.6)
Urinary tract infection	1 (1.0)	0	5 (2.6)
Vaginal infection	1 (1.0)	0	5 (2.6)
Cystitis	0	0	5 (2.6)
Oral herpes	0	2 (2.1)	3 (1.6)
Tonsillitis	2 (2.1)	1 (1.1)	3 (1.6)

No serious infections were reported during the DB period of the study. Three subjects reported serious infections during the OL period of the study; 1 subject who received placebo in the DB period (postoperative wound infection) and 2 subjects who received treatment with adalimumab in the DB period (TB, sinusitis)

The TB case was a 20 year old white male who was PPD negative at Screening and had no known risk factors for TB, reported pulmonary TB on Day 274. Subsequently, the subject was hospitalized and discontinued study drug. The event was ongoing as of Day 380. The investigator considered this event to be probably related to study drug.

Psoriatic Condition

Two subjects with no prior history of psoriasis discontinued adalimumab treatment due to an AE of new onset psoriasis on Day 116 and Day 257. The events were described as mild in severity and reported as probably (psoriasis) and possibly (guttate psoriasis) related to study drug.

Injection Site Reactions

During the DB period of the study, injection site reactions were reported by 8.4% of subjects in the adalimumab treatment group and 3.1% of subjects in the placebo group. Among subjects who received adalimumab at any time during the study, 8.9% reported injection site reactions.

No individual injection site reaction-related AE term was reported by more than 4.2% of subjects in any treatment group. Injection site pain was reported by ≤1.1% of subjects treated with adalimumab

during the DB period. All injection site reactions were considered possibly or probably related to study drug by the investigator, except for 1 event during the OL period which was assessed to be not related.

The most frequently reported injection site reaction-related AE terms in the DB period of the study and among subjects who received adalimumab at any time during the study were injection site reaction and injection site erythema.

Allergic Reactions

No serious allergic reactions were reported during the study. Two subjects, 1 in each of the placebo and adalimumab treatment groups, reported allergic reactions during the DB period of the study (urticaria and eyelid edema, moderate and mild in severity, respectively). No other allergic reactions were reported.

Hepatic-Related Events

Hepatic-related events were infrequent and no individual hepatic-related AE term was reported by more than 2 subjects in any treatment group. One subject in the adalimumab treatment group reported acute hepatitis during the DB period of the study: a male with a relevant history of current moderate alcohol use (2 to 4 drinks/day), who had a positive screening PPD test with subsequent isoniazid prophylaxis and received adalimumab in the DB period of the study, experienced severe acute hepatitis with onset on Day 1. The subject was hospitalized on Day 23. Isoniazid and adalimumab were discontinued due to the event, with the last dose of each drug administered on Day 15. Treatment medication for the event included enoxaparin. The subject was discharged from the hospital on Day 26, and the event was considered resolved on Day 50. The investigator considered this event probably not related to study drug.

Laboratory findings

Statistically significant mean changes in haematology parameters during the DB period of the study, from Baseline to Weeks 4, 8, and 12, were observed between the placebo and adalimumab treatment groups for haemoglobin and platelets. Anaemia and elevated platelet counts can be associated with ongoing inflammation. Overall, mean increases in haemoglobin and mean decreases in platelets were observed for the duration of the study.

Other hematologic parameters remained essentially constant throughout the study, with mean changes from Baseline that were not considered clinically meaningful.

Although some statistically significant differences were observed between the placebo and adalimumab treatment groups, overall, none of the mean changes in clinical chemistry parameters from Baseline during the DB period of the study to Weeks 4, 8, and 12 was considered clinically meaningful.

Overall clinical chemistry parameters remained stable throughout the study duration (from the first dose of adalimumab through 12, 24, 36, 52, and 60 weeks of adalimumab exposure). None of the mean changes from Baseline was considered clinically meaningful. Although a trend for slight increases in cholesterol and triglycerides was noted, these tests were done on non-fasting samples.

Changes in liver function tests meeting the criteria for potential clinical significance (ALT, AST, or alkaline phosphatase ≥2.5 ×ULN or total bilirubin ≥1.5×ULN) were infrequent during the DB period of the study. All alkaline phosphatase and total bilirubin values were <1.5 ×ULN.

Elevations in ALT and AST rarely exceeded 3 × ULN: 1 subject in the adalimumab treatment group (Subject 2102) experienced ALT and AST elevations of ≥8 × ULN (this subject reported an AE of acute hepatitis on Day 1 of the DB period), 1 subject in the placebo group (Subject 4603) experienced an ALT ≥ 3 ×ULN, and 1 subject in the adalimumab treatment group (Subject 502) experienced AST elevations ≥ 3 ×ULN.

Changes in liver function tests meeting the criteria for potential clinical significance were also infrequent during any adalimumab exposure. In addition to those subjects treated with adalimumab experiencing elevated LFTs during the DB period, one additional subject (Subject 4705) had transient AST elevations of ≥5 × ULN during the OL period. No subjects experienced ALT elevation ≥3 × ULN during the OL period. All LFT elevations, other than for the case of acute hepatitis, which resulted in study discontinuation, resolved before the final dose of study drug. All other LFT values were <3 ×≥ ULN throughout any adalimumab exposure during the study.

Shifts in haematology and clinical chemistry parameters were infrequent and were not considered clinically meaningful in the DB period or during any adalimumab exposure. Shifts in urinalysis parameters during the DB period and during any adalimumab exposure were infrequent and were not considered clinically meaningful.

Most elevations in clinical chemistry values were transient and resolved prior to the final value. Four subjects had CTCAE toxicity grade ≥3 at the final visit (that includes cases of hyperuricaemia, elevated uric acid, hyperglycemia and elevated triglycerides).

Safety in special populations

No clinically meaningful differences in AEs were observed by subgroups (sex, age, and weight) examined.

Safety related to drug-drug interactions and other interactions

Drug interactions were not evaluated. No clinically meaningful differences in AEs were observed by subgroups (DMARD and NSAID use) examined.

Discontinuation due to adverse events

Within the DB period and among subjects who received adalimumab at any time during the study, all AEs leading to discontinuation were reported by 1 subject each, with the exception of headache (2 subjects in the Any Adalimumab group). A listing of subjects with treatment-emergent AEs leading to discontinuation that were considered possibly or probably related to study drug by the investigator during the study is provided in table 19.

Table 19 Listing of treatment-emergent adverse events leading to discontinuation possibly or probably related to study drug by randomized treatment group (Safety Analysis Set)

Sex/Race	Onset Study Period	Onset Day[a]	Duration (days)	Preferred Term	Severity	Serious? Yes/No	Relationship to Study Drug	Action Taken
Placebo								
Male/White	DB	17	92	Dyshidrosis	Moderate	No	PR	Medication given (Loprox, Lotriderm) and discontinued from the study.
Adalimumab								
Male/White	OL	199	> 24	Headache	Moderate	No	PS	Patient elected not to continue on study. Temporary interruption to study medication. MRI of brain 17 Nov 2010. No significant finding. Medication taken for headache.
Male/White	OL	148	> 57	Skin lesion	Moderate	No	PS	Concomitant medication taken and dermatology consults.
Male/White	OL	274	> 107	Tuberculosis	Moderate	Yes	PR	Medication.
Female/White	POST	131	6	Stomatitis	Moderate	Yes	PR	Patient withdrawn from study. Study drug stopped. Treatment "Zyrtec" given.
Female/White	DB	83	123	Nausea	Moderate	No	PS	Primperan treatment. Study drug was also interrupted.
				Vomiting	Moderate	No	PS	Primperan treatment. Study drug was also interrupted.
				Weight decreased	Moderate	No	PS	Primperan treatment. Study drug was also interrupted.
Male/White	POST	116	> 104	Psoriasis	Mild	No	PR	Diclocil, Betadine pre-op body wash.
Female/White	POST	257	67	Guttate psoriasis	Mild	No	PS	Clobetasol propionaat.
Male/White	OL	103	64	Pruritus	Severe	No	PR	Interruption and discontinuation.

DB = double-blind; OL = open-label; PR = probably related to study drug; PS = possibly related to study drug

Post marketing experience

No post marketing data is available for the use in axial SpA. The following summarises the experience across other approved indications. The safety profile of adalimumab is well established. Treatment with adalimumab is connected with several potentially serious risks. There have been infrequent post-marketing reports of serious allergic reactions including anaphylaxis following Humira administration. A causal relationship with adalimumab therapy has not been established. Rare post-marketing reports of HSTCL, a rare and aggressive lymphoma, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6 mercaptopurine use for CD and UC. The causal association of HSTCL with adalimumab is not clear. Additionally, rare events of cutaneous vasculitis, reactivation of hepatitis B, demyelinating disorders (e.g. optic neuritis, Guillain−Barré syndrome), intestinal perforation, Stevens-Johnson syndrome, erythema multiforme, angioedema, alopecia, myocardial infarction, cerebrovascular accident, lupus-like syndrome, pulmonary embolism, pleural effusion, pulmonary fibrosis, and sarcoidosis have been reported during post-marketing use of adalimumab as well as cases of diverticulitis, and new onset or worsening psoriasis. These reactions are reported voluntarily from a population of unknown size; therefore, it is not possible to reliably establish a causal relationship to adalimumab exposure.

1.2.3.1. Discussion on clinical safety

The most frequently reported AE during the DB phase were nasopharyngitis, nausea, and headache. Among subjects who received adalimumab at any time during the study through the data cutoff, the most frequently reported AE included nasopharyngitis, spondylitis, diarrhea, headache, nausea, sinusitis, bronchitis, and upper respiratory tract infection. Among subjects who received adalimumab at any time during the study through the data cutoff, the most frequently reported possibly or probably related AEs were nasopharyngitis, sinusitis, bronchitis, upper respiratory tract infection, injection site reactions, and injection site erythema. The frequencies of possibly or probably related AE terms were similar between treatment groups. However, more subjects in the adalimumab treatment group reported injection site reactions (4.2%) and nasopharyngitis (7.4%) compared with placebo (0 and 1.0%, respectively). Other frequently reported (≥3%) possibly or probably related AEs were injection site erythema and nausea. All other events were reported by <3% of subjects in either treatment group.

Overall the majority of AEs reported in the DB phase were mild or moderate in severity. The AEs classified as possibly or probably related to the study drug where AEs already known and reported in previous adalimumab studies.

The SAEs experienced by patients either during the DB period as well as at any time throughout the study were reported by one subject each. The subjects who experienced a serious event (during administration of adalimumab at any time throughout the study) were 13 (6.8%) of whom 4 (2.1%) had a SAE possibly drug-related, as assessed by the investigators. The majority of SAEs were considered not related or probably not related to treatment by the investigator. One death in the adalimumab group (suicide) occurred in the study but was assessed as not related to the study drug. Known serious adverse events with adalimumab or other anti-TNF agents were also evaluated. No cases of opportunistic or parasitic infections, progressive multifocal leukoencephalopathy, malignancies (including lymphomas, NMSC, melanoma, hepatosplenic T-cell lymphoma, and leukemia), lupus-like syndrome, Demyelinating disease, hematologic events, cutaneous and noncutaneous vasculitis, diverticulitis, intestinal perforation related events, intestinal stricture related events, cardiovascular events (including myocardial infarction, cerebrovascular accident, and congestive heart failure), pulmonary embolism, interstitial lung disease, medication error related events, Stevens-Johnson syndrome, erythema multiforme related events, pancreatitis, sarcoidosis, reversible posterior leukoencephalopathy syndrome, or amyotrophic lateral sclerosis were reported during the study.

A total of 10 adverse events (including 2 cases of psoriasis and one case of tuberculosis) leading to discontinuation possibly or probably related to study drug were reported in the adalimumab group.

There were no serious infections reported during the DB period. Three subjects reported serious infections during the OL period of the study; 1 subject in the PBO/ADA treatment group (postoperative wound infection) and 2 subjects in the ADA/ADA treatment group (sinusitis and tuberculosis). The subject in the ADA/ADA treatment group during the OL period of the study who experienced a serious infection of TB was discontinued from the study. The risk of primary as well as reactivated TB is well known and addressed in section 4.4 of the SmPC. The risk of TB occurring in patients receiving adalimumab therapy is already included in the Humira RMP as an important identified risk. In addition to routine Pharmacovigilance measures (which includes the use of specialized questionnaires to identify the results of screening, medical history and administration of TB prophylaxis therapy), the risk of TB is managed via additional minimization tools that educate prescribers on relevant precautions and special safety concerns in order to help prevent the reactivation of TB under adalimumab treatment. Therefore, the CHMP considers that the current RMP adequately addresses risks associated with TB

infection. No new activities in addition to those already being performed are needed to monitor this risk.

Two cases of new onset of psoriasis emerged. Both required discontinuation of the study drug. It may be suspected that the targeted population may run a greater risk to develop psoriasis triggered by adalimumab treatment than others, given the fact that psoriasis is one of the features of the spondyloarthritides and there is a higher risk that an individual belonging to this population have a predisposition to develop this disease than the average individual. New onset or worsening of psoriasis is labelled in the SmPC for Humira. It is also addressed in the RMP as in important identified risk. Therefore, the CHMP considers that the current RMP adequately addresses this risk. No new activities in addition to those already being performed are needed to monitor this risk.

No serious allergic reactions were reported during the study. Two subjects, 1 each in the placebo and adalimumab treatment groups, reported allergic reactions (urticaria and eyelid edema). Allergic reaction is already addressed in the SmPC. It is also addressed in the RMP as in important identified risk. No new activities in addition to those already in place are needed to monitor this risk.

During the study, 8.9% of subjects who received adalimumab reported injection site reactions (including injection site erythema). Injection site reaction is a known and common event with adalimumab administration and is addressed in the SmPC and RMP. It continues to constitute the most frequently reported event, although most of these events are mild to moderate in severity and transient in nature. No new activities beyond those already in place are needed to monitor this risk at this time.

Additional data up to Week 68 became available during the procedure. As of Week 68 of the open-label period of the study, the rates of AEs for patients who had at least 1 dose of adalimumab (Any Adalimumab Safety Set) were generally consistent with AE rates observed during the double-blind period and in clinical trials of adalimumab for other disease indications. There was no indication that increased duration of exposure results in an increased rate of AEs. Safety data presented for the target nr-axSpA population who either has a positive MRI or elevated CRP at baseline are consistent with those observed for the entire study population.

1.2.3.2 Conclusion on clinical safety

Adalimumab was generally well tolerated during each phase of the study. The most common AE was non serious infections, such as nasopharyngitis. No new safety signal has been identified in the Axial SpA clinical development program submitted. The AE pattern in this study does not differ from the known safety profile of adalimumab. Adalimumab has a well characterised safety profile in several authorised indications, including ankylosing spondylitis (AS) or psoriatic arthritis (PsA). Data submitted in this application confirm the known safety profile observed with the approved indications. Overall, the safety profile of adalimumab in the treatment of nr-axSpA appears to be similar with the one known for other approved indications.

In the study M10-791, AEs of special interest for adalimumab have been monitored and no safety signal has been detected. Safety data were also presented for the target nr-axSpA population for adalimumab therapy who either has a positive MRI or elevated CRP at baseline, and the results are consistent with those observed for the entire study population. Further data will become available to further characterise the long term safety of adalimumab in axial SpA patients as soon as the 3-year study is completed.

1.2.3.3 Risk Management plan

The applicant submitted a risk management plan.

Table 20 Extract from Summary of the risk management plan (including only the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Missing Information		
Remission-withdrawal-retreatment axial SpA data	Routine pharmacovigilance activities. Study M13-375	Remission-withdrawal-retreatment is not proposed in the CCDS. A planned remission-withdrawal-retreatment study will complement the safety experience especially on remission-withdrawal-retreatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Study M13-375: To evaluate the efficacy and safety of continuous versus withdrawing therapy with adalimumab in maintaining remission in the target population.	Q3 2015

No additional risk minimisation activities were required.

2. Overall conclusion and benefit-risk assessment

Benefits

Beneficial effects

The submission is based on a single pivotal Phase 3 study, Study M10-791, in about 192 adult subjects with non-AS axial SpA randomized to adalimumab 40mg eow or matching placebo for 12 weeks. Thereafter, all received open label adalimumab. The primary endpoint was the proportion of patients achieving an ASAS40 response at Week 12. The Week 12 (end of DB period) analysis showed that a statistically significantly greater proportion of subjects in the adalimumab treatment group achieved ASAS40 responses compared with placebo. Similar results were observed using the PPP (35.9% versus 14.1%, P = 0.002). Significant effects were also demonstrated at week 12 for all ranked secondary efficacy endpoints, including two MRI endpoints (SPARCC MRI score sacroiliac joints, and for the spine, p=0.003 and 0.001, respectively). In addition a number of "supportive secondary endpoints" were assessed with an overall pattern of results favoring active treatment. This is overall considered a robust effect, and of clinical relevance in terms of symptomatic treatment.

Based on the data available so far from the ongoing study, a clinical benefit of adalimumab treatment was observed for all endpoints throughout the 12-52 week period. Additional data up to 68 weeks showed that the observed clinical response rates at Week 12 were sustained up to Week 68. The duration of Study M10-791 is 3 years. As described in the RMP the MAH will submit the final CSR of Study M10-791 by Q4 2013 which will bring additional data supportive of beneficial long term effect of adalimumab treatment of nr-axSpA patients.

During the procedure the CHMP questioned the reliability, sensitivity, specificity and predictive value of the ASAS classification criteria for axial spondyloarthritis to define a subgroup with early axial spondylarthritis who could benefit the most from adalimumab treatment. The problem of delayed AS diagnosis was acknowledged by the CHMP. It is recognized that there are currently patients who do not have radiographic signs of the disease; but who do not respond adequately to NSAIDs and thereby are in need of an alternative treatment option. Nevertheless, there is a potential to treat patients who have no inflammatory back pain as the diagnosis of nr-axSpA, applying these criteria, does not require the presence of active inflammation as detected by MRI. In response to this concern, and as the data presented showed that patients with evidence of either inflammation on MRI of either the spine or SI joints, or an elevated CRP, achieve better clinical responses to adalimumab, the MAH proposed to require the presence of an elevated CRP or a positive MRI in the target population in addition to having severe active disease despite treatment with NSAIDs. The CHMP agreed with this measure as it allows reducing considerably the possibility of treating patients with non inflammatory disease and thereby identifies a population in whom the benefit/risk balance is positive. For clarification the CHMP required a change to the wording requiring the presence of an elevated CRP and/or a positive MRI in the target population to make clear that patients displaying both signs of inflammation are also covered in the indication. This was accepted by the MAH.

Uncertainty in the knowledge about the beneficial effects

To further study the need for continuous anti-TNF therapy for nr-axSpA patients to maintain clinical response or remission over time, the MAH committed to conduct a post approval randomized controlled remission-withdrawal-retreatment study in nr-axSpA subjects which is endorsed by the CHMP. The results of such a study will provide more information on whether it is possible to discontinue treatment in subjects in whom there is no disease activity following treatment for 24 weeks; what proportion of patients treated early in their disease achieve remission and also on the safety and efficacy of re-treatment after disease flare. The MAH will provide the results of this study by Q3 2015 as described in the RMP.

Risks

Unfavourable effects

The AE pattern in the study supporting this application does not differ from the established safety profile of adalimumab. There were no new safety concerns identified. Adalimumab was generally well tolerated during each phase of the study and the most common AE was non serious infections, such as nasopharyngitis.

Adalimumab has a well characterised safety profile in several authorised indications, including AS or PsA. Data submitted in this application confirm the known safety profile observed with the approved indications. Overall, the safety profile of adalimumab in the treatment of nr-axSpA appears to be similar with the one known for other approved indications.

Uncertainty in the knowledge about the unfavourable effects

In general, treatment with adalimumab is connected with several more serious risks i.e. serious infections, risk of lymphoproliferative disorders, malignancies or demyelination event. These serious risks have not been observed in study M10-791. As described in the RMP, these risks are monitored through extensive ongoing follow up programs (including registries) in rheumatologic diseases with focus on RA; in which long term safety data is collected and reported annually for several years. Additional data up to Week 68 in study M10-791 showed that the rates of AEs for patients were generally consistent with AE rates observed in clinical trials of adalimumab for other indications. As described in the RMP the MAH will submit the final CSR of Study M10-791 by Q4 2013 which will bring additional data on the long term safety of adalimumab treatment of nr-axSpA patients.

Balance

Importance of favourable and unfavourable effects

For AS patients who continue to have active disease despite NSAIDs, adalimumab is an approved therapy. However, nr-axSpA patients, who may have the same signs, symptoms and level of disease activity as AS patients, currently have no treatment alternative to NSAIDs. Traditional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine (SSZ) have not been shown to be effective for axial SpA. Patients with nr-axSpA suffer from signs and symptoms that can have a significant impact on their day to day and/or work-related activities, and therefore require effective therapies. It is acknowledged that there is a group of patients with an inflammatory spinal disease that have not yet led to changes detectable by x-ray, but who still suffer from the same symptoms as those AS patients who have radiologic changes, and who are in need of a therapeutic option when NSAID treatment does not have an adequate effect. Results from study M10-791 showed that treatment with adalimumab 40 mg sc eow conferred a significant clinical benefit to patients with nr-axSpA. These data are considered valuable and of clinical relevance.

The safety profile of adalimumab is well established. Treatment with adalimumab is connected with several potentially serious risks. In Study M10-791 the most common AE was non serious infections, such as nasopharyngitis. No new safety signal has been identified in the Axial SpA clinical development program submitted. The safety profile of adalimumab in the treatment of Axial SpA appears to be similar with the one known for other approved indications.

Benefit-risk balance

The applicant has shown that adalimumab has a robust effect in the studied nr-axSpA patient population and this is of clinical relevance in terms of symptomatic treatment. The safety profile of adalimumab in the studied population does not differ from the established safety profile of adalimumab in other approved indications. Study M10-791 demonstrated that there is a greater likelihood of clinical response among patients with either elevated CRP or positive MRI, with no differences in safety compared to the overall study population. Therefore, nr-axSpA patients who are candidates for adalimumab treatment must have severe active disease, inadequate response to, intolerance to, or contraindication for, NSAIDs, and evidence of inflammation by elevated CRP and/or MRI. Requiring an objective measure of inflammation reduces the potential to treat patients with no inflammatory back pain and thereby allows identifying a population in whom the benefit-risk balance is positive. In addition, long-term efficacy and safety in subjects with up to 68 weeks of adalimumab treatment further support a positive benefit-risk profile for adalimumab in this population.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of adalimumab is considered positive for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or

MRI, who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs.

3. Conclusion

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore does recommend, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6 Change(s) to therapeutic indication(s)	Addition of a new therapeutic indication or modification of an approved one.	II

Extension of indication for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet and Annex II.