London, 24 July 2014
EMA/562197/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Humira

Procedure no. EMEA/H/C/0481/II/127

Marketing authorisation holder (MAH): AbbVie Ltd.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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List of abbreviations

AAA	Anti-adalimumab antibody
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AST	Aspartate aminotransferase
CHMP	Committee for Medicinal Products for Human Use
CHQ-PF50	Child Health Questionnaire - PF50
CNS	Central nervous system
CRP	C-reactive protein
CTC	Common toxicity criteria
DICHAQ	Disability Index of Childhood Health Assessment Questionnaire
DMARD	Disease-modifying anti-rheumatic drug
ELISA	enzyme-linked immunosorbent assay
eow	Every other week
ET	Early termination
GCP	Good Clinical Practices
ILAR	International League of Associations for Rheumatology
ITT	Intent-to-treat
JIA	Juvenile idiopathic arthritis
LOM	Limitation of passive motion
MAH	Marketing Authorisation Holder
MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
OL	Open-label
PDCO	Paediatric Committee
PedACR	Pediatric American College of Rheumatology (scale)
PGA	Physician's global assessment
PIP	Pediatric investigational plan
PK	Pharmacokinetic
QRD	Quality review of documents
SAE	Serious adverse event
SC	Subcutaneous(ly)
SJC	Swollen joint count
SmPC	Summary of Product characteristics
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
VAS	Visual analog scale

1. Background information on the procedure

1.1. Type II variation

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

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Humira	adalimumab	See Annex A

The following variation was requested:

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

The MAH applied for an extension of the indication for the treatment of paediatric subjects with enthesitis-related arthritis (ERA), 6 years of age and older, who have had an inadequate response to, or are intolerant of, conventional therapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package leaflet.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/137/2013 and P/0259/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0259/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Kristina Dunder

Co-Rapporteur: Daniela Melchiorri

Evaluators:
Dr. Ulla Wändel-Liminga
Dr. Helena Möllby
Dr. Åsa Sullivan
Dr. Anette Bern

Evaluators:
Dr. Ciceroni Cinzia
Dr. Marco Massari
Dr. Sara Galluzzo

Submission date:	05 December 2013
Start of procedure:	20 December 2013
Rapporteur's preliminary assessment report circulated on:	13 February 2014
Co-Rapporteur's preliminary assessment report circulated on:	14 February 2014
Joint Rapporteur's updated assessment report circulated on:	14 March 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 March 2014
MAH's responses submitted to the CHMP on:	27 May 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	07 July 2014
PRAC RMP advice and assessment overview adopted by PRAC	10 July 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

2.1. Introduction

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically to the soluble and transmembrane forms of tumor necrosis factor (TNF)-α and inhibits the binding of TNF-α to its receptors.

Adalimumab is approved for the treatment of moderate to severe rheumatoid arthritis, active juvenile idiopathic arthritis, active and progressive psoriatic arthritis, severe ankylosing spondylitis, moderate to severe chronic plaque psoriasis, moderate to severe Crohn's disease, and moderate to severe ulcerative colitis (UC).

The currently approved JIA indication is for the reduction the signs and symptoms of moderately to severely active polyarticular JIA in children 4 years of age and older in the US, for children 2 years and older in the EU, and for children 4 to 17 years of age in Japan.

The MAH is applying for an extension of the indication for Humira as a treatment of "*enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy*".

Targeted disease

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology beginning before the age of 16 years, lasting more than 6 weeks and excluding other known conditions. Enthesitis-related arthritis

(ERA) is one of seven categories according to the classification made by the International League of Associations for Rheumatology (ILAR). The other categories are systemic JIA, oligoarthritis (persisted and extended), polyarthritis (RF positive and RF negative), psoriatic arthritis and undifferentiated arthritis. Approximately 3% to 11% of all JIA cases present as ERA, although the estimates are wide ranging (1.2% to 27.9%). A study in Canada showed that the mean age at diagnosis of JIA (all types) was 6.9 years and the mean age at diagnosis of enthesitis-related JIA was 11.7 years with a difference of 4.8 years.

ERA is defined by the ILAR as, arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:

1) the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain;

2) the presence of human leukocyte antigen-B27 (HLA-B27);

3) onset of arthritis in a male over 6 years of age;

4) acute (symptomatic) anterior uveitis;

5) history of ankylosing spondylitis (AS), ERA, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative.

In addition, the following conditions must not be present in order for a diagnosis of ERA to be made:

1) psoriasis (Ps) or a history of Ps in the patient or first-degree relative;

2) the presence of immunoglobulin M (IgM) RF on at least 2 occasions at least 3 months apart; and

3) the presence of systemic JIA in the patient.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase 3 Efficacy/ Safety	M11-328	5.3.1.1	Evaluate efficacy and safety of adalimumab SC vs. placebo in pediatric subjects with ERA and evaluate PK and immunogenicity of adalimumab in this subject population.	Randomized, double-blind, placebo-controlled multiple-center, multiple dose study with an OL rescue/extension period	Adalimumab 40 mg/0.8 mL (vial) doses administered SC (BSA dosing 24 mg/m2 up to a maximum of 40 mg) eow or matching placebo for adalimumab (0.8 mL, vial):	46	Pediatric subjects with ERA	12-week DB placebo-controlled period and OL period up to 144 weeks	Ongoing; Interim

ERA = enthesitis-related arthritis; PK = pharmacokinetic; SC = subcutaneous; BSA = body surface area; eow = every other week; OL = open-label

2.3.2. Pharmacokinetics

In the Phase 3 Study M11-328, pharmacokinetics and immunogenicity of adalimumab were evaluated through Week 52 in paediatric subjects at least 6 to <18 years old with active ERA. The influence of concomitant treatment with MTX was also evaluated.

A comparison with previous polyarticular juvenile idiopathic arthritis data was also made.

Analytical methods

Serum concentrations of adalimumab and AAA were determined using a validated enzyme-linked immunosorbent assay (ELISA) method. Only serum samples that had adalimumab levels <2.0 µg/mL were selected for AAA concentration measurement.

Pharmacokinetic data analysis

Pharmacokinetic data were analysed using population modelling in NONMEM. Observed plasma concentration data were also described with summary statistics.

Pharmacokinetics in target population

There were 46 subjects enrolled in Study M11-328. A total of 31 subjects were randomized to adalimumab and 15 subjects were randomized to placebo treatment group during the Blinded period (Week 0 to Week 12). Three subjects discontinued early from the study before Week 52.

A summary of demographic characteristics is given below (table 1).

Table 1:

		Mean ± SD (min – max)		
		All Subjects (N = 46)	**Adalimumab Treatment in Blinded Period (N = 31)**	**Placebo Treatment in Blinded Period (N = 15)**
Age (yr)		12.9 ± 2.9 (6 – 18)	13.4 ± 2.9 (6 – 18)	11.9 ± 2.9 (9 – 17)
Weight (kg)		49.4 ± 16.4 (21 – 90)	51.5 ± 15.4 (24 – 90)	44.9 ± 18.0 (21 – 84)
Height (cm)		154.0 ± 16.2 (117 – 183)	156.7 ± 16.2 (117 – 183)	148.5 ± 15.4 (119 – 176)
		N (%)		
Sex	Male	31 (67.4%)	22 (71%)	9 (60%)
	Female	15 (32.6%)	9 (29%)	6 (40%)
Race	White	35 (76.1%)	25 (80.6%)	10 (66.7%)
	Other	11 (23.9%)	6 (19.4%)	5 (33.3%)

Other = Asian, Black, Hispanic, Latino and Mestizo

Summaries of serum trough adalimumab concentration by treatment group in Study M11-328 are presented in table 2 and in figure 1.

Table2:

Treatment (Blinded Period)	Mean ± SD (Min – Max), N							
	Week							
	0	2	4	8	12	24	36	52
Adalimumab eow (N = 31)[a]	0 ± 0 (0 – 0), 29	3.84 ± 1.16 (1.12 – 6.51), 31	5.21 ± 2.60 (0 – 9.51), 31	7.74 ± 4.13 (0 – 14.9), 27	8.63 ± 4.56 (0 – 17.4), 31	10.3 ± 5.60 (0 – 20.2), 29	10.2 ± 5.83 (0 – 20.9), 27	10.2 ± 5.61 (0 – 21.9), 28
Placebo eow (N = 15)[b]	0 ± 0 (0 – 0), 13	0 ± 0 (0 – 0), 15	0 ± 0 (0 – 0), 13	0 ± 0 (0 – 0), 12	0 ± 0 (0 – 0), 14	8.71 ± 4.58 (0 – 14.2), 15	9.48 ± 4.59 (0 – 14.3), 14	10.4 ± 4.97 (0 – 16.9), 15

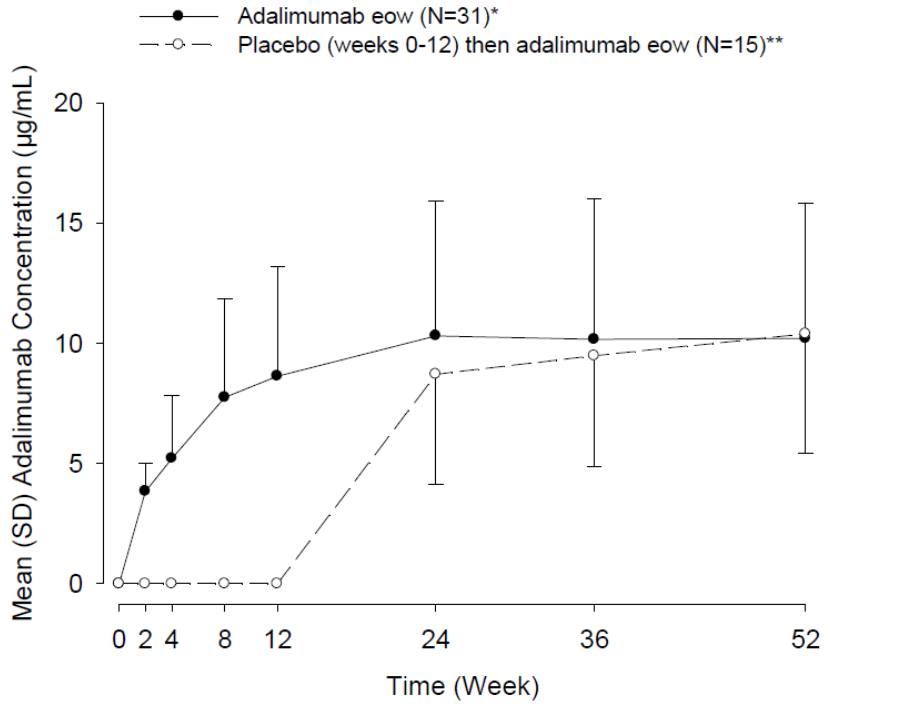
Adalimumab eow = Adalimumab eow Body surface area (BSA) dosing 24 mg/m^2 up to a maximum dose of 40 mg

Placebo eow = Placebo treatment group at Weeks 0 – 12 (Blinded period), then adalimumab eow BSA dosing 24 mg/m^2 up to a maximum dose of 40 mg starting at Week 12 in Open Label period.

a. Two subjects had early escape at Week 4 and two subjects had early escape at Week 8 (Table 14.1__1).

b. One subject had early escape at Week 4 and two subjects had early escape at Week 8 (Table 14.1__1).

Figure 1



* 2 subjects early escaped at Week 4 and 2 subjects early escaped at Week 8.
** One subject early escaped at Week 4 and 2 subjects early escaped at Week 8.

Summaries of serum trough adalimumab concentration (µg/mL) by treatment group and concomitant MTX in Study M11-328 are presented in the table 3.

Table 3:

Treatment (Blinded Period)	Concomitant MTX	Mean ± SD (Min – Max), N							
		Week							
		0	2	4	8	12	24	36	52
Adalimumab eow (N = 16)[a]	Yes	0 ± 0 (0 – 0), 15	3.99 ± 0.881 (3.09 – 6.08), 16	6.15 ± 1.43 (3.32 – 8.53), 16	9.04 ± 2.62 (3.91 – 13.0), 14	9.71 ± 4.25 (0.282 – 17.4), 16	11.8 ± 4.25 (0 – 20.2), 15	11.5 ± 4.27 (0 – 17.6), 14	11.0 ± 4.24 (0 – 15.9), 14
Adalimumab eow (N = 15)[b]	No	0 ± 0 (0 – 0), 14	3.67 ± 1.41 (1.12 – 6.51), 15	4.35 ± 3.29 (0 – 9.51), 15	6.35 ± 5.04 (0 – 14.9), 13	7.49 ± 4.75 (0 – 14.7), 15	8.75 ± 6.56 (0 – 19.2), 14	8.74 ± 7.05 (0 – 20.9), 13	9.43 ± 6.79 (0 – 21.9), 14
Placebo eow (N = 8)[c]	Yes	0 ± 0 (0 – 0), 7	0 ± 0 (0 – 0), 8	0 ± 0 (0 – 0), 6	0 ± 0 (0 – 0), 7	0 ± 0 (0 – 0), 8	8.02 ± 4.51 (0 – 13.8), 8	9.16 ± 4.67 (0 – 14.3), 8	10.3 ± 4.84 (0 – 15.6), 8
Placebo eow (N = 7)[d]	No	0 ± 0 (0 – 0), 7	0 ± 0 (0 – 0), 7	0 ± 0 (0 – 0), 7	0 ± 0 (0 – 0), 5	0 ± 0 (0 – 0), 6	9.49 ± 4.88 (0 – 14.2), 7	9.90 ± 4.88 (0 – 12.5), 6	10.5 ± 5.51 (0 – 16.9), 7

Adalimumab eow = Adalimumab eow Body surface area (BSA) dosing 24 mg/m^2 up to a maximum dose of 40 mg

Placebo eow = Placebo treatment group at Weeks 0 – 12 (Blinded period), then adalimumab eow BSA dosing 24 mg/m^2 up to a maximum dose of 40 mg starting at Week 12 in Open Label period.

a. 2 subjects had early escape at Week 4 (Table 14.1__1).

b. 2 subjects had early escape at Week 8 (Table 14.1__1).

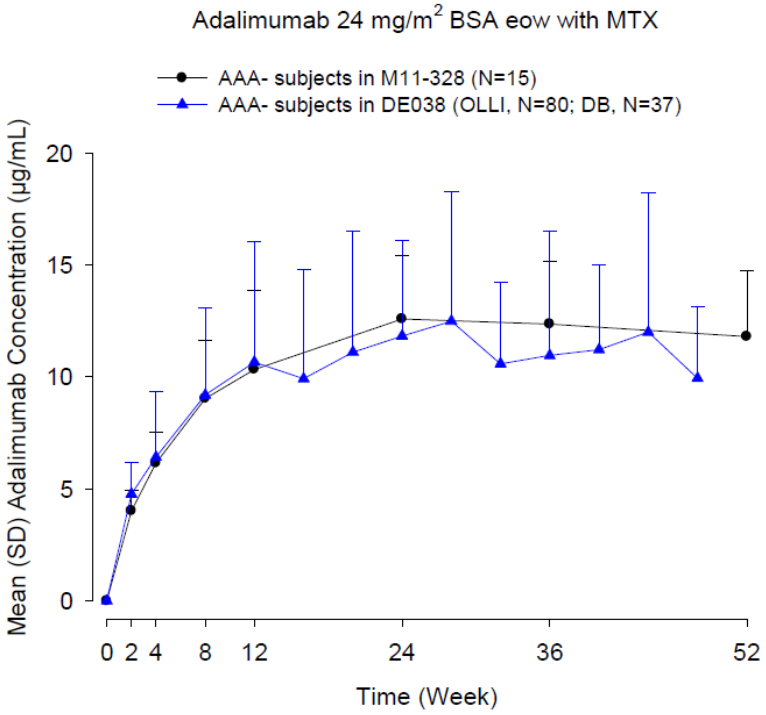
c. 1 subject had early escape at Week 4 (Table 14.1__1).

d. 2 subjects had early escape at Week 8 (Table 14.1__1).

Serum adalimumab concentrations at steady-state appeared to be slightly higher in subjects who received concomitant MTX compared to those who did not.

Study DE038 supported the use of adalimumab in JIA patients aged 4-17 years. DE038 was a multicenter, Phase 3, randomized, double-blind, stratified, parallel-group study in children (ages of 4 to 17 years) with polyarticular JIA. Comparison of serum trough adalimumab concentration by MTX in AAA negative subjects in Study M11-328 and Study DE038 is presented below (Figure 2).

Figure 2



Mean serum adalimumab concentrations observed in Study M11-328 appeared to be similar to those in Study DE038 in AAA negative subjects.

Influence of anti-adalimumab antibodies (AAA) on serum concentration of adalimumab

Among 46 subjects who had samples for pharmacokinetic analysis, 5 subjects were AAA+ during the 52-week of the study. Among the 5 subjects classified as AAA+, two received placebo for the first 12 weeks and then adalimumab treatment (one with MTX and one without), three received adalimumab treatment for 52 weeks (one with MTX and two without). The overall AAA+ rate was 10.9% (5/46) in patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to methotrexate. None of the subjects with an AAA+ sample escaped or terminated early from the study. Adalimumab trough concentrations were below LLOQ in all 5 AAA+ subject when they became AAA+. Two AAA– subjects had at least one adalimumab trough concentration below LLOQ between Week 24 and Week 52.

2.3.3. Pharmacodynamics

Adalimumab is a recombinant, fully human immunoglobulin (IgG1) monoclonal antibody that binds specifically to the soluble and transmembrane forms of tumor necrosis factor (TNF)-α and inhibits the binding of TNF-α to its receptors.

Paediatric dosing is supported by a single-use, 40 mg/0.8 mL vial for subcutaneous (SC) administration (for paediatric use only), which is already approved in the EU. The recommended dose of adalimumab in subjects with ERA is 24 mg/m^2 body surface area (BSA) up to a maximum of 40 mg every other week (eow). This dose was shown t be safe and efficacious in paediatric subjects in previous studies in children with pJIA and it is the dose used in Study M11-328, the first randomized, placebo-controlled study of adalimumab in the treatment of paediatric ERA.

2.3.4. Discussion on clinical pharmacology

The aim of study M11-328 was to evaluate the efficacy and safety of ADA given subcutaneously (sc) every other week (eow) as compared to placebo in paediatric subjects with ERA, and to examine the pharmacokinetics and immunogenicity of ADA following sc administration in this population. There were 46 subjects enrolled (31 subjects randomized to ADA and 15 subjects were randomized to placebo treatment group during the BD (Week 0 to Week 12).

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/mL with concomitant methotrexate.

The development of anti-adalimumab antibodies was associated with trough serum concentration falling below the lower limit of quantitation.

2.3.5. Conclusions on clinical pharmacology

Serum concentration of adalimumab was seen to increase over the first 12 weeks of dosing and steady state was reached between 12 and 24 weeks consistent with the half-life of adalimumab. At week 24, 36 and 52 the serum concentrations were comparable. The overall steady state concentration of adalimumab following eow dosing with 24 mg/m^2 of adalimumab was approximately 10 µg/mL. In subjects receiving MTX the serum trough concentration of adalimumab was slightly higher, about 30%.

The pharmacokinetics of adalimumab in paediatric subjects with Enthesitis Related Arthritis (ERA) is comparable to that of paediatric subjects with polyarticular JIA (i.e. the dose (4 mg/m² body surface

area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection) is considered appropriate from a PK point of view).

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

Study M11-328: A Double-Blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Adalimumab in Pediatric Subjects with Enthesitis Related Arthritis.

Methods

Study M11-328, is a Phase 3, multicenter study conducted in Canada, Mexico, and Europe in paediatric subjects with ERA who were at least 6 years but less than 18 years of age at Baseline. Enrollment is complete and the study is currently ongoing. The MAH provided an interim clinical study report (CSR). The CSR included the results of the study through the 12-week double-blind (DB) period and the open-label (OL) period up to Week 52.

Study participants

The study included paediatric subjects 6 – 17 years of age with ERA

Inclusion criteria were:

1. Age ≥ 6 to < 18 years at Baseline.
2. Diagnosis of ERA as defined by the ILAR prior to subject's sixteenth birthday.

- Subjects must have had disease activity as defined by the fulfillment of the following conditions:
- At least 3 active joints (swelling not due to deformity or joints with LOM + pain and/or tenderness).

3. Evidence of enthesitis in at least 1 location (either documented in the past or present at Baseline).
4. Inadequate response or intolerance to at least 1 nonsteroidal anti-inflammatory drug (NSAID). In addition, subject must also have had inadequate response or intolerance to at least 1 disease-modifying antirheumatic drug (DMARD), either sulfasalazine (SSZ) or MTX. Subjects who had a contraindication to SSZ or MTX use could be enrolled in the study.
5. Updated immunization schedule (abridged)
6. If female, an approved method of birth control (abridged)
7. Parent or legal guardian, as required, signed and dated an informed consent form (abridged).
8. Parent or legal guardian had to be willing to actively supervise storage and administration of study drug (abridged)
9. Subject was judged to be in good health as determined by the principal investigator (abridged)

10. Subject had a negative purified protein derivative (PPD) test and/or QuantiFERON-TB Gold test. If the subject had a positive (≥ 5 mm induration) PPD test and/or QuantiFERON-TB Gold test at Screening, a CXR (post anterior and lateral view) was to be performed for evaluation of active TB disease. If the subject had evidence of a latent TB infection, the subject was to initiate and complete a minimum of 2 weeks of an ongoing course of anti-TB therapy or was to have documented completion of a full course of anti-TB therapy prior to Baseline.

Subjects had to be able and willing to self-administer SC injections or had a qualified person available to administer SC injections.

Exclusion criteria were:

1. Subjects fulfilling a diagnosis of any ILAR JIA subtype other than ERA.
2. Ps or a history of Ps in the subject or first-degree relative.
3. Presence of IgM RF.
4. Presence of systemic JIA.
5. History of inflammatory bowel disease.
6. Previous biologic therapy, including anti-TNF therapy with a potential impact on pediatric ERA.
7. Diagnosis of acute inflammatory joint disease not associated with ERA.
8. Known hypersensitivity to adalimumab or its excipients.
9. Subject had received intra-articular joint injections with corticosteroids within 28 days prior to Baseline.
10. Joint surgery within 2 months prior to Baseline.
11. If entering the study on concomitant MTX or SSZ at Screening/Baseline, subject was not on stable dose of MTX (≤ 15 mg/m^2 with a maximum dose of 25 mg/week) or SSZ (≤ 50 mg/m^2 with a maximum dose of 3 g/day) for 28 days prior to Baseline.
12. Subject was on concomitant DMARDs other than MTX or SSZ within 28 days prior to Baseline.
13. If entering the study on concomitant prednisone (and/or prednisone equivalents), subject was not on a stable dose (≤ 10 mg/day or 0.2 mg/km body weight, whichever was lower) for 14 days prior to Baseline.
14. If entering the study on NSAIDs and/or analgesics, subject was on opioid analgesics within 14 days prior to Baseline or subject was not on stable dose for 14 days prior to Baseline.
15. Subject who had been treated with any investigational drug of chemical or biologic nature within 30 days or 5 half-lives (whichever was longer) of the drug prior to Baseline.
16. Subject had an infection requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the Baseline or oral anti-infectives within 14 days prior to Baseline.
17. History of invasive infection (e.g., listeriosis and histoplasmosis), human immunodeficiency syndrome (HIV).
18. History of moderate to severe congestive heart failure (CHF) (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 have put the subject at risk by participation in the protocol.

19. Evidence of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated nonmetastatic cutaneous squamous cell or basal carcinoma or localized carcinoma in situ of the cervix.
20. History of clinically significant drug or alcohol abuse in the last 12 months.
21. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
22. Positive pregnancy test at Screening or Baseline.
23. Female subject who was pregnant or breastfeeding or considering becoming pregnant during the study.
24. Subject was considered by the investigator, for any reason, to be an unsuitable candidate for the study.
25. Subject had received any live or live/attenuated vaccines within 90 days prior to Screening.
26. Subject with diagnosis and current symptoms of fibromyalgia.
27. Screening laboratory and other analyses that showed any of the following abnormal results:

    ECG with clinically significant abnormalities;

    Aspartate transaminase (AST) or alanine transaminase (ALT) > 1.75 × the upper limit of the reference range;

    Total bilirubin ≥ 3 mg/dL;

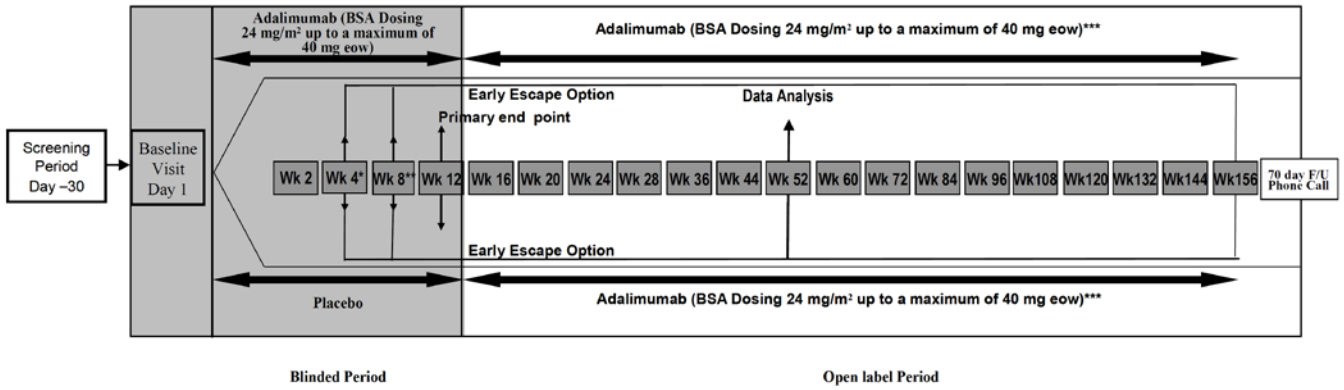
    Serum creatinine > 1.6 mg/dL (141.4 µmol/L);

    Clinically significant abnormal screening laboratory results as evaluated by the investigator.
28. Hepatitis B (HBV): hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the hepatitis B deoxyribonucleic acid polymerase chain reaction (HBV-DNA PCR) qualitative test for hepatitis B core antibody total (HBc Ab)/hepatitis B surface antibody (HBs Ab) positive subjects
29. Prior exposure to natalizumab (Tysabri) or efalizumab (Raptiva).
30. Chronic recurring infections or active TB.
31. Subjects with an active systemic viral infection or any active viral infection that, according to the investigator's clinical assessment, made the subject an unsuitable candidate for the study.

Treatments

Subjects who met enrollment criteria were randomized in a 2:1 ratio to receive either adalimumab (BSA dosing 24 mg/m^2 up to a maximum of 40 mg) eow or matching placebo via SC injection. An early escape option at Weeks 4 and 8 was provided for subjects who either experienced a worsening of disease or failed to improve. Worsening of disease at Week 4 is defined as increase in active joint count (AJC) ≥ 30% with a minimum of at least 2 additional active joints compared to Baseline. Failure to improve at Week 8 is defined as <30% improvement in AJC compared to Baseline.

Figure 3. Study Design Schematic



* Subjects fulfilling protocol defined criteria for worsening of ERA could early escape into OL period.
** Subjects who failed to demonstrate improvement in ERA could early escape into the OL period.
*** Each subject was planned to receive a maximum of 144 weeks of OL adalimumab. The OL period is to continue until Week 156 or until a subject has completed 108 weeks of treatment (from Baseline) or adalimumab has received country and local (if applicable) regulatory approval for ERA, whichever occurs first.

For subjects who completed the blinded period, the OL period began at the Week 12 visit. For subjects who met the criteria for early escape, the OL period began at the Week 4 or Week 8 visit (depending on when the criteria were met). During the OL period, each subject received OL adalimumab eow for a maximum of 144 weeks. Each subject in the study was to have a minimum of 108 weeks of treatment (Baseline to Final Visit) and a maximum of 156 weeks of treatment. If at the time of a subject's Week 108 visit or any subsequent study visit prior to Week 156, adalimumab received country and local regulatory approval for ERA, that visit was the termination visit for that subject.

Objectives

The objectives of this study were to evaluate the efficacy and safety of adalimumab given subcutaneously (SC) every other week (eow) as compared with placebo in paediatric subjects with enthesitis-related arthritis (ERA) and to examine the pharmacokinetics (PK) and immunogenicity of adalimumab following SC administration in this subject population.

Outcomes/endpoints

The primary efficacy variable was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of passive motion [LOM] + pain and/or tenderness)

Ranked secondary efficacy variables analyzed at Week 12 were:

1. Number of sites of enthesitis
2. Tender joint count (TJC) for 72 joints
3. Swollen joint count (SJC) for 68 joints
4. American College of Rheumatology (ACR) Pediatric (Pedi)30 response
5. ACR Pedi50 response
6. ACR Pedi70 response

Other supportive efficacy variables that represent the effect of adalimumab on multiple components of active ERA were assessed during the DB and OL periods of the study

- Number and percent change in active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) (component of ACR Pedi30) (excludes Week 12 as that was the primary variable)
- Number of sites of enthesitis (excluding Week 12)
- Spondyloarthritis Canadian Research Consortium (SPARCC) enthesitis index
- Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)
- TJC for 72 joints (excluding Week 12)
- SJC for 68 joints (excluding Week 12)
- Number of joints with LOM (component of ACR Pedi30)
- Number of digits with dactylitis
- ACR Pedi30/50/70 responses (excluding Week 12)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Inflammation (mean of questions 5 and 6 of the BASDAI)
- BASDAI50
- Physician's global assessment of disease activity (PGA) (component of ACR Pedi30)
- Patient's assessment of total back pain
- Parent's assessment of subject's pain
- High sensitivity C-reactive protein (hs-CRP) (component of ACR Pedi30)
- Parent's global assessment of subject's overall well-being (component of ACR Pedi30)
- Childhood Health Assessment Questionnaire (CHAQ) (component of ACR Pedi30)
- Parent's assessment of subject's eye disease
- Parent's assessment of subject's school attendance

Sample size

Approximately 45 paediatric patients with ERA were planned to be enrolled. With a total sample size of 45 subjects (2:1 randomization: adalimumab 30 subjects, placebo 15 subjects) and an expected percent change of 70% for adalimumab versus 35% for placebo, assuming common standard deviation (SD) of 33%, the study provided 90% power to detect the treatment difference using a 2-sided 1-way ANOVA with type 1 error level alpha = 5%.

Randomisation

An IVRS/IWRS was used to determine the randomization of subjects. Eligible subjects were randomized in a 2:1 DB fashion to adalimumab or placebo. Randomization was not stratified by site, because of the small expected number of subjects per site, or by any other stratification factor.

Blinding (masking)

The investigator, study site personnel, and the subject remained blinded to each subject's treatment throughout the blinded period of the study. The IVRS/IWRS was to provide access to blinded subject treatment information in the case of medical emergency.

Statistical methods

The primary and secondary variables were to be analysed for the intent-to-treat (ITT) population, defined as all randomized subjects who received at least 1 dose of study drug. A Per Protocol (PP) Analysis of the primary and secondary variables was added by Amendment 1 to the Statistical Analysis Plan (dated 20 November 2012) in order to evaluate the impact of major protocol violations on the results of the study. The identification of major protocol deviations was done before unblinding.

In the efficacy analyses, missing or incomplete data were handled using last observation carried forward (LOCF) as the primary method for continuous variables, nonresponder imputation (NRI) as the primary method for dichotomous variables, and as observed cases and LOCF as sensitivity analyses.

The primary efficacy variable was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness). The primary confirmatory analysis was done using an analysis of covariance (ANCOVA) model adjusting for the number of active joints at Baseline at alpha level of 0.05. For subjects who did not have an active joint count at Week 12 or who had escaped early to OL treatment, their last available joint count from the DB period was used.

For the comparison of secondary endpoints between the 2 treatment groups, Fisher's exact test was used for discrete variables, and 1-way ANOVA was used for continuous endpoints. Results in the OL period were reported stratified by the treatment the subject was randomized to in the DB period and overall.

Results

Participant flow

Table 4. Subject Disposition

	Subjects by Randomization Group		
Subject Status	**Placebo N = 15**	**Adalimumab N = 31**	**Total N = 46**
Subjects randomized, n	15	31	46
Completed Week 12 (DB period) and entered OL (ITT), n	12	27	39
Early escaped at Week 4 and entered OL, n	1	2	3
Early escaped at Week 8 and entered OL, n	2	2	4
Discontinued in DB period (up to Week 12) (ITT), n	0	0	0
Discontinued in OL period (up to Week 52) (ITT), n (%)	1 (6.7)	2 (6.5)	3 (6.5)
Primary reason for discontinuation during OL period (ITT), n (%)			
Adverse event	1 (6.7)	1 (3.2)	2 (4.3)
Lack of efficacy	0	1 (3.2)	1 (2.2)

a. Prematurely discontinued prior to or at Week 52.

Recruitment

46 subjects were recruited at 16 study sites in Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and Switzerland.

Conduct of the study

Five subjects were judged to have had major protocol deviations, i.e., protocol deviations with a potential impact on the primary variable of the study, and were excluded from the PP analysis set:

- One subject (adalimumab) violated exclusion criterion 11: If entering the study on concomitant MTX or SSZ at Screening/Baseline, subject not on stable dose of MTX (≤ 15 mg/m^2 with a maximum of 25 mg/week) or SSZ (≤50 mg/kg/day with a maximum of 3 g/day) for 28 days prior to Baseline. (Subject 17302 was on MTX 20 mg weekly from Day –16 to Day 28, when the dose was decreased to 17.5 mg.)
- One subject (adalimumab) received prohibited concomitant medication (opioid analgesic) during the DB period.
- Two subject (both adalimumab) violated inclusion criterion 4: Inadequate response or intolerance to at least 1 NSAID, either SSZ or MTX; subjects who have a contraindication to SSZ or MTX use may be enrolled.
- One subject (placebo) violated inclusion criterion 3: At least 3 active joints (swelling not due to deformity or joints with LOM plus pain and/or tenderness AND evidence of enthesitis in at least 1 location [either documented in past or present at Baseline]). (Subject had only 2 active joints at Baseline.)

Baseline data

Table 5. Demographic Characteristics (ITT)

	Placebo N = 15	Adalimumab N = 31	Total N = 46
Sex (n [%])			
Female	6 (40.0)	9 (29.0)	15 (32.6)
Male	9 (60.0)	22 (71.0)	31 (67.4)
P value[a]	0.514		
Mean age ± SD (years)	11.9 ± 2.85	13.4 ± 2.86	12.9 ± 2.92
P value[a]	0.091		
Age Group (n [%])			
6 to < 9 years	0	2 (6.5)	2 (4.3)
9 to < 12 years	8 (53.3)	5 (16.1)	13 (28.3)
12 to < 15 years	4 (26.7)	12 (38.7)	16 (34.8)
≥ 15 years	3 (20.0)	12 (38.7)	15 (32.6)
P value[a]	0.073		
Race (n [%])[b]			
White	10 (66.7)	25 (80.6)	35 (76.1)
Black	1 (6.7)	0	1 (2.2)
Asian	1 (6.7)	0	1 (2.2)
Other	3 (20.0)	6 (19.4)	9 (19.6)
P value[a]	0.462		
Mean body mass index (BMI) ± SD (kg/m^2)	19.7 ± 4.42	20.7 ± 4.33	20.4 ± 4.34
P value[a]	0.460		
Mean percentile on CDC growth chart ± SD	57.3 ± 36.51	54.4 ± 32.05	55.3 ± 33.18
P value[a]	0.787		

a. *P* value for differences between treatment groups from Fisher's exact test for categorical data and from 1-way ANOVA for continuous data.

b. Non-white races were combined for analysis of race.

Note: Percents calculated on non-missing values.

The majority of subjects in the ITT analysis set were male and white, with a mean age of 12.9 years. No statistically significant differences were observed between the placebo and adalimumab groups.

ERA history

Subjects reported having had symptoms of ERA for a mean of 2.6 years and had been diagnosed with ERA for a mean of 1.9 years prior to Baseline (table 6).

Table 6. Disease Duration (ITT)

Disease characteristic[a]	**Placebo N = 15**	**Adalimumab N = 31**	**Total N = 46**
Duration of ERA diagnosis (years)			
Mean ± SD	2.2 ± 2.44	1.7 ± 1.87	1.9 ± 2.06
Median (min – max)	1.3 (0.3 – 7.1)	0.8 (0.1 – 8.1)	0.8 (0.1 – 8.1)
P value		0.389	
Duration of ERA symptoms (years)			
Mean ± SD	2.7 ± 2.45	2.6 ± 2.25	2.6 ± 2.29
Median (min – max)	1.7 (0.4 – 7.6)	1.9 (0.3 – 9.2)	1.9 (0.3 – 9.2)
P value		0.868	

a. *P* value for differences between treatment groups from 1-way ANOVA.

All subjects were RF negative at Baseline (table 7). The majority of subjects had central laboratory testing for HLA-B27 and were found to be HLA-B27 positive. Subjects who had prior results for HLA-B27 testing were not required to repeat this genetic test; of the 3 subjects who did not have centrally performed HLA-B27 testing, 2 subjects were positive and 1 subject was negative on local testing. Most subjects were ANA negative at Baseline with the majority of those who were positive demonstrating a low-titer. All ANA positive subjects were anti–ds-DNA negative.

Table 7. Baseline RF, HLA-B27, ds-DNA, and ANA (ITT)

	Number (%) Subjects		
	Placebo N = 15	Adalimumab N = 31	Total N = 46
HLA-B27			
Negative	4 (26.7)	8 (28.6)	12 (27.9)
Positive	11 (73.3)	18 (64.3)	29 (67.4)
Equivocal[a]	0	2 (7.1)	2 (4.7)
RF			
Negative (< 14 KU/L)	15 (100)	31 (100)	46 (100)
Positive (≥ 14 KU/L)	0	0	0
ANA			
< 1:40 negative	7 (46.7)	20 (64.5)	27 (58.7)
1:40	4 (26.7)	7 (22.6)	11 (23.9)
1:80	2 (13.3)	0	2 (4.3)
1:160	2 (13.3)	2 (6.5)	4 (8.7)
1:320	0	2 (6.5)	2 (4.3)
ANA pattern[b]			
Homogene	5 (62.5)	5 (45.5)	10 (52.6)
Nucleolar	1 (12.5)	1 (9.1)	2 (10.5)
Speckled	2 (25.0)	5 (45.5)	7 (36.8)
ds-DNA[b]			
< 30 IU/mL	8 (100)	11 (100)	19 (100)
≥ 30 IU/mL	0	0	0

Note: Percents calculated on non-missing values.

a. If prior results were documented for HLA-B27 it was not performed at Screening. HLA-B27 tests reported as equivocal were to be considered negative per the central laboratory.

b. ANA patterns and ds-DNA were not done for subjects who tested ANA negative

Table 8. Summary of ERA Baseline Disease Activity Assessments (ITT)

	Placebo N = 15	Adalimumab N = 31	Total N = 46
PGA Visual Analog Scale (VAS) (0 – 100)			
Mean ± SD	52.6 ± 20.52	53.3 ± 22.47	53.1 ± 21.62
Median (min – max)	51.0 (23.0 – 95.0)	58.0 (1.0 – 90.0)	56.5 (1.0 – 95.0)
P value	0.917		
TJC (0 – 72)			
Mean ± SD	11.9 ± 9.34	13.4 ± 10.49	12.9 ± 10.05
Median (min – max)	8.0 (3.0 – 32.0)	9.0 (3.0 – 43.0)	8.0 (3.0 – 43.0)
P value	0.658		
SJC (0 – 68)			
Mean ± SD	5.2 ± 3.69	6.7 ± 7.30	6.2 ± 6.35
Median (min – max)	4.0 (2.0 – 15.0)	5.0 (0.0 – 34.0)	4.0 (0.0 – 34.0)
P value	0.446		
Joints with LOM (0 – 66)			
Mean ± SD	4.5 ± 4.05	5.1 ± 3.20	4.9 ± 3.47
Median (min – max)	4.0 (0.0 – 14.0)	5.0 (0.0 – 17.0)	4.5 (0.0 – 17.0)
P value	0.550		

	Placebo N = 15	Adalimumab N = 31	Total N = 46
Active joints with arthritis (0 – 68)			
Mean ± SD	6.7 ± 5.29	8.4 ± 7.12	7.8 ± 6.57
Median (min – max)	5.0 (2.0 – 21.0)	6.0 (2.0 – 36.0)	6.0 (2.0 – 36.0)
P value		0.411	
Sites of enthesitis (0 – 35)			
Mean ± SD	7.8 ± 7.49	8.3 ± 8.89	8.1 ± 8.38
Median (min – max)	5.0 (2.0 – 26.0)	4.0 (1.0 – 35.0)	4.0 (1.0 – 35.0)
P value		0.855	
MASES (0 – 13)			
Mean ± SD	3.0 ± 3.36	3.5 ± 4.15	3.4 ± 3.88
Median (min – max)	2.0 (0.0 – 11.0)	2.0 (0.0 – 13.0)	2.0 (0.0 – 13.0)
P value		0.659	
SPARCC enthesitis score (0 – 16)			
Mean ± SD	4.3 ± 3.46	4.5 ± 3.78	4.5 ± 3.64
Median (min – max)	4.0 (0.0 – 13.0)	4.0 (0.0 – 16.0)	4.0 (0.0 – 16.0)
P value		0.854	
Digits with dactylitis (0 – 20)			
Mean ± SD	0.1 ± 0.26	0.4 ± 1.48	0.3 ± 1.23
Median (min – max)	0.0 (0.0 – 1.0)	0.0 (0.0 – 8.0)	0.0 (0.0 – 8.0)
P value		0.367	
hs-CRP (mg/L)			
Mean ± SD	14.4 ± 23.67	6.3 ± 10.10	9.0 ± 16.03
Median (min – max)	7.0 (0.2 – 82.0)	1.7 (0.2 – 45.9)	2.6 (0.2 – 82.0)
P value		0.109	
Baseline BASDAI (0 – 10)			
Mean ± SD	4.7 ± 2.48	4.7 ± 2.49	4.7 ± 2.46
Median (min – max)	4.9 (0.2 – 9.1)	5.0 (0.7 – 8.9)	5.0 (0.2 – 9.1)
P value		0.947	

	Placebo N = 15	Adalimumab N = 31	Total N = 46
Inflammation (mean of BASDAI items 5 and 6) (0 – 10)			
Mean ± SD	4.1 ± 3.00	4.6 ± 3.03	4.4 ± 3.00
Median (min – max)	3.5 (0.0 – 10.0)	4.6 (0.0 – 9.6)	4.2 (0.0 – 10.0)
P value		0.556	
Total back pain VAS (0 – 100)			
Mean ± SD	34.9 ± 30.49	35.4 ± 30.04	35.2 ± 29.85
Median (min – max)	21.0 (0.0 – 92.0)	29.0 (0.0 – 90.0)	27.0 (0.0 – 92.0)
P value		0.962	
Overall well-being, VAS (0 – 100)			
Mean ± SD	49.0 ± 20.84	52.6 ± 25.15	51.4 ± 23.66
Median (min – max)	49.0 (19.0 – 76.0)	53.0 (0.0 – 98.0)	52.0 (0.0 – 98.0)
P value		0.633	
Subject's Pain, VAS (0 – 100)			
Mean ± SD	52.7 ± 27.23	57.3 ± 21.04	55.8 ± 23.03
Median (min – max)	54.0 (1.0 – 90.0)	55.0 (12.0 – 100.0)	55.0 (1.0 – 100.0)
P value		0.529	

Note: *P* value for differences between treatment groups from 1-way ANOVA.

Subjects reported having had symptoms of ERA for a mean of 2.6 years and had been diagnosed with ERA for a mean of 1.9 years prior to Baseline. No statistically significant differences were observed between treatment groups.

The majority of subjects reported prior use of a medication for ERA (Table 8). The most frequently reported (≥20% of all subjects) prior ERA medications were MTX, naproxen, SSZ, diclofenac, and ibuprofen.

Table 9. Prior ERA Medications Used by ≥ 5% of All Subjects (ITT)

Prior Medication	Placebo N = 15	Adalimumab N = 31	Total N = 46
Any prior ERA medication	14 (93.3)	28 (90.3)	42 (91.3)
MTX	6 (40.0)	13 (41.9)	19 (41.3)
Naproxen	4 (26.7)	10 (32.3)	14 (30.4)
SSZ	3 (20.0)	10 (32.3)	13 (28.3)
Diclofenac	4 (26.7)	7 (22.6)	11 (23.9)
Ibuprofen	4 (26.7)	7 (22.6)	11 (23.9)
Indometacin	3 (20.0)	6 (19.4)	9 (19.6)
Prednisone	3 (20.0)	6 (19.4)	9 (19.6)
Methylprednisolone	2 (13.3)	4 (12.9)	6 (13.0)
Deflazacort	1 (6.7)	4 (12.9)	5 (10.9)
Meloxicam	1 (6.7)	3 (9.7)	4 (8.7)
Triamcinolone	1 (6.7)	3 (9.7)	4 (8.7)

A total of 63.0% of subjects previously used DMARDs for their ERA, 69.6% previously used NSAIDs, and 45.7% previously used corticosteroids, with no statistically significant differences observed between treatment groups (Table 9). Of these subjects, the average number of different medications previously used was approximately 3 including at least 1 prior DMARD (MTX or SSZ), with no statistically significant difference observed between treatment groups.

Table 10. Summary of Number of Prior ERA Medications, Prior DMARD, NSAID, and Prior Systemic Corticosteroid Use (ITT)

Prior Medication	Placebo N = 15	Adalimumab N = 31	Total N = 46
Number of different medications per subject[a]			
N	14	28	42
Mean ± SD	2.9 ± 1.61	2.8 ± 1.64	2.8 ± 1.61
Median (min – max)	3 (1 – 6)	3 (1 – 7)	3 (1 – 7)
P value[b]		0.894	
Prior DMARD use, n (%)			
Yes	9 (60.0)	20 (64.5)	29 (63.0)
No	6 (40.0)	11 (35.5)	17 (37.0)
P value[c]		1.000	
Number of different prior DMARDs per subject[d]			
N	9	20	29
Mean ± SD	1.0 ± 0.00	1.2 ± 0.37	1.1 ± 0.31
Median (min – max)	1 (1 – 1)	1 (1 – 2)	1 (1 – 2)
P value[b]		0.235	
Prior NSAID use			
Yes	10 (66.7)	22 (71.0)	32 (69.6)
No	5 (33.3)	9 (29.0)	14 (30.4)
P value[c]		1.000	
Prior corticosteroid use[e]			
Yes	6 (40.0)	15 (48.4)	21 (45.7)
No	9 (60.0)	16 (51.6)	25 (54.3)
P value[c]		0.754	

a. Only for subjects with prior ERA medication.

b. *P* value for difference between treatment groups from 1-way ANOVA.

c. *P* value is for difference between treatment groups from Fisher's exact test.

d. Only for subjects with DMARDs as prior ERA medication.

e. Systemic corticosteroids include oral, injected and rectal preparations and do not include non-systemic preparations (opthalomologicals, dermatologicals, and inhalants).

Table 11. Summary of Concomitant DMARD, NSAID, and Corticosteroid Use (ITT)

	Placebo N = 15	Adalimumab N = 31	Total N = 46	
		n (%)		*P* value[a]
Concomitant DMARD use	11 (73.3)	21 (67.7)	32 (69.6)	1.000
Concomitant NSAID use	14 (93.3)	27 (87.1)	41 (89.1)	1.000
Concomitant corticosteroid use	5 (33.3)	10 (32.3)	15 (32.6)	1.000

a. *P* value for differences between treatment groups from Fisher's exact test.

Numbers analysed

Total number of analysed patients was 46 in the DB phase (15 patients randomized to PLB arm and 31 to ADA arm) whereas it was 43 in the OL phase (discontinuation of 1 patients in the PLB arm and of two patients in the ADA arm).

Outcomes and estimation

Primary efficacy endpoint

In the ITT analysis set (last observation carried forward [LOCF]), a statistically significantly larger decrease in mean percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) was observed in subjects in the adalimumab group (–62.6) compared with the placebo group (–11.6, *P* = 0.039)

A sensitivity analysis using the observed case analysis method, which included only those subjects with an active joint count at Week 12 (excludes early escapers), produced larger decreases in mean percent change from Baseline compared to the ITT (LOCF) analysis in both treatment groups (–32.1 with placebo versus –83.3 with adalimumab). These changes were also statistically significantly different.

Numerically superior, but not statistically significant results were demonstrated for the adalimumab group compared to the placebo group using the PP analysis set (LOCF), which excluded significant protocol violators. In this analysis the placebo group response was higher compared to the primary analysis (ITT [LOCF]) (mean percent change from Baseline –30.2 versus –11.6, respectively), but the response in the adalimumab group was similar in both analyses (and –66.0 versus –62.6, respectively).

Table 12. Percent Change from Baseline at Week 12 in Number of Active Joints with Arthritis (ITT and PP)

	Placebo		Adalimumab		Between Group Difference		
Week 12	**N**	**Mean % Change ± SD**	**N**	**Mean % Change ± SD**	**Difference**	**95% CI**	***P* Value[a]**
Primary analysis							
ITT (LOCF)	15	–11.6 ± 100.5	31	–62.6 ± 59.53	–51.17	–99.69, –2.66	0.039
Sensitivity analyses							
ITT (as observed)	12	–32.1 ± 100.72	27	–83.3 ± 24.85	–51.58	–93.60, –9.55	0.018
PP (LOCF)	14	–30.2 ± 72.38	27	–66.0 ± 57.29	–36.00	–78.31, 6.30	0.093

a. *P* value for difference between treatment groups from ANCOVA with treatment group and number of active joints at Baseline in the model.

Ranked secondary efficacy endpoints

While results for number of sites of enthesitis, TJC, SJC, ACR Pedi50 response, and ACR Pedi70 response were numerically superior in favor of adalimumab, none of the ranked secondary efficacy variables reached statistical significance at Week 12. Given the small sample size in this study, the positive trends observed support the efficacy of adalimumab in the ERA patient population.

Table 13. Mean Change from Baseline and Responder Status at Week 12 for Ranked Secondary Variables (ITT)

Ranked Variables 1 through 3 (LOCF)								
Variable		Baseline	Visit	Change from Baseline		Between Group Difference		
Treatment Group	N	Mean[a] ± SD	Mean[a] ± SD	Mean ± SD	Median (Min to Max)	Difference[b]	95% CI[c]	*P* value[d]
1. Number of sites of enthesitis								
Placebo	15	7.8 ± 7.49	5.1 ± 8.92	–2.7 ± 4.98	–4.0 (–12.0 to 11.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	3.9 ± 6.60	–4.4 ± 6.20	–3.0 (–22.0 to 12.0)	–1.62	(–5.32, 2.08)	0.382
2. TJC for 72 joints								
Placebo	15	11.9 ± 9.34	7.5 ± 8.06	–4.5 ± 8.97	–7.0 (–19.0 to 13.0)	--	--	--
Adalimumab	31	13.4 ± 10.49	5.5 ± 8.77	–7.9 ± 8.25	–6.0 (–28.0 to 8.0)	–3.40	(–8.78, 1.97)	0.209
3. SJC for 68 joints								
Placebo	15	5.2 ± 3.69	2.8 ± 2.83	–2.4 ± 4.66	–3.0 (–11.0 to 5.0)	--	--	--
Adalimumab	31	6.7 ± 7.30	3.2 ± 7.27	–3.5 ± 5.61	–3.0 (–19.0 to 9.0)	–1.12	(–4.49, 2.26)	0.509

Ranked Variables 4 through 6 (NRI)						
	N	Responder	Non-Responder	Difference[b]	95% CI[e]	*P* value[f]
4. ACR Pedi30						
Placebo	15	10 (66.7)	5 (33.3)	--	--	--
Adalimumab	31	21 (67.7)	10 (32.3)	1.1	(–27.9, 30.1)	1.000
5. ACR Pedi50						
Placebo	15	7 (46.7)	8 (53.3)	--	--	--
Adalimumab	31	20 (64.5)	11 (35.5)	17.8	(–12.5, 48.2)	0.341
6. ACR Pedi70						
Placebo	15	4 (26.7)	11 (73.3)	--	--	--
Adalimumab	31	16 (51.6)	15 (48.4)	24.9	(-3.5, 53.4)	0.128

a. Only subjects with both Baseline and visit values are shown.

b. Difference of adalimumab minus placebo.

c. 95% CI for difference of adalimumab minus placebo.

d. *P* value for differences between treatment groups from 1-way ANOVA.

e. 95% CI based on normal approximation.

f. *P* value for differences between treatment groups from Fisher's exact test.

Other efficacy variables

Other supportive efficacy variables that represent the effect of adalimumab on multiple components of active ERA were assessed during the 12-week DB period, as well as additional OL data available through Week 52. While few of these variables achieved statistical significance in favor of adalimumab at Week 12, the majority demonstrated trends in favor of adalimumab with results being sustained or improving further during the OL period.

Table 14. Change from Baseline in Number of Sites of Enthesitis (ITT; LOCF)

Visit Week		Baseline	Visit	Change from Baseline		Between Group Difference		
Treatment Group	N	Mean[a] ± SD	Mean[a] ± SD	Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	7.8 ± 7.49	5.1 ± 8.92	–2.7 ± 4.98	–4.0 (–12.0 to 11.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	3.9 ± 6.60	–4.4 ± 6.20	–3.0 (–22.0 to 12.0)	–1.62	(–5.32, 2.08)	0.382

Table 15. Change from Baseline in SPARCC Enthesitis Index (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	4.3 ± 3.46	1.9 ± 3.71	−2.4 ± 2.69	−2.0 (−9.0 to 3.0)	--	--	--
Adalimumab	31	4.5 ± 3.78	1.9 ± 3.18	−2.6 ± 3.30	−2.0 (−12.0 to 6.0)	−0.25	(−2.22, 1.73)	0.804

Table 16. Change from Baseline in MASES (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	3.0 ± 3.36	2.3 ± 3.71	−0.7 ± 2.28	−1.0 (−6.0 to 4.0)	--	--	--
Adalimumab	31	3.5 ± 4.15	1.8 ± 3.06	−1.7 ± 2.61	−1.0 (−9.0 to 2.0)	−1.01	(−2.60, 0.58)	0.208

Table 17. Change from Baseline in TJC (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	11.9 ± 9.34	7.5 ± 8.06	−4.5 ± 8.97	−7.0 (−19.0 to 13.0)			
Adalimumab	31	13.4 ± 10.49	5.5 ± 8.77	−7.9 ± 8.25	−6.0 (−28.0 to 8.0)	−3.40	(−8.78, 1.97)	0.209

Table 18. Change from Baseline in SJC (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	5.2 ± 3.69	2.8 ± 2.83	−2.4 ± 4.66	−3.0 (−11.0 to 5.0)			
Adalimumab	31	6.7 ±7.30	3.2 ± 7.27	−3.5 ± 5.61	−3.0 (−19.0 to 9.0)	−1.12	(−4.49, 2.26)	0.509

Table 19. Change from Baseline in Number of Joints with LOM (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	4.5 ± 4.05	3.4 ± 3.27	−1.1 ± 3.77	−1.0 (−8.0 to 5.0)			
Adalimumab	31	5.1 ± 3.20	1.9 ± 2.60	−3.3 ± 3.89	−2.0 (−17.0 to 3.0)	−2.19	−4.63, 0.25	0.077

Table 20. Change from Baseline in Number of Digits with Dactylitis (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	0.1 ± 0.26	0.1 ± 0.26	0.0 ± 0.00	0.0 (0.0 to 1.0)			
Adalimumab	31	0.4 ± 1.48	0.1 ± 0.36	−0.4 ± 1.54	0.0 (−8.0 to 2.0)	−0.35	−1.16, 0.45	0.380

Table 21. ACR Pedi30/50/70 Responses (ITT; NRI)

Visit Week Treatment Group	N	Responder	Non-Responder	Between Group Difference Difference[a]	 95% CI[b]	 *P* value[c]
ACR Pedi30						
DB Period						
Week 12						
Placebo	15	10 (66.7)	5 (33.3)			
Adalimumab	31	21 (67.7)	10 (32.3)	1.1	−27.9, 30.1	1.000
OL Period						
Week 24						
Placebo	15	14 (93.3)	1 (6.7)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	41 (89.1)	5 (10.9)	−6.2	−23.5, 11.0	1.000
Week 36						
Placebo	15	13 (86.7)	2 (13.3)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	40 (87.0)	6 (13.0)	0.4	−20.4, 21.3	1.000
Week 52						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	26 (83.9)	5 (16.1)			
Total	46	38 (82.6)	8 (17.4)	3.9	−20.2, 27.9	1.000
ACR Pedi50						
DB Period						
Week 12						
Placebo	15	7 (46.7)	8 (53.3)			
Adalimumab	31	20 (64.5)	11 (35.5)	17.8	−12.5, 48.2	0.341
OL Period						
Week 24						
Placebo	15	13 (86.7)	2 (13.3)			
Adalimumab	31	26 (83.9)	5 (16.1)			
Total	46	39 (84.8)	7 (15.2)	−2.8	−24.3, 18.7	1.000
Week 36						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	39 (84.8)	7 (15.2)	7.1	−16.3, 30.5	0.667
Week 52						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	26 (83.9)	5 (16.1)			
Total	46	38 (82.6)	8 (17.4)	3.9	−20.2, 27.9	1.000
ACR Pedi70						
DB Period						
Week 12						
Placebo	15	4 (26.7)	11 (73.3)			
Adalimumab	31	16 (51.6)	15 (48.4)	24.9	−3.5, 53.4	0.128
OL Period						
Week 24						
Placebo	15	10 (66.7)	5 (33.3)			
Adalimumab	31	23 (74.2)	8 (25.8)			
Total	46	33 (71.7)	13 (28.3)	7.5	−20.9, 35.9	0.730
Week 36						
Placebo	15	9 (60.0)	6 (40.0)			
Adalimumab	31	25 (80.6)	6 (19.4)			
Total	46	34 (73.9)	12 (26.1)	20.6	−7.8, 49.1	0.165
Week 52						
Placebo	15	11 (73.3)	4 (26.7)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	35 (76.1)	11 (23.9)	4.1	−22.7, 30.9	1.000

Table 22. Change from Baseline in BASDAI (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline Mean ± SD	 Median (Min to Max)	Between Group Difference Difference[b]	 95% CI	 *P* value[c]
DB Period								
Week 12								
Placebo	15	4.7 ± 2.48	3.3 ± 2.23	−1.4 ± 2.18	−0.9 (−6.9 to 1.2)			
Adalimumab	31	4.7 ± 2.49	2.2 ± 2.56	−2.5 ± 2.80	−1.8 (−8.0 to 2.4)	−1.14	−2.80, 0.52	0.173

Table 23. Change from Baseline in Inflammation (Mean of BASDAI Items 5 and 6) (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline Mean ± SD	 Median (Min to Max)	Between Group Difference Difference[b]	 95% CI	 *P* value[c]
DB Period								
Week 12								
Placebo	15	4.1 ± 3.00	2.7 ± 2.19	−1.3 ± 2.14	−0.8 (−6.0 to 1.4)			
Adalimumab	31	4.6 ± 3.03	1.6 ± 2.21	−3.0 ± 3.06	−2.1 (−8.8 to 1.0)	−1.69	−3.46, 0.09	0.062

Table 24. BASDAI50 Response (ITT; NRI)

Visit Week Treatment Group	N	Responder (%)	Non-Responder (%)	Between Group Difference		
				Difference[a]	95% CI[b]	*P* value[c]
DB Period						
Week 12						
Placebo	15	4 (26.7)	11 (73.3)			
Adalimumab	31	19 (61.3)	12 (38.7)	34.6	6.4, 62.8	0.057

Table 25. Change from Baseline in PGA (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	52.6 ± 20.52	30.5 ± 30.83	–22.1 ± 23.27	–27.0 (–56.0 to 21.0)			
Adalimumab	31	53.3 ± 22.47	22.0 ± 25.76	–31.4 ± 24.76	–32.0 (–66.0 to 19.0)	–9.29	–24.69, 6.12	0.231

Table 26. Change from Baseline in Patient's Assessment of Back Pain (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	14	37.4 ± 30.10	27.9 ± 21.50	–9.5 ± 23.89	–8.5 (–65.0 to 32.0)			
Adalimumab	28	33.4 ± 28.49	18.8 ± 25.85	–14.6 ± 24.18	–9.0 (–73.0 to 25.0)	–5.14	(–21.08, 10.79)	0.518

Table 27. Change from Baseline in Parent's Assessment of Subject's Pain (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	52.7 ± 27.23	32.8 ± 23.66	–19.9 ± 21.69	–19.0 (–72.0 to 11.0)			
Adalimumab	31	57.3 ± 21.04	24.8 ± 31.18	–32.5 ± 28.98	–36.0 (–86.0 to 26.0)	–12.65	(–29.68, 4.39)	0.142

Table 28. Change from Baseline in hs-CRP (mg/L) (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	14.4 ± 23.67	9.6 ± 16.43	–4.8 ± 23.12	–0.2 (–56.3 to 54.3)			
Adalimumab	31	6.3 ± 10.10	6.8 ± 17.38	0.4 ± 16.39	–0.3 (–25.7 to 73.6)	5.26	(–6.65, 17.18)	0.378

Only 18 subjects (placebo 8, adalimumab 10) had elevated hs-CRP at Baseline.

Table 29. Change from Baseline in CHAQ (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	0.8 ± 0.48	0.7 ± 0.46	–0.1 ± 0.41	–0.1 (–0.6 to 0.8)			
Adalimumab	31	0.8 ± 0.68	0.5 ± 0.65	–0.2 ± 0.56	–0.3 (–1.6 to 1.1)	–0.18	(–0.51, 0.14)	0.263

Table 30. Change from Baseline in Parent's Global Assessment of Subject's Overall Well-Being (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min – Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	49.0 ± 20.84	32.5 ± 22.86	–16.5 ± 10.53	–18.0 (–36.0 to 0.0)			
Adalimumab	31	52.6 ± 25.15	23.4 ± 28.97	–29.2 ± 29.78	–28.0 (–87.0 to 32.0)	–12.73	–28.76, 3.31	0.117

Parent's Assessment of Subject's Eye Disease

Parent's assessment of subject's eye disease was only done for those subjects who reported eye disease in connection with their ERA at a given visit. Three subjects (all randomized to placebo) reported a past history of uveitis at Baseline and during the study, 2 of these subjects reported eye disease in connection with their ERA; one at Week 2 and both from Week 8 to Week 52. As very few subjects experienced uveitis through Week 52, no conclusions can be made from this data regarding the effect of adalimumab on improvement in uveitis symptoms. However, at Week 52 clinically significant improvement in the parent's assessment of subject's eye disease in terms of the subject's ability to function normally as measured on a VAS was observed for these 2 subjects.

Parent's Assessment of Subject's School Attendance

No statistically significant differences were observed between groups at any timepoint during the DB period for any analysis of parent's assessment of subject's school attendance.

When looking at days lost since Baseline to Week 12, both groups missed the same mean number of days from school (3.4 days). When missing values were included as 0, results were similar. When missing values were not included, subjects in the adalimumab group missed fewer days than did subjects in the placebo group (3.3 versus 5.4, respectively). An average of 5 days missed from school per year is reported in healthy children and a United Kingdom study reported that children with JIA miss approximately 15 days a year from school, which was similar to other chronic diseases such as asthma. During the OL period, subjects with any exposure to adalimumab lost an average of 7.8 days from school (days lost since Baseline visit) by Week 52 which is approximately half of that reported for children with JIA overall. Results were similar without missing values and with missing values set to 0. Data were similar using as observed analysis (ITT).

Ancillary analyses

Comparison of results in subpopulations

Subgroup analysis of the primary efficacy variable was done by age, sex, race, HLA-B27 status, hs-CRP status, concomitant DMARD or NSAID use at Baseline, and BMI. Statistically significant differences were observed within subgroups as follows:

- Male subjects in the adalimumab group had a greater percent decrease in the number of active joints with arthritis than males in the placebo group.
- White subjects in the adalimumab group had a greater percent decrease in the number of active joints with arthritis than white subjects in the placebo group.
- HLA-B27 positive subjects in the adalimumab group had a greater percent decrease in the number of active joints with arthritis than HLA-B27 positive subjects in the placebo group. The 3 subjects who did not have centrally performed HLA-B27 were excluded from this analysis.
- Subjects with concomitant NSAID use at Baseline in the adalimumab group had a greater percent decrease in the number of active joints with arthritis than subjects with concomitant NSAID use at Baseline in the placebo group.
- Subjects in the adalimumab group who had a healthy weight at Baseline had a greater percent decrease than subjects with a healthy weight at Baseline in the placebo group.

Overall, sample sizes were too small to provide definitive conclusions regarding differences in benefit between subgroup categories. However, the following trends were noted when comparing mean percent change from Baseline to Week 12 in the number of active joints with arthritis for subgroups within the adalimumab group:

- Subjects who were 6 to < 9 years old (N = 2) had a higher response (mean percent change –84.9) than older subgroups (–58.9 to –63.4, N = 5 – 12 per subgroup).
- A higher response was observed with adalimumab among males (N = 22, mean percent change –70.4) than females (N = 9, mean percent change –43.7).
- Healthy weight (N = 22) and overweight (N = 2) subjects had a higher response (mean percent change –68.0 and –71.9, respectively) than underweight subjects (N = 2) and obese subjects (N = 5) (mean percent change –31.9 and –47.3, respectively).

Table 31. Percent Change from Baseline at Week 12 in Number of Active Joints with Arthritis - Subgroup Analysis (ITT; LOCF)

Subgroup	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[c]	95% CI	*P* Value[d]
Age Categories								
6 to < 9 Years								
Placebo	0	--	--	--	--			
Adalimumab	2	15.0 ± 5.66	2.5 ± 2.12	–84.9 ± 8.46	–84.9 (–90.9 to –78.9)	--	--	--
9 to < 12 Years								
Placebo	8	5.9 ± 2.10	4.0 ± 4.47	–30.6 ± 80.63	–58.3 (–100.0 to 120.0)			
Adalimumab	5	8.0 ± 7.14	3.0 ± 3.46	–63.4 ± 17.95	–66.7 (–88.9 to –40.0)	–32.82	–114.66, 49.02	0.396
12 to < 15 Years								
Placebo	4	3.0 ± 0.82	3.5 ± 3.11	35.4 ± 151.90	–4.2 (–100.0 to 250.0)			
Adalimumab	12	7.0 ± 4.73	3.2 ± 6.55	–58.9 ± 70.46	–92.9 (–100.0 to 100.0)	–94.37	–210.83, 22.10	0.104
≥ 15 Years								
Placebo	3	13.7 ± 8.74	5.7 ± 1.15	–23.3 ± 85.22	–68.8 (–76.2 to 75.0)			
Adalimumab	12	8.8 ± 9.16	5.5 ± 11.42	–62.2 ± 66.86	–100.0 (–100.0 to 72.7)	–38.88	–136.50, 58.74	0.405
Sex								
Male								
Placebo	9	4.2 ± 1.72	3.4 ± 3.64	–3.7 ± 115.18	–50.0 (–100.0 to 250.0)			
Adalimumab	22	7.4 ± 5.59	2.3 ± 4.49	–70.4 ± 48.15	–88.3 (–100.0 to 72.7)	–66.65	–125.78, –7.52	0.028
Female								
Placebo	6	10.3 ± 6.83	5.3 ± 3.50	–23.3 ± 82.33	–54.4 (–100.0 to 120.0)			
Adalimumab	9	10.8 ± 9.93	8.1 ± 13.07	–43.7 ± 81.45	–88.9 (–100.0 to 100.0)	–20.34	–113.46, 72.79	0.645
Race								
White								
Placebo	10	6.6 ± 5.52	4.6 ± 3.10	4.2 ± 105.23	–36.7 (–100.0 to 250.0)			
Adalimumab	25	6.8 ± 4.07	2.9 ± 5.84	–61.0 ± 64.00	–90.9 (–100.0 to 100.0)	–65.17	–124.13, –6.21	0.031
Non-white								
Placebo	5	6.8 ± 5.40	3.4 ± 4.72	–43.1 ± 92.59	–68.8 (–100.0 to 120.0)			
Adalimumab	6	15.0 ± 12.62	8.5 ± 14.38	–69.5 ± 39.11	–82.3 (–100.0 to 2.8)	–26.40	–119.90, 67.11	0.539
HLA-B27 status								
Positive								
Placebo	11	6.3 ± 5.41	4.2 ± 3.25	–4.5 ± 104.13	–40.0 (–100.0 to 250.0)			
Adalimumab	18	8.3 ± 5.96	3.3 ± 6.47	–69.3 ± 54.99	–94.4 (–100.0 to 75.0)	–64.80	–125.22, –4.38	0.036
Negative								
Placebo	4	7.8 ± 5.56	4.3 ± 4.99	–30.9 ± 101.53	–71.9 (–100.0 to 120.0)			
Adalimumab	8	11.3 ± 10.39	6.6 ± 12.92	–54.6 ± 71.30	–86.4 (–100.0 to 100.0)	–23.64	–134.91, 87.63	0.646
hs-CRP status								
Normal								
Placebo	7	6.9 ± 4.63	4.3 ± 3.73	–24.6 ± 75.12	–40.0 (–100.0 to 120.0)			
Adalimumab	21	8.6 ± 5.54	3.3 ± 6.12	–65.9 ± 58.61	–90.9 (–100.0 to 75.0)	–41.35	–97.69, 15.00	0.144

Subgroup	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline[b] Mean ± SD	Change from Baseline[b] Median (Min to Max)	Between Group Difference Difference[c]	Between Group Difference 95% CI	Between Group Difference *P* Value[d]
Above upper limit of normal								
Placebo	8	6.5 ± 6.12	4.1 ± 3.72	–0.1 ± 122.66	–58.3 (–100.0 to 250.0)			
Adalimumab	10	7.9 ± 10.02	5.5 ± 11.65	–55.6 ± 64.03	–76.2 (–100.0 to 100.0)	–55.48	–150.28, 39.33	0.233
Concomitant DMARD use at Baseline								
Yes								
Placebo	11	6.5 ± 5.35	3.7 ± 3.47	–15.9 ± 107.36	–50.0 (–100.0 to 250.0)			
Adalimumab	21	6.5 ± 4.50	2.9 ± 5.99	–64.0 ± 58.65	–90.9 (–100.0 to 75.0)	–48.13	–107.67, 11.41	0.109
No								
Placebo	4	7.3 ± 5.85	5.5 ± 4.12	0.3 ± 91.97	–21.9 (–75.0 to 120.0)			
Adalimumab	10	12.3 ± 9.93	6.4 ± 11.56	–59.7 ± 64.45	–82.9 (–100.0 to 100.0)	–60.00	–153.22, 33.22	0.186
Concomitant NSAID use at Baseline								
Yes								
Placebo	13	6.9 ± 5.65	4.8 ± 3.52	0.1 ± 103.19	–40.0 (–100.0 to 250.0)			
Adalimumab	24	8.4 ± 7.53	4.3 ± 8.57	–59.4 ± 59.00	–80.9 (–100.0 to 100.0)	–59.49	–133.37, –5.62	0.031
No								
Placebo	2	5.0 ± 1.41	0.5 ± 0.71	–87.5 ± 17.68	–87.5 (–100.0 to –75.0)			
Adalimumab	7	8.3 ± 5.96	2.9 ± 7.13	–73.7 ± 64.72	–100.0 (–100.0 to 72.7)	13.76	--	--

Subgroup	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline Mean ± SD	Change from Baseline Median (Min to Max)	Between Group Difference Difference[c]	Between Group Difference 95% CI	Between Group Difference *P* Value[d]
BMI								
Underweight < 5th percentile								
Placebo	2	6.5 ± 4.95	3.5 ± 3.54	–53.3 ± 18.86	–53.3 (–66.7 to –40.0)			
Adalimumab	2	19.5 ± 23.33	19.0 ± 25.46	–31.9 ± 49.10	–31.9 (–66.7 to 2.8)	–21.39	--	--
Healthy weight 5th to < 85th percentile								
Placebo	7	6.3 ± 4.64	4.6 ± 3.31	12.8 ± 118.86	–33.3 (–100.0 to 250.0)			
Adalimumab	22	6.0 ± 2.95	2.6 ± 5.91	–68.0 ± 58.44	–100.0 (–100.0 to 75.0)	–80.82	–148.60, –13.04	0.021
Overweight 85th to < 95th percentile								
Placebo	6	7.2 ± 6.85	4.0 ± 4.47	–26.0 ± 97.35	–75.6 (–100.0 to 120.0)			
Adalimumab	2	14.5 ± 7.78	5.0 ± 5.66	–71.9 ± 23.96	–71.9 (–88.9 to –55.0)	–45.91	--	--
Obese ≥ 95th percentile								
Placebo	0	--	--	--	--			
Adalimumab	5	11.8 ± 7.60	3.6 ± 4.93	–47.3 ± 83.30	–78.9 (–100.0 to 100.0)	--	--	--

Note: Data are not available for the 3 subjects for which testing was done prior to study entry and not reported in the database.

a. Only subjects with both Baseline and visit values are shown.

b. Subjects with a 0 score at Baseline are not included in the analysis of % change.

c. % change from Baseline in adalimumab treated subjects minus % change from Baseline in placebo treated subjects.

d. *P* value for difference between treatment groups from 1-way ANOVA.

Summary of main study

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

Table 32. Summary of Efficacy for trial M 11-328

Title: "A Double-Blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Adalimumab in Pediatric Subjects with Enthesitis Related Arthritis"	
Study identifier	M 11-328
Design	Multicenter, double-blind (DB), placebo controlled. Interim result from the DB period and the open-label (OL) period up to Week 52 submitted with the current application.

	Duration of main phase: Duration of run-in phase: Duration of extension phase:		12-weeks not applicable Ongoing, until Week 156 or until a subject has completed 108 weeks of treatment (from Baseline) or until adalimumab received country and local (if applicable) regulatory approval for ERA
Hypothesis	Superiority		
Treatment groups	Adalimumab		body surface area [BSA] eow dosing 24 mg/m2 up to a maximum of 40 mg 12 weeks early escape option at Weeks 4 (worsening)and 8 (not improved) number randomized: 31
	Placebo		Placebo SC eow 12 weeks number randomized:15
Endpoints and definitions	Primary endpoint	% change in active joint count	mean percent change from Baseline to Week 12 in the number of active joints with arthritis
	Secondary endpoint	Number of sites of enthesitis	Change in number of sites of enthesitis
	Secondary endpoint	TJC	Change in tender joint count for 72 joints
	Secondary endpoint	SJC	Change in swollen joint count for 68 joints
	Secondary endpoint	Pedi30	American College of Rheumatology (ACR) Pediatric 30 response
	Secondary endpoint	Pedi50	American College of Rheumatology (ACR) Pediatric 50 response
	Secondary endpoint	Pedi70	American College of Rheumatology (ACR) Pediatric 70 response
Database lock	Not found. Last Subject Last Visit: 29 November 2012		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	ITT (all subjects who were randomized and received at least 1 dose of study drug) at week 12 LOCF			
Descriptive statistics and estimate variability	Treatment group	adalimumab	placebo	
	Number of subjects	31	15	
	% change in active joint count	–62.6	–11.6	
	Number of sites of enthesitis (SD)	–4.4 (± 6.20)	–2.7 (± 4.98)	
	TJC (SD)	–7.9 (± 8.25)	–4.5 (± 8.97)	

	SJC (SD)	–3.5 (± 5.61)	–2.4 (± 4.66)	
	Pedi30 (%)	21 (67.7)	10 (66.7)	
	Pedi50 (%)	20 (64.5)	7 (46.7)	
	Pedi70 (%)	16 (51.6)	4 (26.7)	

Effect estimate per comparison	Primary endpoint % change in active joint count	Comparison groups	Adalimumab vs placebo
		Difference	–51.17
		95% CI	(–99.69, –2.66)
		P-value	0.039
	Secondary endpoint Number of sites of enthesitis	Comparison groups	Adalimumab vs placebo
		Between group difference	–1.62
		95% CI	(–5.32, 2.08)
		P-value	0.382
	Secondary endpoint TJC	Comparison groups	Adalimumab vs placebo
		Between group difference	–3.40
		95% CI	(–8.78, 1.97)
		P-value	0.209
	Secondary endpoint SJC	Comparison groups	Adalimumab vs placebo
		Between group difference	–1.12
		95% CI	(–4.49, 2.26)
		P-value	0.509
	Secondary endpoint Pedi30	Comparison groups	Adalimumab vs placebo
		Between group difference	1.1
		95% CI	(–27.9, 30.1)
		P-value	1.000
	Secondary endpoint Pedi50	Comparison groups	Adalimumab vs placebo
		Between group difference	17.8
		95% CI	(–12.5, 48.2)
		P-value	0.341
	Secondary endpoint Pedi70	Comparison groups	Adalimumab vs placebo
		Between group difference	24.9
		95% CI	(-3.5, 53.4)
		P-value	0.128

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH provided 1 clinical study (M11-328) to support this application for paediatric ERA. It is a double-blind placebo controlled study, including patients 6-17 years old with ERA and at least 3 active joints, and with an inadequate response to NSAID and MTX/SSZ. After randomisation 2:1 the subjects were followed for 12 weeks, thereafter all subjects received OL adalimumab. There was an early

escape option at week 4 if worsening of disease, and at week 8 if failure to improve. There were in total 3 early escapes in the placebo group and 4 early escapes in the adalimumab group.

The study design was acceptable to the CHMP. It is noted that the chosen primary endpoint is not consistent with the recommendation in the current JIA guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, namely JRA 30 (very similar to PEDI30). ACR PEDI 30 response was a secondary endpoint in this study. During the procedure, the MAH clarified that the percent change in the number of active joints with arthritis was chosen as the primary measure to assess efficacy in Study M11-328 due to the fairly limited paediatric ERA population, and allowed for appropriate powering of the study for the primary endpoint. More than twice the sample size would have been required if the study was powered for ACR Pedi30 as the primary endpoint. The CHMP agreed that the choice of this primary endpoint is understandable due to the fairly limited pediatric ERA population.

Five subjects (4 in the adalimumab group) turned out to be protocol violations. Two of these did not fulfill inclusion criterion 4, inadequate response to NSAID and MTX/SSZ. The MAH clarified that all included subjects had prior NSAID use, and that 2 of the 4 subjects without prior DMARD use had contraindications for this. This was considered acceptable by the CHMP.

The adalimumab treated group is older, 24 subjects out of 31 were 12-18 years, as compared to 7 subjects out of 15 in the placebo group. The MAH sufficiently addressed the raised concern of scarce representation of patients aged 6 to <9 years reporting a literature review by conducting a retrospective analysis using UK CPRD. Although data on ERA patients were extracted by JIA studied population and numbers were limited using specific terms, overall results support a lower distribution of incidence of ERA patients in age categories 6 to 11 years.

Efficacy data and additional analyses

The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 52 of the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Paediatric ACR 50 response, and Paediatric ACR 70 response.

In the primary ITT analysis, a clinically relevant statistically significant difference was demonstrated, but when 1 subject was excluded from the placebo group, the results for this group improved from -11 to -30.2%, and the difference between the treated and untreated group diminished from 51 to 36%, which is not statistically significant. However, due to the limited number of patients the sensitivity analyses should be interpreted with caution. Exclusion of very few or single patients might have a conspicuous impact on magnitude of effect and statistical significance, and the interpretation should base on the overall pattern rather than individual analyses. With this in mind there is no reason to question the consistency between primary and sensitivity results because of the differences in magnitude of effect as well as in p-values.

Although the primary end point was met, there was no difference in response at all between groups in the dichotomous secondary endpoint ACR PEDI 30%, which is the recommended primary endpoint in the draft guideline for clinical investigations of JIA. This seems to be caused by an unexpectedly good response in the placebo group, 66.7% versus 67.7% in the adalimumab group. This may be considered problematic, but on the other hand, the PEDI70 result appeared consistent with primary endpoint

results, 51% and 26.7% responders in the adalimumab and placebo groups, respectively. The MAH clarified that the greatest difference towards placebo was seen in number of joints with loss of motion, function (CHAQ), and number of arthritis. Although not reaching statistical significance, a substantial number of subjects achieved at least 30% improvement in these parameters. More subjective parameters, such as parent´s and physician´s global assessments, showed less degree of improvement. The CHMP also acknowledged that the higher difference between the treated and placebo group observed for ACR Pedi50 and 70, which is due to lower response in the placebo groups, points towards a true treatment effect with adalimumab compared to placebo.

For the other supportive efficacy variables, all supportive efficacy variables showed numerical improvement in the adalimumab group, however, none reached statistical significance.

During the procedure, the MAH clarified that the efficacy of adalimumab for the clinical features, such as arthritis and enthesitis, observed in ERA has been demonstrated in studies of polyarticular JIA in children and in axial spondyloarthritis (SpA) (ankylosing spondylitis [AS] and non-radiographic axial SpA [nr-axSpA]), psoriatic arthritis (PsA), and non-PsA peripheral SpA in adults. Studies in all of these indications have demonstrated either statistically significant improvements, or trends for improvement, in favor of adalimumab therapy for clinical signs and symptoms of inflammatory arthritis (i.e., swollen and tender joints), enthesitis, physician assessment of disease activity, health-related quality of life (HRQoL), and laboratory evidence of inflammation.

PK data in the paediatric ERA population were comparable to that observed in paediatric subjects with polyarticular JIA and in adults with AS. Mean serum adalimumab trough concentrations at steady state for paediatric subjects (age ≥6 to <18 years) with ERA in Study M11-328 were 7.5 – 11.8 µg/mL between Weeks 12 to 24 following doses of 24 mg/m^2 (up to 40 mg) eow. Subjects with polyarticular JIA had similar mean steady-state serum adalimumab trough concentrations of 4.5 – 10.5 µg/mL [Study DE038; age ≥ 4 to < 18 years old; following doses of 24 mg/m^2 (up to 40 mg) eow] and 6.1 – 8.5 µg/mL [Study M10-444; age ≥ 2 to < 4 years old; following doses of 24 mg/m^2 (up to 20 mg) eow]. Additionally, adult subjects with AS in Study M03-607 had mean trough concentrations of 6.4 – 8.6 µg/mL between Weeks 12 and 24 following administration of adalimumab 40 mg eow.

Mean serum adalimumab trough concentrations were slightly higher in Study M11-328 for subjects on adalimumab in combination with MTX (9.7 – 11.8 µg/mL, n = 16) compared to adalimumab without MTX (7.5 – 9.4 µg/mL, n = 15). This was consistent with previous adalimumab studies, including polyarticular JIA and adult AS. Additionally, the rate of anti-adalimumab antibody positive (AAA+) subjects was similar across paediatric ERA, polyarticular JIA, and adult AS indications.

In order to demonstrate a consistent relationship between serum adalimumab trough concentrations and clinical response in paediatric subjects with JIA, an exposure-response analysis was conducted by the MAH to compare the percent change from Baseline in the number of active joints with arthritis, to that in Study DE038 (paediatric subjects with polyarticular JIA). For each study, all subjects with available data for adalimumab trough concentrations and efficacy were included in the analysis. The time point selected for comparison was the end of the placebo-controlled, DB period in Study M11-328 (Week 12), and the end of the open-label lead-in (OL-LI) phase in Study DE038 (Week 16, with PK sampling at either Week 12 or Week 16). The results showed that improvement in percent change from Baseline in the number of active joints with arthritis was similar in paediatric ERA and polyarticular JIA subjects categorized into comparable trough concentration categories.

The CHMP was also of the opinion that the baseline disease activity characteristics highlight that the enrolled subjects had moderately active disease and that the sought indication should include the word "active". The MAH therefore agreed to update the indication as follows: “Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1)”.

2.4.3. Conclusions on the clinical efficacy

The applicant has demonstrated a clinically relevant effect on the percent change of active joints in patients with ERA. In the primary ITT analysis, a statistically significant effect difference between treated and untreated patients was demonstrated (-62.6 vs 11.6 %, p=0.039). PK data in children with ERA was similar to children with polyarticular juvenile arthritis (approved indication).

The paediatric disease enthesitis related arthritis (ERA) has many similarities to ankylosing spondylitis (AS), afflicting the adult population. In fact, one of the classification criteria is history of this disease in adult first degree relatives. Humira has demonstrated effect in AS and has been used in this indication since 2006. An important feature of both AS and ERA is enthesitis, and it is noted that adalimumab showed effect on enthesitis and MASES enthesitis index toward 12 weeks in studies on these indications.

Extrapolation from approved indications was discussed and the MAH pointed to the similar clinical features and common manifestations of other indications such as AS, non-radiographic axial Spondyloarthritis and Psoriatic arthritis, of which AS is the most important, where adalimumab has a well-documented effect.

2.5. Clinical safety

2.5.1. Introduction

The mechanism of action of TNF antagonists, including adalimumab, is inhibition of an immunologically active cytokine, episodes of infections, malignancies, central nervous system (CNS) demyelinating disease, immunologic reactions and lupus-like illness were specifically evaluated as AEs of special interest. Congestive heart failure (CHF) has also been an event specifically examined in studies with TNF antagonists and was also evaluated as an AE of special interest.

Patient exposure

In the study M11-328 interim CSR (R&D/12/735) a total of 46 paediatric subjects with ERA were randomized and all subjects received ≥1 dose of study drug. Of the 46 patients treated with study drug, 7 subjects early escaped during the DB period and continued in the OL period (3 subjects from the placebo treatment arm and 4 subjects from the adalimumab treatment arm). In total 3 subjects early escaped at week 4, 4 subjects early escaped at week 8, and 39 subjects completed the DB period through week12. 43 subjects completed week 52 of the OL period, and 3 subjects discontinued from the study prior to week 52, all the OL period.

Adverse events

Study period Double blind period

The overview of TEAEs during the DB period and at any time after the first injection of adalimumab is presented in Table 33.

No deaths or fatal AEs occurred through Week 52 of the study. During the DB period, most subjects (63.0%) reported ≥ 1 TEAE; of these, a greater percentage of subjects who received adalimumab reported at least 1 AE (67.7%) compared with subjects who received placebo (53.3%). The proportions of subjects who reported at least 1 AE that was considered related to study drug by the Investigator were similar.

During the DB period, 1 subject in the adalimumab treatment group reported 2 SAEs (abdominal pain upper and headache) which were considered possibly related to study drug by the Investigator. Among

subjects who received at least 1 dose of adalimumab at any time during the study, the majority (93.5%) experienced at least 1 AE and 47.8% reported an AE that was considered by the Investigator to be at least possibly related to study drug from the first dose of adalimumab onwards.

Table 4. Overview of Subjects with TEAEs (Safety Analysis Set and Any Adalimumab Set)

	DB Period, n (%)			
Subjects with:	Placebo N = 15	Adalimumab N = 31	Total N = 46	Any Adalimumab[a] n (%) N = 46
Any AE	8 (53.3)	21 (67.7)	29 (63.0)	43 (93.5)
Any AE at least possibly drug-related[b]	4 (26.7)	9 (29.0)	13 (28.3)	22 (47.8)
Any severe AE	0	0	0	3 (6.5)
Any serious AE	0	1 (3.2)	1 (2.2)	5 (10.9)
Any AE leading to discontinuation of study drug	0	0	0	3 (6.5)
Death[c] or any fatal AE	0	0	0	0

a. TEAEs are counted from first dose of adalimumab onward.
b. As assessed by the investigator.
c. Includes non-treatment-emergent.
Cross reference: CSS (R&D/13/717) Table 8

During the DB period, a greater percentage of subjects who received adalimumab (21/31, 67.7%) reported at least 1 AE compared with subjects who received placebo (8/15, 53.3%). The most frequently reported AEs (reported by ≥2 subjects in any treatment group) included upper respiratory tract infection, headache, gastroenteritis, injection site pain, nausea, ALT increased, abdominal pain upper, and syncope.

Nine subjects in the adalimumab treatment group reported possibly or probably related AEs compared to 4 subjects in the placebo group.

Table 5. Most Frequently Reported AEs (≥ 2 Subjects in Any Treatment Group) in DB Period of Study M11-328 (Safety Set)

	DB Period, n (%)		
MedDRA 15.1 PT	Placebo N = 15	Adalimumab N = 31	Total N = 46
Subjects with any AE	8 (53.3)	21 (67.7)	29 (63.0)
Upper respiratory tract infection	2 (13.3)	3 (9.7)	5 (10.9)
Headache	0	4 (12.9)	4 (8.7)
Injection site pain	1 (6.7)	3 (9.7)	4 (8.7)
Nausea	1 (6.7)	2 (6.5)	3 (6.5)
ALT increased	0	3 (9.7)	3 (6.5)
Abdominal pain upper	1 (6.7)	2 (6.5)	3 (6.5)
Syncope	0	2 (6.5)[a]	2 (4.3)
Gastroenteritis	0	2 (6.5)	2 (4.3)

a. Both events of syncope were nonserious, assessed by the Investigator as probably not related to study drug, and spontaneously resolved within a few minutes.
Cross reference: CSS ([R&D/13/717) Table 9

All AEs were considered mild or moderate in severity by the Investigator and most subjects (n = 16) reported AEs that were considered by the Investigator to be not related or probably not related to study drug.

Entire study including open label period

Among subjects who received at least 1 dose of adalimumab at any time during the study including the open label period, the majority experienced at least 1 AE (43/46, 93.5%).

Of the most frequently reported AEs (reported by ≥ 3 subjects), upper respiratory tract infection, headache, nasopharyngitis, gastroenteritis, and pharyngitis were reported in > 10% of subjects.
Three subjects who had received only adalimumab throughout the study reported at least 1 severe AE (blood pressure increased and weight increased [in the same subject] and juvenile arthritis [worsening of ERA, 2 subjects]). Twenty-two subjects reported AEs that were considered possibly or probably related to study drug by the Investigator.

Table 6. Most Frequently Reported AEs (≥ 3 Subjects) in Study M11-328 – Any Adalimumab

MedDRA 15.1 PT	Any Adalimumab, n (%) N = 46
Subjects with any AE	43 (93.5)
Upper respiratory tract infection	12 (26.1)
Headache	8 (17.4)
Nasopharyngitis	7 (15.2)
Gastroenteritis	6 (13.0)
Pharyngitis	5 (10.9)
Juvenile arthritis	4 (8.7)
ALT increased	4 (8.7)
Injection site pain	4 (8.7)
Adverse drug reaction[a]	4 (8.7)
Nausea	4 (8.7)
Diarrhea	4 (8.7)
Abdominal pain	3 (6.5)
Injection site erythema	3 (6.5)
Pyrexia	3 (6.5)
Paronychia	3 (6.5)
Pharyngotonsillitis	3 (6.5)
Sinusitis	3 (6.5)
Post-traumatic pain	3 (6.5)

Note: Juvenile arthritis represents worsening of ERA.
Note: TEAEs are counted from first dose of adalimumab onward.
a. The following verbatim terms were coded to adverse drug reaction: nausea after MTX, vomiting once weekly after MTX, adverse drug reaction to MTX, and vomiting due to medication (Olfen).
Cross reference: CSS (R&D/13/717) Table 10

Three subjects prematurely discontinued due to AEs, all during the OL period (Ps; juvenile arthritis [worsening of ERA] and pain; and injection site pain and injection site pruritus).

Other Adverse events reported in the study:

- Infections: During the DB period, a greater proportion of subjects in the adalimumab group reported at least 1 treatment-emergent infection (9/31, 29.0%) compared with the placebo group (3/15, 20.0%).
Infections reported in 2 or more subjects included upper respiratory tract infection, gastroenteritis, cystitis, and paronychia. All other infections during the DB period were reported by no more than 1 subject each. Among subjects who received at least 1 dose of adalimumab at any time during the study, 37 out of 46 subjects (80.4%) reported at least 1 treatment-emergent infection. The most frequently reported infections were upper respiratory tract infection, nasopharyngitis, gastroenteritis, and pharyngitis with all other infections being reported by no more than 3 subjects each. All infections were considered by the Investigator to be mild or moderate in severity and all were nonserious events with the exception of 1 subject (appendicitis requiring hospitalization, OL period). Among subjects who received at least1 dose of adalimumab at any time during the study, 23 infections were considered by the Investigator to be possibly (20 events) or probably related (3 events) to study drug. One subject reported a parasitic infection (acarodermatitis, placebo group, DB period) considered by the Investigator to be not related to study drug.

- Vasculitis: One subject experienced a non-serious event of treatment-emergent cutaneous vasculitis (OL period), which was considered possibly related to study drug by the Investigator.

- Worsening or new onset psoriasis (Ps): One subject experienced a non-serious event of new onset Ps (OL period), which was considered possibly related to study drug by the Investigator.

- Liver event: One subject experienced a non-serious liver event (hepatocoellular injury, adalimumab group, DB period). The event was considered not related to study drug by the Investigator.

- Injection site reaction: During the DB period, 3 subjects in the adalimumab group reported an injection site reaction compared to 1 subject in the placebo group. Among subjects who received at least 1 dose of adalimumab, 5 subjects (10.9%) reported an injection site reaction. All injection site reactions were considered by the Investigator as mild in severity and all were probably or possibly related to study drug with the exception of 1 event.

While 3 subjects had CTCAE toxicity grade ≥3 hematology or clinical chemistry value during the study, all resolved by Week 52 and were considered not clinically meaningful. Mean changes from Baseline to final vital signs values were overall small and not clinically significant and shifts from normal to high or low final vital signs values were infrequent and not clinically meaningful.

Serious adverse event / deaths / other significant events

No deaths were reported during the study

Five subjects reported a total of 8 SAEs.

Two subjects had events that were considered by the Investigator to be possibly related to study drug (abdominal pain upper and headache in 1 subject in the DB period and appendicitis in 1 subject in the OL period). The subject who experienced abdominal pain upper and headache in the DB period also experienced juvenile arthritis (worsening of ERA) and pain (OL period), both of which were considered not related by the Investigator.

The remaining 3 subjects had events that were considered probably not or not related to study drug by the Investigator (musculoskeletal chest pain and concussion [OL period] and juvenile arthritis [worsening of ERA; posttreatment from OL period]).
One SAE was considered severe by the Investigator (juvenile arthritis [worsening of ERA]; post treatment from OL period); all other SAEs were considered mild or moderate in severity.

One subject, a 13-year-old white male who was randomized to the adalimumab group, was hospitalized due to abdominal pain upper and headache on Day 67 (DB period), both intermittent but lasting 20 days. Both events were considered mild and possibly related to study drug by the Investigator. The Investigator reported "psychosomatic, gastroenteritis" as an alternative cause of the events. On Day 220 (Day 138 of the OL period), the subject reported juvenile arthritis (worsening of ERA) and pain, requiring hospitalization. Both events were considered moderate in intensity and not related to study drug by the Investigator. Both events were ongoing as of Day 317. The Investigator reported "natural progression of disease" as an alternative cause of the events. The subject prematurely discontinued from the study as a result of the juvenile arthritis (worsening of ERA) and pain.
One subject, a 13-year-old white male who was randomized to the adalimumab group, experienced appendicitis on Day 242 (Day 158 of the OL period). He was hospitalized and underwent an appendectomy. The event lasted 10 days, and was considered by the Investigator as moderate in severity and to be possibly related to study drug. The Investigator reported "possibly related infection, histology floride ulcerous-phlegmonous appendicitis and periappendicitis, purulent serositis" as an alternative cause of the event.
One subject, a 14-year-old white female randomized to the placebo group who early escaped to OL adalimumab at Week 8, was hospitalized due to musculoskeletal chest pain on Day 77 (Day 23 of the

OL period). The event lasted 15 days, was considered by the Investigator as moderate in severity and probably not related to study drug. The Investigator reported "probable enthesitis" as an alternative cause of the event

One subject, a 13-year-old white female randomized to the placebo group, sustained a concussion on Day 309 (Day 250 of the OL period) and was hospitalized. The event lasted 4 days, was considered by the Investigator as moderate in severity and not related to study drug. The Investigator reported "accident" as an alternative cause of the event.

One subject, a 15-year-old white female randomized to the adalimumab group, was hospitalized for juvenile arthritis (worsening of ERA) on Day 299 (32 days post-treatment). The event was intermittent over 8 days and was considered by the Investigator as severe and not related to study drug. The Investigator reported "worsening of ERA" as an alternative cause of the event.

Laboratory findings

For subjects who received at least 1 dose of adalimumab at any time during the study, the majority of haematology and chemistry parameters demonstrated infrequent shifts from Baseline to the Week 52 visit.

Shifts in haematocrit (normal to high in 9 subjects) and platelets (high to normal in 12 subjects) most likely represent normalization of systemic inflammation in study subjects.

Shifts from abnormal normal in 8 subjects) and BUN (high to normal in 9 subjects) and shifts in albumin from normal to high in 9 subjects and from high to normal in 7 subjects were not clinically meaningful.

Review of the specific laboratory values for these parameters revealed all values were Common Toxicity Criteria (CTC) grade <3 throughout the study without clinically significant abnormalities.

Three subjects had at least 1 clinically significant (CTC for AEs [CTCAE] toxicity grade ≥3) haematology or clinical chemistry value (white blood cell count [WBC], lymphocyte, ALT and triglyceride values in adalimumab subjects, and neutrophil counts in a placebo subject). All of these abnormalities returned to grade <3 while continuing treatment with study drug.

Ten subjects had at least 1 potentially clinically significant liver function test (LFT) value. One of these subjects (in the adalimumab group) experienced an elevation in ALT >5 × ULN (upper limit of normal), which returned to <3 × ULN at the next visit. All other subjects had mildly elevated LFT values (generally maximum values ≤ 3 × ULN) that were mostly transient.

Mean changes from Baseline to final vital sign values were overall small and not statistically significant between treatment groups.

Discontinuation due to adverse events

Three subjects prematurely discontinued due to AEs, all during the OL period (Ps; juvenile arthritis [worsening of ERA] and pain; and injection site pain and injection site pruritus). The events reported were consistent with the known safety profile of adalimumab.

Post marketing experience

Humira is approved since 2003 and is currently approved in the EU for active polyarticular juvenile idiopathic arthritis. The safety profile in children is well characterised and the main adverse events in children are infections.

A total of 42,630 patients have been treated with adalimumab in AbbVie sponsored clinical studies and registries with an estimated subject exposure of 43,225.9 patient years (PYs AE rates across approved indications for events of special interest to those that were reported in Study M11-328 are compared in Table 33.

Table 33.

Table 2. Overview of Treatment-Emergent Events of Special Interest for Subjects in the RA, Polyarticular JIA, PsA, AS, nr-axSpA, Adult CD, UC, Adult Ps, and ERA Clinical Development Programs

	RA N = 15152 PYs = 24810.4		Polyarticular JIA N = 228 PYs = 662.4		PsA N = 837 PYs = 997.5		AS N = 2026 PYs = 2119.5		nr-axSpA N = 190 PYs = 580.8		Adult CD N = 3606 PYs = 4145.4		UC N = 1308 PYs = 2545.1		Adult Ps N = 3035 PYs = 5070.0		ERA N = 46 PYs = 42.6	
Events of Special Interest Categories	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs	E	E/100 PYs
SAE	6448	26.0	90	13.6	121	12.1	240	11.3	40	10.1	1497	36.1	491	19.3	411	8.1	8	18.8
AE leading to discontinuation	2445	9.9	21	3.2	82	8.2	163	7.7	20	5.1	699	16.9	310	12.2	241	4.8	5	11.7
Severe AE	6607	26.6	56	8.5	139	13.9	240	11.3	42	10.6	2006	48.4	486	19.1	503	9.9	4	9.4
Infection	23401[a]	95.1[a]	1017	153.5	978	98.0	1971	93.0	377	95.4	5050[b]	129.2[b]	2319	91.1	4436	87.5	86	201.9
Serious infection	1154	4.7	19	2.9	28	2.8	37	1.7	8	2.0	283	6.8	92	3.6	87	1.7	1	2.3
Cutaneous vasculitis	34	0.1	0	0	0	0	2	< 0.1	0	0	4	< 0.1	2	< 0.1	4	< 0.1	1	2.3
Worsening/new onset of psoriasis	156	0.6	4	0.6	60	6.0	55	2.6	0	0	71	1.7	24	0.9	155	3.1	1	2.3
Demyelinating disorder	15	< 0.1	0	0	0	0	1	< 0.1	0	0	6	0.1	3	0.1	1	< 0.1	0	0
Liver failure and other liver event	124	0.5	0	0	10	1.0	19	0.9	2	0.5	25	0.6	20	0.8	31	0.6	1	2.3
Injection site reaction	3385[a]	13.8[a]	831	125.5	279	28.0	256	12.1	28	7.1	1047[b]	26.8[b]	278	10.9	559	11.0	11	25.8

Table 2. Overview of Treatment-Emergent Events of Special Interest for Subjects in the RA, JIA, PsA, AS, nr-axSpA, Adult CD, UC, Adult Ps, and ERA Clinical Development Programs (continued)

AE = adverse event; AS = ankylosing spondylitis; CD = Crohn's disease; E = number of events; E/100 PYs = events per 100 patient years; ERA = enthesitis related arthritis; JIA = juvenile idiopathic arthritis; nr-axSpA = non-radiographic axial spondyloarthritis; Ps = psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SAE = serious adverse event; UC = ulcerative colitis

a. Excludes Study M02-498, which only reported AEs that were serious in nature. For these categories, N = 14216 and PYs = 24601.5.

b. Excludes Study M06-808, which only reported AEs that were serious in nature. For these categories, N = 2933 and PY = 3907.9.

Note: Events of special interest are shown through 31 December 2012.

Cross reference: Adalimumab Investigator's Brochure Edition 19 Table 65, Table 66 (Release date – 07 May 2013), Study M11-328 CSR (R&D/12/735)

2.5.2. Discussion on clinical safety

All subjects received at least 143 days of ADA treatment, with a maximum exposure to ADA of 385 days.

The most common AEs are those frequently observed with ADA treatment, the majority (86.9%) of reported AEs were mild-moderate in severity and only a minority was severe (6.5%).

The AEs by SOC most commonly reported according to severity grade and clinical interest are: gastrointestinal disorders (mild 28.3%, moderate 2.2%); general disorders and administration site conditions (mild 28.3, moderate 4.3%); infections and infestations (mild 58.7, moderate 21.7%); nervous system disorders (mild 23.9; moderate 4.3%); investigations (mild 13.0, severe 2.2).

In particular, infections and infestations were reported in 80.4% of patients with the most common being gastroenteritis, nasopharyngitis, pharyngitis, upper respiratory tract infection. All infections during DB as well as OL phases were moderate or mild in severity, with the exception of 1 serious event of appendicitis requiring hospitalization during the OL phase.

There are no deaths reported during the study. 2/5 subjects reported in all 3 SAEs, possibly related to study drug. In one case two SAE (abdominal pain upper and headache) as possibly related to study drug, and in another case report appendicitis was regarded as possibly related to study drug.

Changes in laboratory findings were not clinically significant and overall reflect ADA safety profile.

Few patients prematurely discontinued study drugs, the majority complete the treatment period.

A total of 42,630 patients have been treated with adalimumab in the MAH's sponsored clinical studies and registries with an estimated subject exposure of 43,225.9 patient years (PYs). Safety data for Study M11-328 were comparable to already approved indications and no new safety signals were identified in the paediatric ERA population with the rate of overall adverse events (AEs), serious adverse events (SAEs), and severe AEs similar to rates observed in clinical trials for other indications. The rate of overall infections was higher in the paediatric ERA population compared to other indications with the most frequently reported infections those commonly observed in the general population including upper respiratory tract infection, nasopharyngitis, gastroenteritis, and pharyngitis. In addition, the rate of serious infections is within the range observed in approved indications. There were no deaths or AEs of malignancy, opportunistic infection, tuberculosis (TB), lupus-like syndrome, hematological disorders (including pancytopenia), or demyelinating disease reported through Week 52.

In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

Long -term data for the adalimumab-treated ERA population will be available through the OL extension of Study M11-328 (as described in the RMP).

2.5.3. Conclusions on clinical safety

Adalimumab was generally well tolerated during the study M11-328. The most reported common AEs were upper respiratory tract infection, headache, nasopharyngitis, gastroenteritis, and pharyngitis.

The safety profile observed was consistent with previous clinical trials for adalimumab.

During the procedure, the MAH has provided data supporting safety of adalimumab in other related indications, such as Ankylosing spondylitis (AS), non-radiographic axial Spondyloarthritis and Psoriatic arthritis. This approach is considered acceptable, since it is acknowledged that there are significant clinical similarities between these diseases and ERA. In fact, one of the classification criteria is history of AS in adult first degree relatives.

Long -term data for the adalimumab-treated ERA population will be available through the OL extension of Study M11-328 (as described in the RMP).

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 10.3, the PRAC considers by consensus that the risk management system for adalimumab (Humira) in the treatment of enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB; • Reactivation of hepatitis B; • Pancreatitis; • Lymphoma; • HSTCL; • Leukemia; • NMSC; • Melanoma; • Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin); • Demyelinating disorders (including MS, GBS, and optic neuritis); • Immune reactions (including lupus-like reactions and allergic reactions); • Sarcoidosis; • CHF; • MI; • CVA; • ILD; • Pulmonary embolism; • Cutaneous vascultis; • SJS and erythema multiforme; • Worsening and new onset of Ps; • Haematologic disorders; • Intestinal perforation; • Intestinal strictures in CD; • Liver failure; • Elevated ALT levels; • Autoimmune hepatitis;

	• Medication errors and maladministration
Important potential risks	• Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma); • Vasculitis (non-cutaneous); • PML; • RPLS; • ALS; • Colon cancer in UC patients; • Infections in infants exposed to adalimumab in utero; • Medication errors with paediatric vial; • Off-label use.
Missing information	• Subjects with immune-compromised conditions (i.e., subjects with HIV, post-chemotherapy, organ transplant); subjects with a history of clinically significant drug or alcohol abuse; • Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischemic heart disease, CHF, recent cerebrovascular accidents; • Subjects with history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals, or antifungals, history of viral hepatitis; • Subjects with history of cancer, lymphoma, leukaemia, or lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of demyelinating disorders; • Children < 18 years of age for PsA, AS, Ps, UC, SpA, HS, ERA, and uveitis indications; • Children < 4 years of age for pedPs; • Children < 2 years of age for JIA; • Children < 6 years of age for pedCD and pedERA; • Pregnant and lactating women; • Subjects with renal or liver impairment; • Patients taking concomitant biologic therapy; • Long-term RA data beyond 10 years; • Long-term JIA data beyond 7.5 years; • Episodic treatment in JIA;

	• Long-term AS data beyond 5 years; • Long-term axial SpA data beyond 1 year; • Short- and long-term peripheral SpA data; • Remission-withdrawal-retreatment axial SpA data; • Long-term pedERA data; • Long-term PsA data beyond 3 years; • Long-term Ps data beyond 6 years; • Episodic treatment in Ps; • Short- and long-term HS data; • Long-term CD data beyond 5 years; • Episodic treatment in CD; • Long-term pedCD data beyond 2 years; • Long-term UC data; • Episodic treatment in UC; • Short- and long-term uveitis data

The PRAC agreed.

Pharmacovigilance plans

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

Actions	Milestone / Exposure	Milestones / Calendar Time	Study Status
Ongoing Pharmacovigilance Actions			
Study DE013 (RA)	10 years	31 December 2012	Ongoing.
PedERA (long-term data from study M11-328)	Up to 204 weeks	September 2016	Ongoing.
Pregnancy Registry (Study M03-604)	--	Annual interim reports with PSUR	Ongoing.
Interim data from Registry for CD patients (Study P06-134)	--	February 2013	Ongoing.
Interim data from Registry for CD patients (Study P06-134)	--	February 2014	Ongoing.
Interim data from Registry for CD patients (Study P06-134)	--	February 2015	Ongoing.
Registry for CD patients (Study P06-134)	6 years	August 2016	Ongoing.
Study M06-807 (pedCD)	5 years	November 2015	Ongoing.
PedCD registry (P11-292)	Submission of final protocol	31 March 2013	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2014	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2015	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2016	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2017	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2018	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2019	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2020	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2021	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	--	August 2022	Ongoing.
Interim data from Registry for pedCD patients (Study P11-292)	10 years	August 2023	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2013	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2014	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2015	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2016	Ongoing.

Actions	Milestone / Exposure	Milestones/ Calendar Time	Study Status
Interim data from Registry for Ps patients (Study P10-023)	--	February 2017	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2018	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2019	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2020	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2021	Ongoing.
Interim data from Registry for Ps patients (Study P10-023)	--	February 2022	Ongoing.
Registry for Ps patients (Study P10-023)	10 years	February 2023	Ongoing.
Evaluation of treatment interruptions with the Ps registry (Study P10-023)	10 years	February 2023	Ongoing.
Study M04-717 (pedPs)	TBD	January 2014	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2013	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2014	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2015	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2016	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2017	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2018	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2019	Ongoing.
Interim data from Registry for JIA patients (Study P10-262)	--	August 2020	Ongoing.
Registry for JIA patients (Study P10-262)	10 years	August 2021	Ongoing.
Evaluation of treatment interruptions with the JIA registry (Study P10-262)	10 years	31 December 2021	Ongoing.
Study M10-444 (JIA) compassionate use study	6 months	31 December 2012	Ongoing.
Proposed Pharmacovigilance Actions			
Long-term UC data			
Study M10-223	TBD	TBD	Ongoing.
Interim data from Registry for UC (Study P11-282)	--	August 2013	Ongoing.

Actions	Milestone / Exposure	Milestones / Calendar Time	Study Status
Interim data from Registry for UC (Study P11-282)	--	August 2014	Ongoing.
Interim data from Registry for UC (Study P11-282)	--	August 2015	Ongoing.
Actions	Milestone/ Exposure	Milestones/ Calendar Time	Study Status
Proposed Pharmacovigilance Actions (Continued)			
Interim data from Registry for UC (Study P11-282)	--	August 2016	Ongoing.
Interim data from Registry for UC (Study P11-282)	--	August 2017	Ongoing.
Interim data from Registry for UC (Study P11-282)	--	August 2018	Ongoing.
Interim data from Registry for UC (Study P11-282)	6 years	August 2019	Ongoing.
Short- and long-term SpA data			
Study M10-791	3 years	December 2013	Ongoing.
Study M10-883	2 years	TBD	Ongoing.
Remission-withdrawal-retreatment axial SpA data			
Study M13-375	Up to 76 weeks	31 August 2015	Planned
Long-term pedERA data			
Study M11-328	Up to 204 weeks	September 2016	Ongoing.
Short- and long-term HS data			
Study M11-313	TBD	TBD	Planned.
Study M11-810	TBD	TBD	Planned.
Study M12-555	TBD	TBD	Planned.
Short- and long-term Uveitis data			
Study M10-880	TBD	TBD	Ongoing.
Study M10-877	TBD	TBD	Ongoing.
Study M11-327	TBD	TBD	Ongoing.

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

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

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks		
Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, and legionellosis, and TB	Routine pharmacovigilance with use of specialized questionnaires to identify the results of screening, medical history, administration of prophylaxis, outcomes and special reporting in PSURs of cases by geographic region of origin.**Error! Reference source not found.** Monitoring through long-term clinical studies and registries.	Warnings for active TB or other severe infections such as sepsis, and opportunistic infections including invasive fungal infections, parasitic infections, and the higher risk of infections in the geriatric population in the Warning section and information on infections in the Adverse Reactions section of the CCDS. Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections in some local labels (e.g., EU-SmPC). Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
Reactivation of hepatitis B	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding hepatitis B reactivation is included in the Warning section of the CCDS, and reactivation of hepatitis B is also listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS. Risk Minimisation actions in the form of an educational program addressing serious infections in general is ongoing (Annex 8).

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks (continued)		
Pancreatitis	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Pancreatitis is listed as an adverse reaction identified in clinical trials in the Adverse Reactions section of the CCDS.
Lymphoma	Routine pharmacovigilance activities for patients beyond 30 years of age. Enhanced pharmacovigilance activities for pediatric, and young adult patients (30 years of age and younger). Monitoring through long-term clinical studies and registries.	Warning regarding lymphoma and malignancies in the adult and paediatric population in the Warning section and information on rates from clinical trials is included in the Adverse Reactions section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
HSTCL	Routine pharmacovigilance activities for patients beyond 30 years of age. Enhanced pharmacovigilance activities for pediatric, and young adult patients (30 years of age and younger). Monitoring through long-term clinical studies and registries.	Warning regarding hepatosplenic T-cell lymphoma and malignancies in the adult and paediatric population in the Warning section and information on rates from post-marketing is included in the Adverse Reactions section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
Leukemia	Routine pharmacovigilance activities for patients beyond 30 years of age. Enhanced pharmacovigilance activities for pediatric, and young adult patients (30 years of age and younger). Monitoring through long-term clinical studies and registries.	Warning regarding leukemia and malignancies in the adult and paediatric population in the Warning section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks (continued)		
NMSC	Routine pharmacovigilance activities for patients beyond 30 years of age. Enhanced pharmacovigilance activities for pediatric, and young adult patients (30 years of age and younger). Monitoring through long–term clinical studies and registries.	Warning regarding NMSC and malignancies in the adult and paediatric population in the Warning section and rates for NMSC from clinical trials are included in the Adverse Reactions section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
Melanoma	Routine pharmacovigilance activities for patients beyond 30 years of age. Enhanced pharmacovigilance activities for pediatric, and young adult patients (30 years of age and younger). Monitoring through long–term clinical studies and registries.	Warning regarding malignancies in the adult and paediatric population in the Warning section and melanoma is listed as an adverse reaction identified in clinical trials in the Adverse Reactions section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	MCC is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS. Information regarding MCC is also added to the adverse reaction and Warnings and Precautions sections of the EU-SmPC. Risk Minimisation actions in the form of an educational program is ongoing (Annex 8).
Demyelinating disorders	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning on demyelinating disorders is included in the Warning section of the CCDS. Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks (continued)		
Immune reactions (including lupus-like reactions and allergic reactions)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warnings regarding serious allergic reactions and lupus-like reactions are included in the Warning section of the CCDS. Anaphylaxis is also listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Sarcoidosis	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Sarcoidosis is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
CHF	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding congestive heart failure including worsening and new onset in the Warning section of the CCDS. Contraindication for moderate to severe heart failure with instructions to stop adalimumab if symptoms become worse in these patients in some local labels (e.g., EU.SmPC). Risk Minimisation actions in the form of an educational programme is ongoing (Annex 8).
Myocardial infarction	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	MI is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Cerebrovascular accident	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	CVA is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks (continued)		
ILD	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Interstitial lung disease is listed as an AE identified in clinical studies in the Adverse Reactions section of the CCDS.
Pulmonary embolism	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Pulmonary embolism is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Cutaneous vasculitis	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Cutaneous vasculitis is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
SJS	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	SJS is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Erythema multiforme	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Erythema multiforme is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Worsening and new onset of Ps	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Worsening and new onset of Ps is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reaction section of the CCDS.
Haematologic disorders	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding haematologic reactions is included in the Warning section of the CCDS.
Intestinal perforation	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Intestinal perforation is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Identified Risks (continued)		
Intestinal stricture in CD	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding small bowel obstruction and intestinal stricture is included in Section 4.4 of the SmPC.
Liver Failure	Routine pharmacovigilance activities will include surveillance of events of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis and acute hepatitis. Monitoring through long-term clinical studies and registries.	Liver failure is listed as an adverse reaction identified in post-marketing surveillance in the Adverse Reactions section of the CCDS.
Elevated ALT levels	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	The risk of elevated ALT levels is addressed in the Adverse Reactions section of the CCDS.
Autoimmune hepatitis	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding autoimmune hepatitis is added to the adverse reaction section of the EU-SmPC upon request by the EMA. Information regarding autoimmune hepatitis will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
Medication error and maladministration	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Ongoing monitoring of Product Quality Complaints Call-In Center.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Potential Risks		
Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Warning regarding malignancies and malignancies in the paediatric population in the Warning section and information on rates from clinical trials are included in the Adverse Reactions section of the CCDS. Educational Programme (Annex 8).
Vasculitis (non-cutaneous)	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding vasculitis (non-cutaneous) will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
Progressive multifocal leukoencephalopathy	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding progressive multifocal leukoencephalopathy will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
Reversible posterior leukoencephalopathy syndrome	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding reversible posterior leukoencephalopathy syndrome will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
ALS	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding ALS will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Important Potential Risks (continued)		
Colon cancer in UC patients	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Information regarding colon cancer in UC patients will be updated in the Adverse Reaction section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
Infection in infants exposed to adalimumab in utero	Routine pharmacovigilance activities. Monitoring through registries.	Information regarding the risk for infection in infants exposed to adalimumab in utero will be updated in the Pregnancy section of the CCDS if further evidence for the association with TNF antagonist treatment becomes available.
Medication errors with paediatric vial	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	No additional risk minimization activities required. Detailed usage description of the single use paediatric vial outlined in the Patient leaflet and the vial is clearly labelled for single use only.
Off-label use	Routine pharmacovigilance activities. Monitoring through long-term clinical studies and registries.	Surveillance of literature and spontaneous reports.
Missing Information		
Subjects with immune-compromised conditions (i.e., subjects with HIV, post-chemotherapy, organ transplant); subjects with a history of clinically significant drug or alcohol abuse	Monitoring through registries.	Warnings regarding patients with immune compromised conditions are included in several places in the Warning section of the CCDS.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischemic heart disease, CHF, recent cerebrovascular accidents	Monitoring through registries.	Warnings regarding patients with a history of recurring infections congestive heart failure, including worsening and new onset, are included in the Warning section of the CCDS. Contraindication for moderate to severe heart failure included in some local labels (e.g., EU-SmPC).
Subjects with history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals, or antifungals, history of viral hepatitis	No additional activities since this population is contraindicated.	Warning regarding infections included in the Warning section of the CCDS. Contraindications for active TB or other severe infections such as sepsis, and opportunistic infections included in some local labels (e.g., EU-SmPC).
Subjects with history of cancer, lymphoma, leukaemia, or lymphoproliferative disease; subjects with history of neurologic symptoms suggestive of demyelinating disorders	No additional activities since caution statement included in the product information.	Warnings regarding patients with a history of malignancy and pre-existing or recent-onset demyelinating disorders are included in the Warning section of the CCDS.
Children < 18 years of age for PsA, AS, Ps, UC, SpA, HS, and uveitis indications	Routine Pharmacovigilance activities and assessment of AE profiles of patients by age and paediatric indications, when approved. Incidence of PsA in children is low; therefore, no additional activities and studies are planned. Studies in children with, Ps, CD, and UC are either ongoing or under development. The SpA, HS, and uveitis paediatric development will be considered once the adult efficacy, safety and pharmacokinetic data are available.	The Dosage section of the CCDS addresses the lack of information in paediatric patients. However, with the completion of paediatric trials for, CD, UC, Ps, SpA, HS, and uveitis, this information will be communicated and the CCDS and local label changes made according to the findings.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Children < 2 years of age for JIA indications	Routine pharmacovigilance activities. No actions beyond routine pharmacovigilance planned for children < 2 years of age with JIA based on low prevalence in this age group and benefit/risk considerations.	The Dosage section of the CCDS addresses the lack of information in these paediatric patients. Routine pharmacovigilance will characterise the overall safety of paediatric patients and adalimumab use. Safety findings will be communicated in future PSURs and updates will be made to the CCDS and local labels as necessary. An ongoing registry (Study P10-262) for JIA will include children ≥ 2 years of age and will complement the safety experience gained from spontaneous post-marketing AE reporting for all patients on adalimumab.
Children < 6 years of age for pedCD and pedERA indications	Incidence of pedCD in children younger than 6 years is low and also hard to be diagnosed. Incidence of pedERA in children younger than 6 years is low.	The Dosage section of the CCDS addresses the lack of information in paediatric patients.
Pregnant and lactating women	Routine pharmacovigilance activities. The safety profile of adalimumab is not established for pregnant or lactating women. A pregnancy exposure registry (Study M03-604) was set up by AbbVie to monitor planned and unplanned pregnancies in women exposed to adalimumab.	The Pregnancy section of the CCDS currently addresses the risks to women who may become pregnant while being treated with adalimumab. It also addresses the risk to infants who are exposed in utero and the lack of data on nursing.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Subjects with renal or liver impairment	Monitoring through registries.	The Pharmacokinetics section of the CCDS indicates that adalimumab has not been studied in these patient populations and that there are no specific recommendations about the dose or the use of adalimumab in these patients.
Patients taking concomitant biologic therapy	No additional activities as it is anticipated that inclusion of these medications would seriously jeopardise the safety.	Warning regarding concomitant use with anakinra and abatacept is included in the Warning section of the CCDS. Combinations with other biologics are not specifically addressed in the CCDS, but available data on combinations with other DMARDs are described in the Dosage and Clinical Trials section of the CCDS.
Long-term RA data beyond 10 years	Routine pharmacovigilance activities. 10-year long-term study (Study DE013).	Information on clinical data up to 5 years exposure is currently included in the Clinical Trials section of the CCDS.
Long-term JIA data beyond 7.5 years	Routine pharmacovigilance activities. 10-year registry (Study P10-262).	Information on clinical data up to 2 years exposure is included in the Clinical Trials section of the CCDS. Clinical data up to 7.5 years exposure is available.
Episodic treatment in JIA data	Routine pharmacovigilance activities. Evaluation of treatment interruptions with the JIA registry (Study P10-262).	Episodic treatment is not proposed in the CCDS. An ongoing registry for JIA will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Long-term AS data beyond 5 years	Routine pharmacovigilance activities.	Information on clinical data up to 6 months exposure is included in the Clinical Trials section of the CCDS. Clinical data up to 5 years exposure is available.
Long-term axial SpA data	Routine pharmacovigilance activities (Study M10-791).	Information on clinical data available will be included in the Clinical Trials section of the CCDS.
Short- and long-term peripheral SpA data	Routine pharmacovigilance activities (Study M10-883).	Information on clinical data available will be included in the Clinical Trials section of the CCDS with the addition of the peripheral SpA indication.
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.
Long-term pedERA data	Routine pharmacovigilance activities. Study M11-328	Information on clinical data available will be included in the Clinical Trials section of the CCDS with the addition of the pedERA indication.
Long-term PsA data beyond 3 years	Routine pharmacovigilance activities.	Information on clinical data up to 3 years exposure is included in the Clinical Trials section of the CCDS.
Long-term Ps data beyond 6 years	Routine pharmacovigilance activities. 10-year registry (Study P10-023).	Information on clinical data up to 3 years exposure included in Clinical Trials section of the CCDS. Clinical data up to 6 years exposure is available.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Episodic treatment in Ps data	Routine pharmacovigilance activities. Evaluation of treatment interruptions with the Ps registry (Study P10-023).	Episodic treatment is not proposed in the CCDS. An ongoing registry for Ps will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.
Short- and long-term data for HS	Routine pharmacovigilance activities. Studies M11-313, M11-810, M12-555.	Information on clinical data available will be included in the Clinical Trials section of the CCDS with the addition of the HS indication.
Long-term CD data beyond 5 years	Routine pharmacovigilance activities. 6-year registry (Study P06-134).	Information on clinical data up to 3 years exposure is included in the Clinical Trials section of the CCDS. Clinical data up to 5 years exposure is available.
Episodic treatment in CD data	Routine pharmacovigilance activities. Evaluation of treatment interruptions defined as dosing holidays of at least 70 days with the CD registry (Study P06-134).	An ongoing registry for CD will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.
Long-term pedCD data beyond 2 years	Routine pharmacovigilance activities. Long-term open-label study (Study M06-807) and 10-year registry (P11-292).	Information on clinical data is included in the Clinical Trials section of the CCDS with the addition of the pedCD indication. Clinical data up to 108 weeks exposure is available.
Long-term UC data	Routine pharmacovigilance activities. Long-term open-label study (Study M10-223). UC registry (Study P11-282) planned.	Information on clinical data available will be included in the Clinical Trials section of the CCDS with the addition of the UC indication.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information (continued)		
Episodic treatment in UC data	Routine pharmacovigilance activities. Evaluation of treatment interruptions defined as dosing holidays of at least 12 weeks with the UC registry (Study P11-282).	A planned registry for UC will complement the safety experience especially on episodic treatment gained from spontaneous post-marketing AE reporting for all patients on adalimumab.
Short- and long-term uveitis data	Routine pharmacovigilance activities. Studies M10-880, M10-877, M11-327.	Information on clinical data available will be included in the Clinical Trials section of the CCDS with the addition of the uveitis indication.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

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

Section 4.1 Therapeutic indications

[...]

Juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis

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

Enthesitis-related arthritis

Humira is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy (see section 5.1).

Section 4.2 Posology and method of administration

Enthesitis-related arthritis
The recommended dose of Humira for patients with enthesitis-related arthritis 6 years of age and older is 24 mg/m² body surface area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' height and weight (Table 1).
Humira has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Section 4.8 Undesirable effects
Humira was studied in ~~8,152~~**8,198** patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long standing disease, ~~polyarticular~~ juvenile idiopathic arthritis **(polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis)** as well as **axial spondyloarthritis (**ankylosing spondylitis **and**, axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, Crohn's disease, ulcerative

colitis and psoriasis patients. ~~The data in Table 2 is based on t~~The pivotal controlled studies involv**ed**~~ing~~ 5,~~312~~ **343** patients receiving Humira and ~~3,133~~**3,148** patients receiving placebo or active comparator during the controlled period~~ and spontaneous reporting~~.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 6.1% for patients taking Humira and ~~5.8~~**5.7**% for control
treated patients.

Malignancies and lymphoproliferative disorders
No malignancies were observed in ~~203~~ **249** paediatric patients ~~aged 2 to 17 years~~ with an exposure of ~~605.3~~**655.6** patient years during Humira trials in **patients with** juvenile idiopathic arthritis (**polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis**)~~ patients~~. In addition, no malignancies were observed in 192 paediatric patients with an exposure of 258.9 patient years during
a Humira trial in paediatric patients with Crohn's disease.

Hepato-biliary events

In controlled Phase 3 trials of Humira in patients with rheumatoid arthritis and psoriatic arthritis with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of Humira-treated patients and 1.6% of control-treated patients.

In controlled Phase 3 trials of Humira in patients with plaque Psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of Humira-treated patients and 1.8% of control-treated patients.
~~In the JIA trial the few transaminase elevations were small and similar in the placebo and adalimumab exposed patients, and mostly occurred in combination with methotrexate.~~
In controlled Phase 3 trials of Humira in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of Humira-treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of Humira in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

Section 5.1 Pharmacodynamic properties

Enthesitis-related arthritis
The safety and efficacy of Humira were assessed in a multicenter, randomised, double-blind study in 46 paediatric patients (6 to 17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m^2 body surface area (BSA) of Humira up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open-label (OL) period during which patients received 24 mg/m^2 BSA of Humira up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved with mean percent decrease of -62.6% (median percent change -88.9%) in patients in the Humira group compared to -11.6% (median percent change -50.0%) in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the OL period through Week 52 of the study. Although not statistically significant, the majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 50 response, and Pediatric ACR 70 response.

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and the occurrence of adverse events.

Patients in **rheumatoid arthritis studies**~~RA Studies~~ I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-

adalimumab antibodies were identified in **5.5% (**58/1053**) of** ~~(5.5%)~~ patients treated with adalimumab, compared to **0.5% (**2/370**)** ~~(0.5%)~~ on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with polyarticular juvenile idiopathic arthritis **who were 4 to 17 years**, anti-~~,~~adalimumab antibodies were identified in **15.8% (**27/171**)** of **patients** ~~subjects (15.8%)~~ treated with adalimumab. In patients not given concomitant methotrexate, the incidence was **25.6% (**22/86**)** ~~(25.6%),~~ compared to **5.9% (**5/85) ~~(5.9%)~~ when adalimumab was used as add-on to methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 10.9% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.6% (3/22), compared to 8.3% (2/24) when adalimumab was used as add-on to
methotrexate.

Section 5.2 Pharmacokinetic properties

In patients with **polyarticular** JIA who were 2 **to** <4 years old or aged 4 and above weighing <15 kg dosed with ~~Humira~~ **adalimumab** 24 mg/m^2 , the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/ml (101% CV) **for adalimumab without concomitant methotrexate** ~~Humira monotherapy~~ and 7.9 ± 5.6 µg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/mL (102% CV) for adalimumab without concomitant methotrexate~~Humira monotherapy~~ **and10.9 ± 5.2 µg/mL (47.7% CV) with concomitant methotrexate**.

The Package Leaflet has been updated accordingly.

Editorial changes have also been made to section 4.1, 4.2, 5.1 and 5.2 of the SmPC.

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

The applicant has demonstrated a clinically relevant effect on the percent change of active joints in patients with ERA. In the primary ITT analysis, a statistically significant effect difference between treated and untreated patients was demonstrated (-62.6 vs 11.6 %, p=0.039). PK data in children with ERA was similar to children with polyarticular juvenile arthritis (approved indication).

The paediatric disease enthesitis related arthritis (ERA) has many similarities to ankylosing spondylitis (AS), afflicting the adult population. In fact, one of the classification criteria is history of this disease in adult first degree relatives. Humira has demonstrated effect in AS and has been used in this indication since 2006. Extrapolation from approved indications was discussed and the MAH pointed to the similar clinical features and common manifestations of other indications such as AS, non-radiographic axial

Spondyloarthritis and Psoriatic arthritis, of which AS is the most important, where adalimumab has a well-documented effect.

Uncertainty in the knowledge about the beneficial effects

The key secondary endpoints did not reach statistical significance, however the CHMP noted that in most cases the adalimumab group showed a slight improvement in response of variable size.

Risks

Unfavourable effects

Adalimumab was generally well tolerated during the study M11-328. The most reported common AEs were upper respiratory tract infection, headache, nasopharyngitis, gastroenteritis, and pharyngitis.

The safety profile observed was consistent with previous clinical trials for adalimumab.

The MAH has provided data supporting safety of adalimumab in other related indications, such as Ankylosing spondylitis (AS), non-radiographic axial Spondyloarthritis and Psoriatic arthritis. This approach is considered acceptable, since it is acknowledged that there are significant clinical similarities between these diseases and ERA.

Uncertainty in the knowledge about the unfavourable effects

No new safety concerns were observed in the pivotal study. Long term safety data for the adalimumab-treated ERA population is limited, but will become available through the OL extension of Study M11-328 (as described in the RMP).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The current therapeutic arsenal for the targeted population is limited, among TNF-blockers only etanercept is approved for this condition in children aged 12 years and older. The importance of having access to adalimumab for the treatment of children with ERA is acknowledged. No signals have emerged that would raise suspicion of particular risks in the ERA population. It is recognized that data is limited due to the low number of subjects, but the safety profile of Humira is well characterized both in the adult and the paediatric population. Humira is approved for the use in children aged 2 years and older and the CHMP concluded that the ERA and the pJIA populations are comparable from a safety perspective.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

In one pivotal study a clinically relevant effect, difference in terms of per cent change in the number of active joints has been demonstrated. Although secondary endpoints were not met slight differences in response favouring Adalimumab over placebo were observed at week 12. Moreover, the difference between Adalimumab and placebo group in terms of PEDI 70 at week 12 consistently support the clinical relevant effect of the primary endpoint. Importantly, the efficacy is further supported by the fact that Humira has a well-documented effect in AS, which can be regarded as the corresponding disease in adults.

No signals have emerged that would raise suspicion of particular risks in the ERA population. It is recognized that data is limited due to the low number of subjects, but the safety profile of Humira is well characterized both in the adult and the paediatric population and long term safety data for the adalimumab-treated ERA population will become available through the OL extension of Study M11-328 (as described in the RMP).

In summary, a clinically relevant effect of Adalimumab has been demonstrated for the primary endpoint in the dedicated ERA pivotal study which is further supported by the corresponding well documented effect in AS. No safety issues have emerged, and the safety profile of Humira in paediatric use is well characterized through trials, registry data and post marketing experience from the pJIA indication.

The benefit-risk balance of adalimumab for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy, is considered positive.

4. Recommendations

☒ The application for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older is approvable since other concerns and major objections have all been resolved.

Final Outcome

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

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

Extension of Indication to include the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance.

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

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- **Additional risk minimisation measures**

The MAH shall ensure that the Educational programme is implemented for currently authorised indications. This programme shall ensure that physicians who intend to prescribe Humira are aware of:

- the risk of serious infections, sepsis, tuberculosis and other opportunistic infections
- the risk of heart failure
- the risk of central nervous system demyelination
- the risk of malignancies
- the Patient Alert Card is to be given to patients using Humira

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0259/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this <group of> variation<s>. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Humira EMEA/H/C/00481/II/127 for further information.

6. Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 24 July 2014.
1. Rapporteur's initial Assessment Report dated 13 February 2014.
2. Co-Rapporteur's initial Assessment Report dated 13 February 2014.
3. CHMP Request for supplementary information as agreed by the CHMP on 20 March 2014.

4. Joint Rapporteur/Co-Rapporteur assessment report on the responses provided by the MAH, dated 07 July 2014.

8. PRAC RMP advice and assessment overview adopted by PRAC on 10 July 2014.