Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Adalimumab

Proprietary Product Name: Humira

Sponsor: Abbott Australasia Pty Ltd (AbbVie Pty Ltd)

First round evaluation date: 30 December 2012

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
AP	Antero-posterior
AS	Ankylosing spondylitis
ASAS	Assessments in Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate transaminase
BASDAI	Bath Ankylosing Spondylitis disease activity index
BASFI	Bath Ankylosing Spondylitis functional index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette-Guérin
BUN	Blood urea nitrogen
CD	Crohn's disease
CDC	Centers for Disease Control
CHF	Congestive heart failure
CNS	Central nervous system
CRP	C-reactive protein
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTX-II	Type II collagen C-telopeptide
CVA	Cerebrovascular accident

Abbreviation	Meaning
CXR	Chest x-ray
DAE	Discontinuation due to adverse event
DB	Double-blind
DMARD	Disease-modifying anti-rheumatic drugs
ECG	Electrocardiogram
eow	Every other week
EQ-5D	European Quality of Life – 5 Dimensions questionnaire
F	Female
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-S	Health Assessment Questionnaire modified for spondyloarthropathies
HCP	Heath care provider
HCRU	Health care resource utilization
HLA-B27	Human leukocyte antigen-B27
hs-CRP	High sensitivity C-reactive protein
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system

Abbreviation	Meaning
IWRS	Interactive web response system
LOCF	Last observation carried forward
LFT	Liver function test
M	Male
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMP-3	Matrix metalloproteinase 3
MOS	Medical outcomes study
MRI	Magnetic resonance imaging
MTX	Methotrexate
NMSC	Non-melanoma skin cancer
nr-axSpA	Non-radiographic axial SpA
NRI	Non-responder imputation
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OC	Observed case
OL	Open-label
PA	Posterior-anterior
PASS	Patient acceptable symptom state
PGA	Physician's Global Assessment of Disease Activity
PML	Progressive multifocal leukoencephalopathy
POR	Proof of receipt
PPD	Purified protein derivative
PPP	Per-protocol population

Abbreviation	Meaning
Ps	Psoriasis
PsA	Psoriatic arthritis
PT	Preferred term
PTGA	Patient's Global Assessment
PY	Patient-year
RBC	Red blood cell
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SF-36™V2	Short Form-36 Health Status Survey™ Version 2
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SJC	Swollen joint count
SOC	System organ class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States

Abbreviation	Meaning
VAS	Visual analog scale
WBC	White blood cell
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem Questionnaire
$VEGF_A$	Vascular endothelial growth factor A

1. Clinical rationale

The sponsor justified the development of adalimumab for the treatment of Non-Radiographic Axial Spondyloarthritis (nr-axSpA) with the following argument: "*Currently, there is an unmet medical need in patients with nr-axSpA who have disease features similar to patients with Ankylosing Spondylitis (AS), but who do not fulfil the modified New York criteria for AS by virtue of not having evidence of structural damage in the form of radiographic sacroiliitis*." This patient group does not respond to traditional Disease-modifying anti-rheumatic drugs (DMARDs) such as Methotrexate (MTX) and sulfasalazine. Nonsteroidal anti-inflammatory drug (NSAIDs) provide some symptom relief but do not control the disease. Whilst adalimumab and other anti-TNF therapies have been approved for the indication of Ankylosing spondylitis (AS), patients with nr-axSpA do not have access to (approved) treatments other than NSAIDs.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One efficacy/safety study: Study M10-791.
- Three files containing tabulations of pooled safety data.

2.2. Paediatric data

The submission did not include paediatric data. There are no plans for a paediatric development program for non radiographic axial spondyloarthritis.

2.3. Good clinical practice

The studies presented in the present application were conducted in accordance with Good Clinical Practice.

3. Pharmacokinetics

There were no new pharmacokinetic data contained in the dossier.

4. Pharmacodynamics

There were no new pharmacodynamic data contained in the dossier.

5. Dosage selection for the pivotal studies

The sponsor did not conduct dose finding studies for the present application. The dose selected for development appears to be based on the approved dose for the indication of AS.

6. Clinical efficacy

6.1. Non-radiographic axial SpA

6.1.1. Pivotal efficacy studies

6.1.1.1. Study M10-791

6.1.1.1.1. Study design, objectives, locations and dates

Study M10-791 was a multicentre, randomised, double blind, placebo controlled, parallel group efficacy and safety study of 12 weeks duration followed by an open-label follow on phase. The study was conducted at 37 study sites in Australia, Belgium, Canada, Czech Republic, France, Germany, The Netherlands, Spain, United Kingdom, and the United States from 11 August 2009 to 19 October 2011.

6.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Subject was ≥18 years of age
- Subject must have had an inadequate response to NSAIDs, intolerance to one of more NSAID, or had a contraindication for NSAIDs as defined by the study investigator
- Chronic back pain of at least 3 months duration with onset at age < 45 years
- MRI evidence of active inflammatory lesions of sacroiliac joints (past or present) with definite bone marrow oedema/osteitis, suggestive of sacroiliitis associated with SpA plus one or more of the clinical criteria listed below:

  OR

  Positive HLA-B27 plus two or more of the clinical criteria listed below other than HLA-B27 positivity:

  - Inflammatory back pain defined as the presence at Screening of at least four out of the following five 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)
  - Crohn's Disease (CD) or ulcerative colitis (UC) (past or present)

  - Good prior response to an NSAID – back pain was not present anymore or much better 24 to 48 hours after a full dose of an NSAID
  - Family history of SpA
  - Positive HLA-B27
  - Elevated CRP
- Baseline disease activity as defined by having a Total Back Pain VAS score ≥40 mm and BASDAI ≥4
- If female, subject is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile or practicing an approved method of birth control
- In good health as determined by the Principal investigator (PI) based upon the results of medical history, laboratory profile, physical examination, Chest x-ray (CXR) and a 12-lead electrocardiogram (ECG) performed at Screening;
- Negative Purified protein derivative (PPD test) (or equivalent) and CXR, or currently receiving, or have documented completion of a course of anti- Tuberculosis (TB) therapy

The exclusion criteria included:

- Diagnosis of AS (as defined by the modified New York criteria) at or prior to the screening visit
- Past or present diagnosis of Psoriasis (Ps) or Psoriatic arthritis (PsA)
- Prior exposure to any biologic therapy with a potential therapeutic impact on Spondyloarthritis (SpA) including anti-Tumor necrosis factor (TNF) therapy
- If entering the study on concomitant DMARDs, subject was not on stable dose of MTX (≤25 mg per week) and/or Sulfasalazine (SSZ) (≤3 g per day) and/or hydroxychloroquine (≤400 mg per day) for 28 days prior to the Baseline visit
- If entered the study on concomitant oral corticosteroids, subject was not on stable dose of prednisone (≤10 mg per/day) or oral corticosteroid equivalents for at least 14 days prior to the Baseline visit
- Subject had received cyclosporine or other second line anti-rheumatic therapy (except MTX, SSZ, hydroxychloroquine, or azathioprine) within 28 days prior to the Baseline visit
- 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
- Infection(s) requiring treatment with intravenous antibiotics, antivirals or antifungals within 30 days prior to the Baseline visit or oral antibiotics, antivirals or antifungals within 14 days prior to the Baseline visit
- Subject with extra-articular manifestations (for example, Inflammatory bowel disease (IBD) and uveitis) that were not clinically stable for at least 30 days prior to study entry
- Subject had a history of inflammatory arthritis of a different etiology other than axial SpA (for example rheumatoid arthritis, gout, systemic lupus erythematosus, polyarticular or systemic juvenile idiopathic arthritis)
- History of central nervous system (CNS) demyelinating disease or neurologic symptoms suggestive of CNS demyelinating disease
- History of listeriosis, histoplasmosis, chronic or active hepatitis B infection, human immunodeficiency virus infection, immunodeficiency syndrome, chronic recurring infections or active TB

- History of moderate to severe congestive heart failure (New York Heart Association (NYHA) class III or IV), recent Cerebrovascular accident (CVA) and any other condition which, in the opinion of the investigator, would put the subject at risk by participation in the protocol
- Evidence of dysplasia or history of malignancy (including lymphoma and leukaemia) other than a successfully treated non-metastatic cutaneous squamous cell, basal cell carcinoma, or localised carcinoma *in situ* of the cervix
- Female subjects who are pregnant or breastfeeding or considering becoming pregnant during the study
- History of clinically significant drug or alcohol abuse in the last 12 months
- Clinically significant abnormal screening laboratory results as evaluated by the investigator
- If entering the study on concomitant azathioprine, subject not on stable dose (≤150 mg/day) for 28 days prior to the Baseline visit or on azathioprine and another concomitant immunosuppressive drug at study entry
- If entering the study on concomitant NSAIDs and/or analgesics, subject on opioid analgesics (other than tramadol) within 14 days prior to Baseline visit or subject not on stable doses of NSAIDs and/or analgesics for 14 days prior to the Baseline visit
- Spinal surgery within 2 months prior to Baseline

6.1.1.1.3. Study treatments

The study treatments were:

1. Adalimumab 40 mg
2. Placebo

Study treatments were self-administered subcutaneously every 2 weeks. After Week 12 all subjects were treated with adalimumab 40 mg every 2 weeks in an open-label manner.

Subjects could continue on stable doses of MTX, SSZ, hydroxychloroquine, azathioprine, prednisone and/or NSAIDs. Doses of these concomitant medications were to remain stable for the first 24 weeks of participation (except as medically required due to an adverse event (AE)). Dose adjustments or induction of treatment with these agents were permitted after Week 24. Subjects on stable doses of analgesics were allowed to continue during the study. However, opioid analgesics (except for tramadol) were prohibited from Baseline to Week 24. Only one intra-articular corticosteroid injection for a peripheral joint was to be allowed during the first 24 weeks of the study.

Prohibited medications included:

- All biologic therapy with a potential therapeutic impact on SpA including but not limited to: Enbrel® (etanercept), Remicade® (infliximab), Orencia® (abatacept), Kineret® (anakinra), Rituxan® (rituximab), Tysabri® (natalizumab), Actemra® (tocilizumab), Raptiva® (efalizumab), Simponi® (golimumab), and Cimzia® (certolizumab)
- Live vaccines
- Rifampin/pyrazinamide combination
- All other second-line anti-rheumatic therapies other than MTX, SSZ, azathioprine, or hydroxychloroquine
- Opioid analgesics (other than tramadol) until Week 24, and at any time during the study high potency opiates such as methadone, hydromorphone, and morphine

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measure was Assessments in Spondyloarthritis International Society (ASAS40) response at Week 12. ASAS40 response was defined as improvement of ≥40% and absolute improvement of ≥20 units (on a scale of 0 to 100) from Baseline in three or more of the following four domains with no deterioration in the potential remaining domain:

1. Patient's Global Assessment; Represented by the Patient's Global Assessment (PTGA) disease activity Visual analog scale (VAS) score (0 to 100 scale)
2. Pain; Represented by the total back pain VAS score (0 to 100 scale)
3. Function; Represented by the Bath Ankylosing Spondylitis functional index (BASFI) score (0 to 100 scale)
4. Inflammation; Represented by the mean of the two morning stiffness-related BASDAI VAS scores (that is, the average of items 5 and 6 of the BASDAI)

The secondary efficacy outcome measures were:

- ASAS20 response (improvement of ≥20% and absolute improvement of ≥10 units from Baseline in three or more of the four ASAS domains
- BASDAI50 (50% improvement from Baseline in BASDAI)
- Mean change in Short Form-36 Health Status Survey™ Version 2 (SF-36v2) physical component
- ASAS partial remission (absolute score of <20 units for each of the four ASAS domains)
- ASAS5/6 response (20% improvement in five out of the following six domains: BASFI, total back pain, Patient's Global Assessment (PTGA) disease activity, inflammation [questions 5 and 6 of the BASDAI], lateral lumbar flexion from BASMI, and acute phase reactant [pooled C-reactive protein (CRP)])
- Mean change in Health Assessment Questionnaire modified for spondyloarthropathies (HAQ-S)
- Mean change in High sensitivity C-reactive protein (hs-CRP)
- Mean change in spondyloarthritis Research Consortium of Canada (SPARCC) Magnetic resonance imaging (MRI) score for sacroiliac joints
- Mean change in SPARCC MRI score for the spine

Non-ranked secondary efficacy outcome measures were:

- ASAS50 response (improvement of ≥50% and absolute improvement of ≥20 units from Baseline in three or more of the four domains)
- ASAS70 response (improvement of ≥70% and absolute improvement of ≥30 units from Baseline in three or more of the four domains)
- ASDAS (a composite score of BASDAI questions 2, 3, and 6; PTGA-Disease Activity; and pooled CRP)
- Swollen joint count (SJC) (66 joints)
- Tender joint count (TJC) (68 joints)
- Bath Ankylosing Spondylitis disease activity index (BASDAI)
- Inflammation (mean of BASDAI questions 5 and 6)
- Bath Ankylosing Spondylitis Metrology Index (BASMI)

- Chest expansion
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- Plantar fascia enthesitis
- Dactylitis
- PGA (VAS)
- Nocturnal pain VAS
- Total back pain VAS
- PTGA-disease activity (VAS)
- PTGA-pain (VAS)
- BASFI

Health-Related Quality of Life outcome measures were:

- HAQ-S
- SF-36™v2
- Work Productivity and Activity Impairment – Specific Health Problem Questionnaire (WPAI-SHP)
- European Quality of Life – 5 Dimensions questionnaire (EQ-5D)
- Patient acceptable symptom state (PASS)
- Medical outcomes study (MOS) Sleep Scale
- Health Care Resource Utilization (HCRU) survey

Biochemical markers used as outcome measures were: serum Matrix metalloproteinase 3 (MMP-3), urine Type II collagen C-telopeptide (CTX-II) and Vascular endothelial growth factor A ($VEGF_A$). The safety outcome measures were: AEs, vital signs and clinical laboratory tests.

6.1.1.1.5. Randomisation and blinding methods

Randomisation was performed centrally in a ratio of 1:1 (active:placebo) using an Interactive voice response system (IVRS)/ Interactive web response system (IWRS). Active and placebo drug were identical in appearance and labelling. Except for the active ingredient (adalimumab) the ingredients of active and placebo treatments were identical.

6.1.1.1.6. Analysis populations

The efficacy analysis was intended to be performed on the Intent-to-Treat (ITT) population which included all subjects who were randomised and received at least one dose of double blind study medication. Seven subjects were excluded from analysis because the study investigator at one site did not follow the protocol. The remaining subjects were included in the Full analysis set (FAS) which was subsequently used for the efficacy analysis. A confirmatory analysis was performed on the per-protocol population which included all ITT subjects that completed the double blind period and did not meet any major protocol violation during the double blind period. The safety population included all subjects who received at least one dose of double blind study drug.

6.1.1.1.7. Sample size

The sample size calculation used prior data from the ATLAS study, in which the ASAS40 responses at Week 12 were 13.1% for placebo and 39.9% for adalimumab. Hence, 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 (97 in each group) would provide approximately 90% power with a 1:1 randomization ratio, based on a two-sided chi-square test with a significance level of 0.05.

6.1.1.1.8. Statistical methods

Hypothesis tests were performed using a two-sided Pearson's chi-square test with α of 0.05. Missing data were imputed using non-responder imputation (NRI) for categorical outcome variables (that is, subjects with missing ASAS40 responses were to be imputed as non-responders); and Last observation carried forward (LOCF) for continuous outcome variables. For continuous variables hypothesis tests were performed using 95% confidence interval (CI). There was no adjustment for multiplicity for the primary efficacy outcome measure.

6.1.1.1.9. Participant flow

A total of 192 subjects were randomised but all seven subjects from one centre were excluded from the FAS because of study investigator non-compliance with the protocol. Hence 185 subjects were randomised and included in the FAS: 91 in the adalimumab group and 94 in the placebo. All of these subjects were included in the FAS. There were 87 subjects in the adalimumab group and 92 in the placebo that completed to Week 12. There were 68 subjects in the adalimumab group and 74 in the placebo that completed to Week 68. The safety analysis included all 192 subjects that received study treatment.

6.1.1.1.10. Major protocol violations/deviations

Ten (11.0%) subjects in the adalimumab group and ten (10.6%) in the placebo had protocol deviations with regard to inclusion/exclusion criteria. One (1.1%) subjects in the adalimumab group and three (3.2%) in the placebo received excluded concomitant treatment.

6.1.1.1.11. Baseline data

There were 101 (54.6%) females, 84 (45.4%) males and the age range was 19 to 72 years. However, there were only two subjects over the age of 65 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in disease duration and axial SpA related medical history. HLA-B27 was positive in 75 (82.4%) subjects in the adalimumab group and 69 (73.4%) in the placebo. MRI of the sacroiliac joints was positive in 46 (50.5%) subjects in the adalimumab group and 43 (45.7%) in the placebo. Prior treatment was similar for the two groups. Concomitant treatment was similar for the two groups. Nineteen (20.9%) subjects in the adalimumab group and 17 (18.1%) in the placebo had no concomitant DMARDs during the study (thus representing monotherapy).

6.1.1.2. Results for the primary efficacy outcome

The primary efficacy outcome demonstrated superiority for adalimumab relative to placebo at Week 12. In the FAS, there were 33 (36.3%) ASAS40 responders in the adalimumab group and 14 (14.9) responders in the placebo group, $p < 0.001$. In the ITT population, there were 33 (34.7%) responders in the adalimumab group and 14 (14.4) in the placebo, $p < 0.001$. The subgroup analyses indicated that subjects with abnormal pooled CRP at baseline had greater response than those with normal pooled CRP (Table 1). Subjects with shorter duration of symptoms were more likely to respond to adalimumab. There was no effect for gender, age group, concomitant DMARDS or HLA-B27 status. For those subjects with no concomitant DMARDs at baseline (monotherapy) there were five (26.3%) responders in the adalimumab group and none in the placebo. In the group randomised to adalimumab, ASAS40 response was maintained to endpoint: 40 (48.8%) subjects at Week 24, 42 (58.3%) at Week 52 and 48 (69.6%) at Week 68.

Table 1. 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 category			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 from lab data			0.398[d]
Positive	11/69 (15.9)	30/75 (40.0)	
Negative	3/23 (13.0)	3/16 (18.8)	
Equivocal	0/2	0/0	
HLA-B27 status from medical history			0.416
Positive	11/70 (15.7)	30/75 (40.0)	
Negative	3/24 (12.5)	3/16 (18.8)	
Concomitant use of DMARDs at Baseline[e]			0.812
Yes	3/16 (18.8)	8/17 (47.1)	
No	11/78 (14.1)	25/74 (33.8)	

Table 1. (cont)

Subgroup	n/N (%) of Subjects[a] Placebo N = 94	Adalimumab N = 91	Interaction *P* value[b]
Concomitant use of NSAIDs at Baseline[e]			N.C.
Yes	14/74 (18.9)	28/72 (38.9)	
No	0/20	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)	
Symptom duration			0.022
< 5 years	2/34 (5.9)	16/33 (48.5)	
≥ 5 years	11/56 (19.6)	17/55 (30.9)	

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. Only positive and negative HLA-B27 categories were used for logistic regression.

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. N.C. = not able to calculate.

6.1.1.3. Results for other efficacy outcomes

There was a statistically and clinically significant improvement in the adalimumab group relative to placebo at Week 12 for all the secondary efficacy outcome measures, and this improvement was maintained to endpoint (Week 52 or 68 depending on the outcome measure) (Table 2). These measures included the quality of life outcome measures. However, there was no significant difference between the treatment groups in serum MMP-3, urine CTX-II and $VEGF_A$ (Table 7.1.1.1.10).

There were no analyses to investigate drug-drug or drug-disease interactions; and drug dose, drug concentration and relationship to response.

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

There were no pooled analyses of efficacy.

Table 2. Summary of Supportive Secondary Efficacy Endpoints (FAS, OL Population; OC)

	% of Subjects OR Mean Change from Baseline								
	Week 12			Week 24			Week 68		
Endpoint	PBO	ADA	*P* Value	PBO/ADA	ADA/ADA	Combined	PBO/ADA	ADA/ADA	Combined
Reduction of Signs and Symptoms Variables									
ASAS20	31.9%	53.4%	0.004	65.2%	72.0%	68.4%	77.3%	82.6%	79.9%
ASAS40	15.4%	37.5%	< 0.001	55.1%	48.8%	52.0%	64.0%	69.6%	66.7%
ASAS50	9.9%	31.8%	< 0.001	49.4%	43.9%	46.8%	60.0%	59.4%	59.7%
ASAS70	4.4%	15.9%	0.010	27.0%	30.5%	28.7%	40.0%	36.2%	38.2%
ASAS5/6	6.6%	31.8%	< 0.001	37.1%	50.0%	43.3%	44.0%	55.1%	49.3%
ASAS partial remission	5.5%	17.0%	0.014	23.6%	29.6%	26.5%	34.7%	37.7%	36.1%
BASDAI50	15.6%	36.4%	0.002	48.3%	52.4%	50.3%	61.3%	68.1%	64.6%
PTGA-Disease Activity	–9.7	–22.5	< 0.001	–31.6	–34.6	–33.0	–39.5	–40.3	–39.9
Total back pain	–11.5	–23.8	< 0.001	–34.0	–35.2	–34.5	–42.1	–42.7	–42.4
Inflammation[a]	–1.2	–2.3	0.001	–3.5	–3.6	–3.6	–4.2	–4.0	–4.1
BASDAI total score	–1.1	–2.0	0.005	–3.0	–3.2	–3.1	–3.8	–3.9	–3.8
ASDAS clinically important improvement	14.1%	40.5%	< 0.001	64.0%	64.9%	64.4%	65.3%	74.6%	69.8%
ASDAS major improvement	3.5%	20.2%	< 0.001	27.9%	22.1%	25.2%	43.1%	40.3%	41.7%
ASDAS inactive disease state	4.5%	25.0%	< 0.001	29.2%	42.0%	35.3%	42.7%	52.2%	47.2%
ASDAS score	–0.4	–1.1	< 0.001	–1.4	–1.5	–1.5	–1.7	–1.8	–1.7
PGA	–13.4	–21.7	0.024	–32.0	–34.8	–33.3	–39.3	–39.9	–39.6

Table 2. (cont) Summary of Supportive Secondary Efficacy Endpoints (FAS, OL Population; OC)

	% of Subjects OR Mean Change from Baseline								
	Week 12			Week 24			Week 68		
Endpoint	PBO	ADA	*P* Value	PBO/ADA	ADA/ADA	Combined	PBO/ADA	ADA/ADA	Combined
Reduction of Signs and Symptoms Variables (continued)									
PTGA-Pain	–10.1	–22.1	< 0.001	–33.6	–33.4	–33.5	–40.9	–39.4	–40.2
hs-CRP	–0.4	–5.0	< 0.001	–4.6	–4.6	–4.6	–4.6	–3.6	–4.1
Nocturnal pain	–8.5	–24.9	< 0.001	–32.4	–36.0	–34.1	–39.9	–42.3	–41.1
Quality of Life Variables									
HAQ-S disability index	–0.14	–0.28	0.025	–0.38	–0.40	–0.39	–0.51	–0.41	–0.46
	Week 12			Week 24			Week 52		
	PBO	ADA	*P* Value	PBO	ADA	*P* Value	PBO	ADA	*P* Value
SF-36v2 PCS	2.0	5.5	0.001	7.0	7.4	7.2	9.4	9.9	9.6
WPAI-SHP absenteeism	2.3	–7.2	0.005	–4.5	–6.4	–5.5	–3.4	–5.1	–4.2
WPAI-SHP activity impairment	–3.6	–14.9	0.002	–18.7	–22.7	–20.6	–25.7	–30.8	–28.2
MOS sleep scale quantity	–0.3	0.3	0.004	0.0	1.1	0.6	–0.1	0.2	0.1
EQ-5D (UK version)	0.04	0.12	0.037	0.17	0.20	0.18	0.23	0.21	0.22
EQ-5D (US version)	0.03	0.08	0.038	0.12	0.13	0.12	0.15	0.14	0.15

a. Mean of BASDAI Questions 5 and 6.

6.3. Evaluator's conclusions on clinical efficacy

Non-radiographic axial SpA

Efficacy has been demonstrated for adalimumab in comparison with placebo for the indication of nr-axSpA over a 12 week period. The response rate was both clinically and statistically significant. The response was maintained in an open label follow-on study for up to 68 weeks. Response was greater in subjects with elevated CRP at baseline and with shorter duration of symptoms. For those subjects with no concomitant DMARDs at baseline (monotherapy) there were five (26.3%) responders in the adalimumab group and none in the placebo.

The ASAS worked on developing criteria for axial SpA that include patients with and without definite radiographic sacroiliitis because "*radiographic changes may reflect the consequences of inflammation (structural damage) rather than inflammation itself, which may be readily detectable by magnetic resonance imaging (MRI), often years before the appearance of radiographic sacroiliitis*".[1] These criteria were developed using questionnaires, logistic regression, sensitivity and specificity analysis and were voted on by the members of the ASAS (Figure 1).

Figure 1. ASAS classification criteria for Axial SpA (copied from Figure 2, Rudawaleit 2009a)

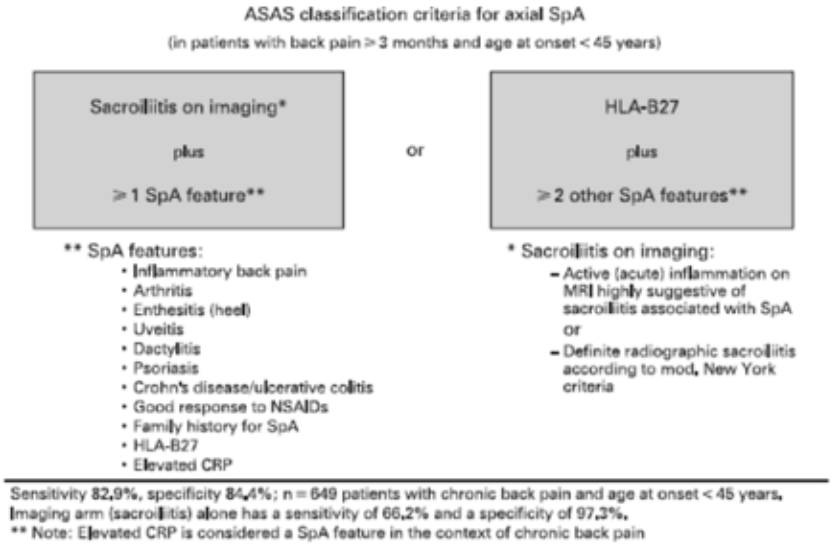

Figure 2 Final set of classification criteria for axial spondyloarthritis (SpA) selected by the Assessment of SpondyloArthritis international Society (ASAS). The criteria encompass both patients with and without definite radiographic sacroiliitis. According to the criteria, a patient with chronic back pain (≥3 months) and age at onset less than 45 years can be classified in the presence of sacroiliitis (either definite radiographic sacroiliitis or active inflammation of sacroiliac joints on magnetic resonance imaging (MRI), which is highly suggestive of sacroiliitis associated with SpA) plus at least one typical SpA feature, or in the presence of HLA-B27 plus at least two other SpA features. Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset less than 45 years. The imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%. **Elevated C-reactive protein (CRP) is considered a SpA feature in the context of chronic back pain. NSAID, non-steroidal anti-inflammatory drug.

Radiographic axial SpA is currently an indication for adalimumab but non-radiographic SpA is currently not an indication. In order to demonstrate the efficacy and safety of adalimumab in non-radiographic axial SpA subjects with AS, PsA and RA (all current indications) needed to be excluded from the study population. The inclusion criteria and exclusion criteria satisfactorily define the study population (and this study population is the same as that intended for treatment).

[1] Rudwaleit M. et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. Ann Rheum Dis 2009;68:777–783.

The indication of nr-axSpA could be considered to be an extension of AS, which is currently an approved indication for adalimumab. This supports the dose regimen chosen for development for nr-axSpA.

The primary efficacy outcome measure was ASAS40 response. This measure was a previously validated outcome measure and was developed independent of the development program. There were a large number of secondary outcome measures, all of which can be rationally applied to nr-axSpA. All of these outcome measures were supportive of efficacy compared with placebo over 12 weeks, and maintenance of efficacy for up to 68 weeks.

The limitations of the efficacy data include:

- Few elderly subjects were included in Study M10-791 (only two subjects over the age of 65 years)
- There were no analyses to investigate drug-drug or drug-disease interactions; and drug dose, drug concentration, and relationship to response.
- Nr-axSpA is a chronic condition and there were no efficacy data extending beyond 68 weeks.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: Study M10-791.

The sponsor provided some summary tables of safety data across all clinical trials of adalimumab. These tables relate to proposed changes in Product Information document for event rates for infection, malignancy and withdrawal due to AEs. These rates have been adjusted to include data for the indication of nr-axSpA. The rates presented in the draft PI do correspond with those presented in the tabulations. It was difficult to find these data within the tabulations and some of the crosschecks performed by the evaluator required use of the word search tool in Adobe reader.

7.2. Pivotal studies that assessed safety as a primary outcome

There were no additional pivotal studies that assessed safety as a primary outcome.

7.3. Patient exposure

In Study M10-791, there were 190 subjects exposed to adalimumab, of whom 164 (86.3%) were exposed for ≥175 days, 147 (77.4%) were exposed for ≥343 days and 69 (36.3%) for ≥427 days. Total patient-years exposure was 193.3 years.

7.4. Adverse events

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

During the double blind phase there were 141 treatment emergent adverse events (TEAEs) reported in 55 (57.9%) subjects in the adalimumab group and 152 in 57 (58.8%) in the placebo. The most commonly reported TEAE was nasopharyngitis, occurring in 11 (11.6%) subjects (Table 3). There were 33 infectious AEs in 28 (29.5%) subjects in the adalimumab group (corresponding to 153.5 events per 100 patient years) and 38 in 28 (28.9%) subjects in the placebo group (corresponding to 171.2 events per 100 patient years). During the double blind phase there were no reports of serious infectious AE, opportunistic infections (excluding TB),

TB, lymphomas, Non-melanoma skin cancer (NMSC), malignancies (excluding NMSC and lymphomas) or demyelinating disease.

Table 3. Summary of TEAEs Experienced by ≥ 3% of Subjects During the double-blind (DB) 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)
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)

MedDRA= Medical Dictionary for Regulatory Activities

Throughout the study there were 797 TEAEs reported in 151 (79.5%) subjects treated with adalimumab (corresponding to an event rate of 412.3 per 100 patient years). The most commonly reported TEAEs were nasopharyngitis and spondylitis, occurring in 34 (17.9%) subjects and 20 (10.5%) respectively (Table 4). The infectious AEs were predominantly upper respiratory tract infections (Table5). There were three subjects with serious infectious AEs, one of which was TB. There were no reports of opportunistic infections (excluding TB), lymphomas, NMSC, malignancies (excluding NMSC and lymphomas) or demyelinating disease.

Table 4. Summary of TEAEs 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	34 (17.9)
Spondylitis[a]	20 (10.5)
Bronchitis	18 (9.5)
Headache	18 (9.5)
Diarrhea	16 (8.4)
Sinusitis	14 (7.4)
Upper respiratory tract infection	14 (7.4)
Nausea	13 (6.8)
Fatigue	10 (5.3)
Injection site reaction	10 (5.3)
Spondyloarthropathy[a]	10 (5.3)
Abdominal pain upper	9 (4.7)
Anxiety	8 (4.2)
Gastroenteritis	8 (4.2)
Insomnia	8 (4.2)
Rhinitis	8 (4.2)
Back pain	7 (3.7)
Cystitis	7 (3.7)
Injection site erythema	7 (3.7)
Myalgia	7 (3.7)
Pyrexia	7 (3.7)
Asthenia	6 (3.2)
Depression	6 (3.2)
Hypertension	6 (3.2)
Oropharyngeal pain	6 (3.2)
Pharyngitis	6 (3.2)
Pruritus	6 (3.2)
Urinary tract infection	6 (3.2)

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

Table 5. Summary of Treatment-Emergent Infections Experienced by >2 Subjects in Any Treatment Group by DB Period and Any Adalimumab Treatment throughout the Study (Safety Analysis Set; Any Adalimumab Safety Set)

	Number (%) of Subjects		
	DB 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)	100 (52.6)
Nasopharyngitis	3 (3.1)	11 (11.6)	34 (17.9)
Bronchitis	2 (2.1)	1 (1.1)	18 (9.5)
Upper respiratory tract infection	4 (4.1)	3 (3.2)	14 (7.4)
Sinusitis	2 (2.1)	1 (1.1)	14 (7.4)
Gastroenteritis	3 (3.1)	2 (2.1)	8 (4.2)
Rhinitis	2 (2.1)	2 (2.1)	8 (4.2)
Cystitis	0	0	7 (3.7)
Pharyngitis	0	3 (3.2)	6 (3.2)
Urinary tract infection	1 (1.0)	0	6 (3.2)
Influenza	0	2 (2.1)	5 (2.6)
Vaginal infection	1 (1.0)	0	5 (2.6)
Viral infection	2 (2.1)	0	5 (2.6)
Tonsillitis	2 (2.1)	1 (1.1)	4 (2.1)
Vulvovaginal mycotic infection	0	0	4 (2.1)
Oral herpes	0	2 (2.1)	3 (1.6)

During the double blind phase, injection site reaction related TEAEs were reported by eight (8.4%) subjects in the adalimumab group and three (3.1%) in the placebo. Overall, 19 (10.0%) subjects reported injection site AEs during treatment with adalimumab.

Nine (4.7%) subjects reported allergic reaction-related TEAEs following treatment with adalimumab and one subject during placebo (Table 6). Three of these reactions were considered to be possibly or probably related to treatment with adalimumab.

Table 6. Listing of Treatment-Emergent Allergic Reactions by Randomized Treatment Group (Safety Analysis Set)

Age/Sex/Race	Onset Study Period	Onset Day[a]	Duration (days)	Preferred Term	Severity	Serious? Yes/No	Relationship to Study Drug	Action Taken
33/M/W	DB	4	4	Eyelid edema	Mild	No	Probably related	None
61/M/W	OL	103	64	Pruritus	Severe	No	Probably related	Discontinued study drug
36/M/W	OL	89	2	Pruritus	Mild	No	Possibly related	Treated with Claratyne

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

During the double blind phase there were 63 treatment related TEAEs reported in 31 (32.6%) subjects in the adalimumab group and 39 in 21 (21.6%) in the placebo. Throughout the study there were 263 treatment related TEAEs reported in 86 (45.3%) subjects treated with adalimumab (corresponding to an event rate of 136.1 per 100 patient years). The most commonly reported treatment related TEAE occurring in subjects treated with adalimumab was nasopharyngitis, occurring in 20 (10.5%) subjects (Table 7).

Table 7. Summary of TEAEs 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	86 (45.3)
Eye disorders	
Conjunctivitis	2 (1.1)
Gastrointestinal disorders	
Diarrhea	5 (2.6)
Nausea	4 (2.1)
Aphthous stomatitis	3 (1.6)
General disorders and administrative site conditions	
Injection site reaction	10 (5.3)
Injection site erythema	7 (3.7)
Pyrexia	5 (2.6)
Fatigue	3 (1.6)
Asthenia	2 (1.1)
Injection site pain	2 (1.1)
Injection site pruritus	2 (1.1)
Infections and infestations	
Nasopharyngitis	20 (10.5)
Bronchitis	10 (5.3)
Sinusitis	10 (5.3)
Upper respiratory tract infection	9 (4.7)
Rhinitis	5 (2.6)
Gastroenteritis	4 (2.1)
Cystitis	3 (1.6)
Oral herpes	3 (1.6)
Vaginal infection	3 (1.6)
Vulvovaginal mycotic infection	3 (1.6)
Pharyngitis	2 (1.1)
Pneumonia	2 (1.1)
Tinea infection	2 (1.1)
Tonsillitis	2 (1.1)
Urinary tract infection	2 (1.1)
Vulvovaginal candidiasis	2 (1.1)
Musculoskeletal and connective tissue disorders	
Spondylitis[a]	2 (1.1)
Spondyloarthropathy[a]	2 (1.1)
Tendon pain	2 (1.1)
Nervous system disorders	
Headache	4 (2.1)
Respiratory, thoracic, and mediastinal disorders	
Oropharyngeal pain	5 (2.6)
Cough	2 (1.1)
Nasal congestion	2 (1.1)
Skin and subcutaneous tissue disorders	
Pruritus	3 (1.6)
Eczema	2 (1.1)
Vascular disorders	
Hypertension	2 (1.1)

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

7.4.3. Deaths and other serious adverse events

During the double blind phase there were no deaths. There were three serious AEs (SAEs) reported in three (3.2%) subjects in the adalimumab group and five in one (1.0%) subject in the placebo.

Throughout the study there were two deaths reported: one suicide 40 days after ceasing treatment; one on Day 649 (after the Week 68 cut off date) due to opioid toxicity. There were 24 SAEs reported in 19 (10.0%) subjects treated with adalimumab (corresponding to an event rate of 12.4 per 100 patient years). There was no clear pattern to the SAEs.

7.4.4. Discontinuation due to adverse events

During the double blind phase there was four discontinuation due to adverse events (DAEs) reported in two (2.1%) subjects in the adalimumab group and one in one (1.0%) subject in the placebo. Throughout the study there were 16 DAEs reported in 12 (6.3%) subjects treated with adalimumab (corresponding to an event rate of 8.3 per 100 patient years). There was no clear pattern to the AEs leading to discontinuation.

7.5. Laboratory tests

7.5.1. Liver function

During treatment with adalimumab three (1.6%) subjects had elevated alanine aminotransferase (ALT), two (1.1%) had elevated aspartate aminotransferase AST and two had elevated Gammaglutamyltransferase (GGT), reported as AEs.

7.5.2. Other clinical investigations

There were no clinically significant changes in haematology or clinical chemistry parameters.

7.5.3. Vital signs

There were no significant changes in the mean values for vital signs during the study.

7.6. Postmarketing experience

No postmarketing data were included in the submission.

7.7. Evaluator's overall conclusions on clinical safety

Exposure to adalimumab for the indication of nr-axSpA is limited, with total exposure being 190 subjects of whom 147 were exposed for ≥343 days and total patient-years exposure was 193.3 years.

The rate of TEAEs during the 12 week double blind phase was similar to that for placebo. The rate of infections was similar to that for placebo. Injection site related AEs were more common with adalimumab than placebo: 8.4% subjects compared with 3.1% respectively. These injection site reactions were mild in nature. Allergic reactions were more common with adalimumab than placebo: nine (4.7%) subjects compared with one respectively. The rate of SAEs was similar for the two treatment groups. The rate of DAE was similar for the two treatment groups.

Overall, in those subjects exposed to adalimumab the profile of AEs was similar to that previously reported for adalimumab. There were three subjects with serious infectious AEs, one of which was TB. There were no reports of opportunistic infections (excluding TB), lymphomas, NMSC, malignancies (excluding NMSC and lymphomas) or demyelinating disease.

There were two deaths during the study, neither of which appeared to be related to study treatment.

There were no new safety concerns apparent in the clinical data.

There were no indications of drug interactions, or of concomitant medication (including DMARDs) contributing to an increased risk of AEs.

The safety data is limited by the relatively small number of subjects exposed to adalimumab of the indication of nr-axSpA. However, the indication is similar to AS, and the patient group studied similar to others previously studied for other indications that adalimumab is already approved for. Hence, the adverse effects profile of adalimumab for the indication of nr-axSpA can be expected to be the same as that for the previously approved indications.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

Efficacy has been demonstrated for adalimumab in comparison with placebo for the indication of nr-axSpA over a 12 week period. The response rate was both clinically and statistically significant. The response was maintained in an open label follow-on study for up to 68 weeks. Response was greater in subjects with elevated CRP at baseline and with shorter duration of symptoms. For those subjects with no concomitant DMARDs at baseline (monotherapy) there were five (26.3%) responders in the adalimumab group and none in the placebo.

The indication of nr-axSpA could be considered to be an extension of AS, which is currently an approved indication for adalimumab. This supports the dose regimen chosen for development for nr-axSpA.

The primary efficacy outcome measure was ASAS40 response. This measure was a previously validated outcome measure and was developed independent of the development program. There were a large number of secondary outcome measures, all of which can be rationally applied to nr-axSpA. All of these outcome measures were supportive of efficacy compared with placebo over 12 weeks, and maintenance of efficacy for up to 68 weeks.

The limitations of the efficacy data include:

- Few elderly subjects were included in Study M10-791 (only two subjects over the age of 65 years)
- There were no analyses to investigate drug-drug or drug-disease interactions; and drug dose, drug concentration and relationship to response.
- Nr-axSpA is a chronic condition and there were no efficacy data extending beyond 68 weeks.

8.2. First round assessment of risks

Exposure to adalimumab for the indication of nr-axSpA is limited, with total exposure being 190 subjects of whom 147 were exposed for≥343, and total patient-years exposure was 193.3 years.

The rate of TEAEs during the 12 week double blind phase was similar to that for placebo. The rate of infections was similar to that for placebo. Injection site related AEs were more common with adalimumab than placebo: 8.4% subjects compared with 3.1% respectively. These injection site reactions were mild in nature. Allergic reactions were more common with adalimumab than placebo: nine (4.7%) subjects compared with one respectively. The rate of SAEs was similar for the two treatment groups. The rate of DAE was similar for the two treatment groups.

Overall, in those subjects exposed to adalimumab the profile of AEs was similar to that previously reported for adalimumab. There were three subjects with serious infectious AEs, one of which was TB. There were no reports of opportunistic infections (excluding TB), lymphomas, NMSC, malignancies (excluding NMSC and lymphomas) or demyelinating disease.

There were two deaths during the study, neither of which appeared to be related to study treatment.

There were no new safety concerns apparent in the clinical data.

There were no indications of drug interactions or of concomitant medication (including DMARDs) contributing to an increased risk of AEs.

The safety data is limited by the relatively small number of subjects exposed to adalimumab of the indication of nr-axSpA. However, the indication is similar to AS and the patient group studied similar to others previously studied for other indications that adalimumab is already approved for. Hence, the adverse effects profile of adalimumab for the indication of nr-axSpA can be expected to be the same as that for the previously approved indications.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, was considered to be favourable.

9. First round recommendation regarding authorisation

The evaluator recommended that adalimumab should be approved for the additional indication of:

Non-Radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in patients with non-radiographic axial spondyloarthritis.

10. Clinical questions

The only questions raised by the evaluator concerned the draft Product Information document and discussion of these are beyond the scope of this AusPAR.

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

11.1. Second round benefit-risk assessment

11.1.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of adalimumab in the proposed usage were considered to be unchanged from those identified in the First Round Evaluation.

11.1.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of adalimumab in the proposed usage were considered to be unchanged from those identified in the First Round Evaluation.

11.1.3. Second round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, was considered to be favourable.

11.2. Second round recommendation regarding authorisation

The evaluator recommended that adalimumab should be approved for the additional indication of:

Non-Radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in patients with non-radiographic axial spondyloarthritis.

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