EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2015
EMA/CHMP/177541/2015
Committee for Medicinal Products for Human Use (CHMP)

# Extension of indication variation assessment report

Invented name: Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/II/0134

Marketing authorisation holder (MAH): AbbVie Ltd.

## Note

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

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# List of abbreviations

AAA Anti-adalimumab antibody

AE Adverse event

BSA Body surface area

CD Crohn's disease

CDLQI Children's Dermatology Life Quality Index

CL/F Clearance

CRP C-reactive protein

eow Every other week

IgG1 Immunoglobulin G1

ITT Intent-to-treat

IV Intravenous

JIA Juvenile idiopathic arthritis

LOCF Last observation carried forward

MTX Methotrexate

NRI Nonresponder imputation

NSAID Non-steroidal anti-inflammatory drug

PASI Psoriasis Area and Severity Index

PDCO Pediatric Committee

PedsQL Pediatric Quality of Life Inventory

PGA Physician's Global Assessment of Psoriasis

PIP Pediatric Investigational Plan

PK Pharmacokinetic

Ps Psoriasis

PsA Psoriatic arthritis

PT Preferred term

RA Rheumatoid arthritis

SC Subcutaneous (injection)

TNF-α Tumor necrosis factor-alpha

TNF-β Tumor necrosis factor-beta

UC Ulcerative colitis

UVB Ultraviolet B

# 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 8 July 2014 an application for a variation.

This application concerns the following medicinal product:

| **Centrally authorised Medicinal product(s): For presentations: See Annex A** | **International non-proprietary name:** |
|---|---|
| Humira | adalimumab |

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

The Marketing authorisation holder (MAH) applied for a new indication for treatment of chronic plaque psoriasis in children and adolescents from 4 years of age, based on data from study M04-717 'A multicentre, randomised, double-dummy, double-blind study evaluating two doses of adalimumab versus methotrexate in paediatric subjects with chronic plaque psoriasis. 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.

The MAH has also taken the opportunity to make some minor editorial amendments to the SmPC and Package Leaflet.
A revised RMP version 11.2 was included as part of this application.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

***Information on paediatric requirements***

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0324/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0324/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0324/2013.

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

***Scientific advice***

The MAH received Scientific Advice from the CHMP on 22 March 2007. The Scientific Advice pertained to clinical aspects in relation to paediatric development of the dossier.

## *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

| Timetable | Dates |
|---|---|
| Submission date | 8 July 2014 |
| Start of procedure: | 25 July 2014 |
| Rapporteur's preliminary assessment report circulated on: | 15 September 2014 |
| PRAC Rapporteur's preliminary assessment report circulated on: | 18 September 2014 |
| PRAC Rapporteur's assessment report endorsed by PRAC on: | 9 October 2014 |
| Rapporteur's updated assessment report circulated on: | 17 October 2014 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 23 October 2014 |
| MAH's responses submitted to the CHMP on: | 19 December 2014 |
| PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 26 January 2015 |
| Rapporteur's preliminary assessment report on the MAH's responses circulated on: | 26 January 2015 |
| PRAC Rapporteur's updated assessment report on the MAH's responses circulated on: | 12 February 2015 |
| PRAC Rapporteur's assessment report on the MAH's responses endorsed by PRAC on: | 12 February 2015 |
| Rapporteur's updated assessment report on the MAH's responses circulated on: | 20 February 2015 |
| CHMP opinion: | 26 February 2015 |

# 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 (in adults), moderate to severe Crohn's disease, and moderate to severe ulcerative colitis (UC).

The psoriasis indication in adults reads as follows:

“Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA”.

Psoriasis is a chronic immune-mediated proliferative disease of the skin. In the UK, the incidence rates for individuals with psoriasis that are <20 years of age is 110 per 100,000 person years for males and 121 per 100,000 person years for females. In the Stanford Psoriasis Life History Survey, 27% of patients reported the onset before the age of 16, 10% before the age of 10, 6.5% before the age of 5, and 2% before the age of 2.

The MAH sought to add the following new indication to the product labeling for Humira: “treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy” based on data from study M04-717, a randomized, double-blind, double-dummy, multicenter study in pediatric subjects with severe chronic plaque psoriasis.

## *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 MAH.

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

- Tabular overview of clinical studies

| Type of Study | Study ID | Objectives of the Study | Study Design and Type of Control | Test Products; Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis | Duration of Treatment | Study Status; Type |
|---|---|---|---|---|---|---|---|---|
| Efficacy | M04-717 | Efficacy and safety | 4-period, randomized, double-dummy, multicenter study in pediatric subjects 4 through 17 years of age with severe chronic plaque psoriasis PeriodA (initialtreatment) Double-blind, 16 weeks 0.4 mg/kg or 0.8 mg/kg adalimumab eow or methotrexate weekly PeriodB (withdrawal) Up to 36 weeks, no treatment PeriodC (re-treatment) Double-blind, 16 weeks 0.4 mg/kg or 0.8 mg/kg adalimumab PeriodD(long-term follow-up) 52 weeks, double-blind/open-label 0.4 mg/kg or 0.8 mg/kg adalimumab or no treatment | Adalimumab 0.4 mg/kg or 0.8 mg/kg up to a maximum of 20 mg or 40 mg, respectively administered SC or methotrexate 0.1 mg/kg at Week 0A and then up to 0.4 mg/kg, maximum dose of 25 mg/week administered orally | 114 | Pediatric subjects 4 through 17 years of age with severe chronic plaque psoriasis | Up to 120 weeks | Ongoing; interim |

## 2.3.2. Pharmacokinetics

The clinical pharmacology and immunogenicity of adalimumab have been characterized in adult healthy subjects, as well as in adult subjects with RA, PsA, AS, CD, psoriasis and UC. In addition, the clinical pharmacology and immunogenicity of adalimumab in paediatric subjects with polyarticular JIA, enthesitis-related arthritis (ERA), and CD have also been studied. These data have been provided and assessed by the CHMP in previous submissions.

Pharmacokinetics in target population

Population PK analyses were conducted using Non-Linear Mixed Effects Modeling in NONMEM, combining the serum adalimumab concentration data in paediatric subjects from different indications. The data from all subjects enrolled into the 5 pediatric studies (Studies DE038 (JIA), M06-806 (Crohn's disease), M10-444 (JIA), M11-328 (ERA) and M04-717 (psoriasis)) that received adalimumab and had at least one adalimumab concentration above the lower limit of quantitation were included in the population pharmacokinetic analyses (total of 524 subjects (age 2-18 years)). For the Phase III study in psoriasis

patients, only PK data available at the time of the interim analysis were included (cut-off date 02 Dec 2013). The summary of the demographic data stratified by indication is presented in table 1.

**Table 1. Summary demographics per indication**

| CHARACTERISTICS | | RHEUMATOID ARTHRITIS | CROHN'S DISEASE | PSORIASIS | ALL SUBJECTS (N=524) |
|---|---|---|---|---|---|
| ANTI-ADALIMUMAB ANTIBODY | NEGATIVE | 194 (85.8%) | 183 (96.8%) | 83 (76.1%) | 460 (87.8%) |
| | POSITIVE | 32 (14.2%) | 6 (3.2%) | 26 (23.9%) | 64 (12.2%) |
| CONCOMITANT MTX MEDICATION | NO | 108 (47.8%) | 189 (100.0%) | 109 (100.0%) | 406 (77.5%) |
| | YES | 118 (52.2%) | | | 118 (22.5%) |
| RACE | BLACK | 4 (1.8%) | 11 (5.8%) | | 15 (2.9%) |
| | CAUCASIAN | 208 (92.0%) | 166 (87.8%) | 98 (89.9%) | 472 (90.1%) |
| | ORIENTAL/ASIAN | 3 (1.3%) | 4 (2.1%) | 5 (4.6%) | 12 (2.3%) |
| | OTHER | 11 (4.9%) | 8 (4.2%) | 6 (5.5%) | 25 (4.8%) |
| SEX | FEMALE | 159 (70.4%) | 84 (44.4%) | 61 (56.0%) | 304 (58.0%) |
| | MALE | 67 (29.6%) | 105 (55.6%) | 48 (44.0%) | 220 (42.0%) |

The variables anti-adalimumab antibodies (AAA), age, sex, race, weight (WTKG), body surface area (BSA), Albumin (ALB), CRP, CRCL, BILI, GOT, GPT, Methotrexate (MTX), IND (describing the indications RA, PS, and CD) were tested as covariates on CL/F and V2/F in the forward inclusion process.

Results

In addition to the significant AAA effect on apparent clearance the final model included the covariates body surface area (BSA), MTX concomitant use, Baseline albumin concentration (ALB) on CL/F and BSA on V2/F. PK parameters were not different between disease indications, when adjusted for the significant covariates.

VPCs stratified by indication as well as by age showed agreement between observed concentrations and simulations without any systematic deviations.

Evaluation of immunogenicity

The frequency and impact of Anti-adalimumab antibodies (AAA) was evaluated using interim PK and efficacy data available from the Phase III study in pediatric psoriasis patients (n=94). Serum measurement of AAA were obtained at baseline (Week 0A) and at Weeks 11A, 16A, 12B, 16B, 0C, 11C, 0D, 8D, and 16D (where A, B, C and D denotes period).

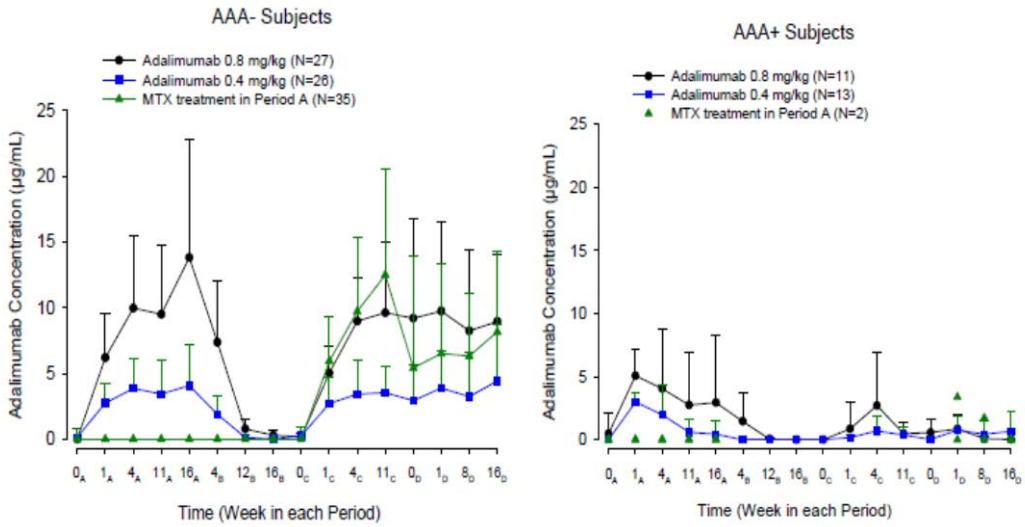
Samples were analyzed for screening and confirmatory AAA assay using a validated double antigen immunoassay, detecting free (unbound) AAA. Consistent with previous studies with adalimumab only, samples in which the adalimumab concentration was low (<2 µg/mL) were analyzed for AAA. The LLOQ for AAA was established at 10.31 ng/mL in undiluted serum and 1.031 ng/mL in 10% diluted serum. For those samples with a quantifiable AAA concentration (above 20 ng/mL), additional suppression tests (addition of adalimumab serum) were performed to evaluate the specificity of the AAA response.

**Results**

In the initial double-blind period (Period A), the percentage of subjects with AAA+ samples was approximately 13% (10 of 77 subjects) following treatment with adalimumab 0.8 mg/kg and adalimumab 0.4 mg/kg. After withdrawal of adalimumab in Period B, the percentage of subjects with AAA+ samples increased to 26.8% (11 of 41 subjects). Of the 11 subjects who had AAA+ samples, 6 subjects were measured as AAA+ only during withdrawal (Period B). Upon re-treatment (Period C), the percentage of subjects with AAA+ samples decreased to approximately 10% (3 of 30 subjects) for the adalimumab groups, which was similar to the rates observed prior to treatment withdrawal (Period A).

There was a significant impact of AAA on the exposure to adalimumab, as illustrated in Figure 3.

**Figure 1** Interim Mean + SD Serum Adalimumab Concentrations Versus Time Profiles Stratified by AAA+ Status




The impact of AAA on clinical outcome was also evaluated using the interim data. The primary efficacy endpoints were the proportion of subjects achieving a ≥PASI 75 response and a PGA score of 0/1 at Week 16A. Interim analysis of the primary efficacy by AAA status was performed at Week 16A (Table 3).

**Table 2** Proportion of Subject Achieving PASI 75/PGA Response by AAA Status at Week 16A (InterimAnalysis)

| | Responder (n/N, %) | | | |
|---|---|---|---|---|
| | 0.8 mg/kg | | 0.4 mg/kg | |
| | AAA+ | AAA– | AAA+ | AAA– |
| **Non-Responder Imputation** | | | | |
| ≥ PASI 75 | 3/5, 60% | 19/33, 57.6 | 2/5, 40% | 15/34, 44.1 |
| PGA 0,1 | 3/5, 60% | 20/33, 60.6 | 1/5, 20% | 15/34, 44.1 |
| **Last Observation Carried Forward** | | | | |
| ≥ PASI 75 | 3/5, 60% | 19/33, 57.6 | 2/5, 40% | 15/34, 44.1 |
| PGA 0,1 | 3/5, 60% | 20/33, 60.6 | 1/5, 20% | 15/34, 44.1 |

Ten subjects were AAA+ at Week 16A; five in the 0.8 mg/kg and five in the 0.4 mg/kg group. The proportion of AAA+ subjects achieving PASI 75 and PGA 0/1 response at Week 16A was similar to AAA– subjects except for PGA 0/1 responders in the 0.4 mg/kg group.

## 2.3.3. Pharmacodynamics

***Mechanism of action***

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

## 2.3.4. Discussion on clinical pharmacology

The population pharmacokinetic model adequately described the data in paediatric patients with chronic plaque psoriasis. As described for the interim PK analysis the effect of AAA+ on adalimumab CL is substantial, causing a five-fold increase.

The presence of anti-adalimumab antibodies (AAA) significantly reduced adalimumab serum exposures in pediatric subjects with psoriasis in Study M04-717. In the initial double-blind treatment period (Period A), there were only 10 of 77 AAA+ subjects (13%); 5 subjects in the adalimumab 0.8 mg/kg dose group and 5 subjects in the adalimumab 0.4 mg/kg group. In the 0.8 mg/kg group, 3 of 5 AAA+ subjects achieved a PASI 75 or PGA 0,1 response by Week $16_A$. The serum adalimumab trough concentration values in these subjects at Week $16_A$ were 0, 0, and 1.03 µg/mL. The number of AAA+ subjects in each treatment group was too small to make a definitive conclusion regarding the impact of AAA+ on efficacy; therefore, an additional PK/PD analysis was conducted by the MAH to assess the impact of AAA on efficacy. The relationship between adalimumab exposure (trough serum concentrations) and primary efficacy endpoints in Study M04-717 was examined in AAA– subjects. The percentage of AAA– subjects achieving a PASI 75 response or a PGA score of 0,1 at Week $16_A$ was plotted against measured adalimumab trough concentrations categorized into quartiles. Of the 33 subjects in the lower 2 quartiles, 25 subjects were in the 0.4 mg/kg group. Similarly, of the 34 subjects in the upper 2 quartiles, 26 subjects were in the 0.8 mg/kg group. The exposure-response relationship for PASI 75 and PGA 0,1 showed that lower adalimumab concentrations are associated with lower PASI 75 and PGA 0,1 response rates. The proportion of subjects with PASI 75 and PGA 0,1 responses in the first quartile was about 31%. Therefore, the response rate in AAA+ subjects may be lower than observed in Study M04-717 (3 of 5 subjects), based on the comparison to adalimumab trough concentration in AAA– subjects. It is important to note that the number of AAA+ subjects in each treatment group is too small to make a definitive conclusion regarding the impact of AAA+ on efficacy.

**Prevalence of AAA+ by Indication**

The prevalence of AAA+ was also assessed in studies for different pediatric indications, including psoriasis, JIA, ERA, and CD. In Study M04-717, immunogenicity data for pediatric subjects with psoriasis was plotted separately for the primary treatment phase (Period A) and re-treatment phase (Period C; longer term continuous adalimumab administration). It is noteworthy to mention that subjects with JIA received adalimumab as monotherapy or in combination with MTX. The rate of AAA+ in subjects with pediatric psoriasis was 13%, which was in the range observed for other indications.

Differentiation of AAA+ subjects by the adalimumab dose groups, 0.8 mg/kg and 0.4 mg/kg, was also investigated in Periods A and C of Study M04-717. At the end of Period A (Week $16_A$), there were 5 subjects in each dose group, whereas at the end of Period C, there were 2 subjects that were AAA+ in the 0.8 mg/kg group and 1 subject that was AAA+ in the 0.4 mg/kg group.

The prevalence of AAA ranged from 3.3% in subjects with CD to 25.6% for subjects with JIA. In the presence of MTX, the prevalence of AAA in subjects with JIA was 5.9 %, suggesting that co-administration of MTX is associated with lower prevalence of AAA. The prevalence of AAA in subjects with psoriasis at the end of Period A (Week $16_A$) was 13% and at the end of a longer term administration (end of Period C) was 7.9%, which was between the ranges observed for other indications.

The prevalence of AAA+ status across age groups was also investigated for Study M04-717. The number of AAA+ subjects and total subjects in each quartile who received adalimumab 0.8 mg/kg are also listed. The AAA+ incidence appeared to be comparable for the first 3 quartiles over an age range of 5 to 16 years, with only small differences (1 to 2 subjects). In the fourth quartile (age range of 16 to 18 years), only 1 of 17 subjects (5.9%) was AAA+.

### 2.3.5. Conclusions on clinical pharmacology

The PK/PD analysis suggested a reduction in efficacy in AAA+ pediatric psoriasis patients, as described in the SmPC for all indications. The CHMP concluded that the prevalence of AAA+ appears comparable in this population vs. other indications. Body size was also a significant predictor of adalimumab PK supporting the use of weight based dosing. In addition, albumin was identified as a covariate affecting CL, however this effect was modest and does not warrant dose-adjustment. Disease was not a significant covariate in the model and thus it may be concluded that the pharmacokinetics in this new patient population is similar to that in previously treated paediatric patients.

## *2.4. Clinical efficacy*

### 2.4.1. Dose response study(ies)

No dose response studies have been performed. The efficacy of two doses of adalimumab was evaluated in the performed main efficacy study.

### 2.4.2. Main study

Study M04-717: “A Multicenter, Randomized, Double-Dummy, Double-Blind Study Evaluating Two Doses of Adalimumab versus Methotrexate (MTX) in Pediatric Subjects with Chronic Plaque Psoriasis (Ps)”.

***Methods***

Study M04-717, is a Phase 3, randomized, 4-period, double-blind, double-dummy, multicentre clinical trial conducted in paediatric subjects from 4 through 17 years of age with severe chronic plaque psoriasis.

***Study participants***

The study included paediatric subjects 4-17 years of age with chronic plaque psoriasis.

The main inclusion criteria were:

1. Subject was ≥4 years and <18 years of age;
2. Subject weighed ≥13 kg;
3. Subject failed to respond to topical therapy;
4. Subject needed systemic treatment to control his/her disease and met one of the following:
    - PGA ≥4
    - Body surface area (BSA) involved >20%
    - Very thick lesions with BSA >10%
    - PASI >20
    - PASI >10 and at least one of the following:
        - Active PsA unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs)
        - Clinically relevant facial involvement
        - Clinically relevant genital involvement
        - Clinically relevant hand and/or foot involvement
        - Children's Dermatology Life Quality Index (CDLQI) >10

The main exclusion criteria were:

1. Prior biologic use other than prior treatment with etanercept;

2. Treatment with etanercept therapy within 4 weeks prior to the baseline visit;
3. MTX use within the past year or prior MTX use at any time where the subject did not adequately respond or did not tolerate MTX;
4. Contraindication for treatment with MTX during the study;
5. Erythrodermic Ps, generalized or localized pustular Ps, medication-induced or medication-exacerbated Ps, or new onset guttate Ps;
6. Infection(s) requiring treatment with intravenous (IV) anti-infectives within 30 days prior to the baseline visit or oral anti-infectives within 14 days prior to the baseline visit.

***Treatments***

Subjects who met enrolment criteria were randomized in a 1:1:1 ration to either methotrexate, adalimumab 0.4 mg/kg or adalimumab 0.8 mg/kg.

At the time of data cut-off for the Study M04-717 interim CSR (02 December 2013), 69 subjects (60.5%) had completed the study (through Period D); 24 subjects (21.1%) had discontinued from the study, 18 of whom discontinued during Period D; and 21 subjects (18.4%) were still ongoing in the study (in Period D).

The study design for study M04-717 is shown below (figure 4). The study is comprised of 4 periods and the objective of each period is shown in the table below.

**Figure 4. Study design schematic**

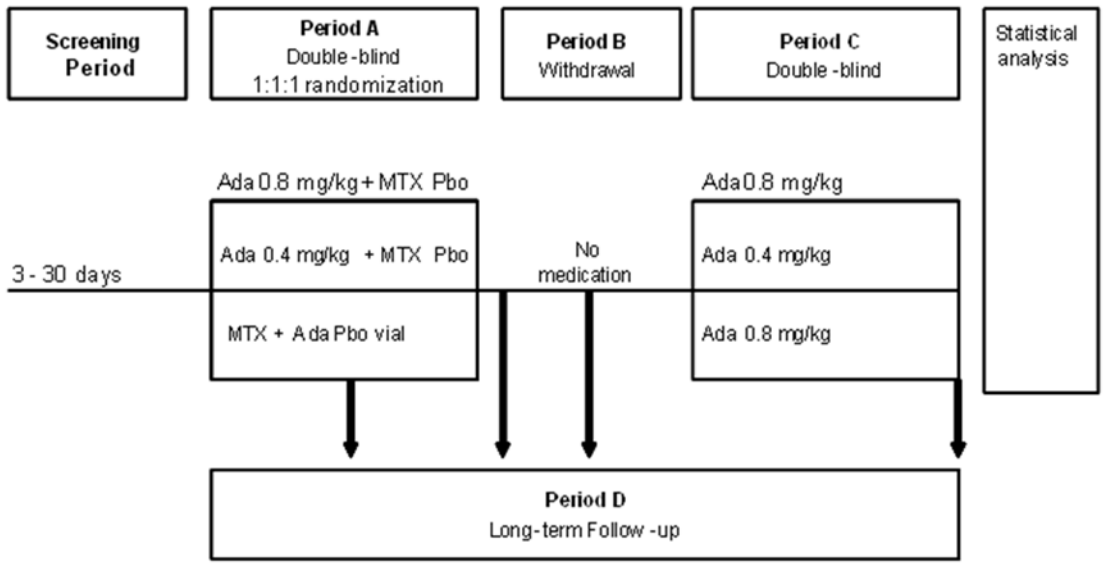



**Table 4. Summary of Study M04-717 design**

| Period | Description | Duration (For an Individual Subject) |
|---|---|---|
| Period A | Primary Treatment Phase: Subjects received treatment via randomization to adalimumab 0.8 mg/kg,[a] adalimumab 0.4 mg/kg,[b] or MTX[c] in 1:1:1 ratio | 16 weeks |
| Period B | Withdrawal Phase: Responders from Period A were withdrawn from active treatment and monitored for loss of disease control | Up to 36 weeks |
| Period C | Re-Treatment Phase: Subjects from Period B who had experienced loss of disease control were treated with adalimumab | 16 weeks |
| Period D | Long-Term Follow-Up Phase: Subjects from Periods A, B, and C who met entry criteria to Period D received adalimumab or were observed off-treatment (if disease remained under control during Period B) | 52 weeks |

a. Adalimumab 0.8 mg/kg: single SC loading dose of 0.8 mg/kg (up to a maximum dose of 40 mg) at Week $0_A$, followed by eow dosing beginning at Week $1_A$.

b. Adalimumab 0.4 mg/kg: single SC loading dose of 0.4 mg/kg (up to a maximum dose of 20 mg) at Week $0_A$, followed by eow dosing beginning at Week $1_A$.

c. MTX: a MTX dose of 0.1 mg/kg at Week $0_A$ (up to a maximum dose of 7.5 mg/week), followed by weekly MTX dosing up to 0.4 mg/kg (up to a maximum dose of 25 mg/week) for the remainder of Period A if there were no tolerability issues.

Discontinuation:

13 subjects randomized to adalimumab 0.4 mg/kg discontinued from the study, whereas 8 subjects randomized to adalimumab 0.8 mg/kg and 3 subjects randomized to MTX discontinued from the study. Lack of efficacy was the most reported primary reason for discontinuation. Two subjects discontinued because of an adverse event as primary reason (1 subject randomized to adalimumab 0.4 mg/kg had an event of moderate Ps flare in Period C and 1 subject initially randomized to MTX, but receiving adalimumab 0.8 mg/kg, had an event of severe urticaria in Period D).

***Objectives***

The objectives of the study were to determine the safety and efficacy of two doses of adalimumab versus MTX in pediatric subjects with severe chronic plaque psoriasis, to determine the time to loss of disease control, the ability to regain response upon re-treatment, and to examine the pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration in this subject population

***Outcomes/endpoints***

The primary efficacy endpoints were:

- The proportion of subjects achieving a ≥PASI 75 response at Week 16A, adalimumab 0.8 mg/kg versus MTX.
- The proportion of subjects achieving a PGA "cleared" or "minimal" (0 or 1) at Week 16A, adalimumab 0.8 mg/kg versus MTX.

The a priori defined order of the statistical hypotheses is:

- Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a PASI 75 response at Week 16A

- Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a PGA "cleared" or "minimal" (0 or 1) at Week 16A.

The following secondary variables were evaluated per the ranking order:

1. The proportion of subjects achieving a PASI 90 at Week 16A, adalimumab 0.8 mg/kg versus MTX

2. The proportion of subjects achieving a PASI 100 at Week 16A, adalimumab 0.8 mg/kg versus MTX

3. Change from baseline in the CDLQI scores at Week16A, adalimumab 0.8 mg/kg versus MTX

4. Change from baseline in the PedsQL scores at Week16A, adalimumab 0.8 mg/kg versus MTX

5. The proportion of subjects achieving PGA "cleared" or "minimal" (0 or 1) upon completion of re-treatment (Period C), according to the original randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg).

6. Time to loss of disease control (Period B), according to the original randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg and MTX).

***Sample size***

The sample size calculation was based on the following assumed responder rates (Table 5).

**Table 5. Assumed responder rates in sample size calculation**

| | Without prior Etanercept 30% of population | | With prior Etanercept 70% of population | | Total population | |
|---|---|---|---|---|---|---|
| | Adalimumab 0.8mg/kg | MTX | Adalimumab 0.8mg/kg | MTX | Adalimumab 0.8mg/kg | MTX |
| PASI 75 w16 | 72% | 35% | 62% | 25% | 69% | 32% |
| PGA 0,1 w16 | 62% | 30% | 52% | 20% | 59% | 27% |

With these assumptions, the total of 111 subjects (37 subjects in each group) provided 90% power for the comparison of adalimumab 0.8 mg/kg versus MTX in PASI 75 response rate and 80% power for the comparison of adalimumab 0.8 mg/kg versus MTX in PGA response rate.

***Randomisation***

Subjects were randomized to receive adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or MTX in a 1:1:1 ratio, respectively. Randomization was stratified by prior treatment with etanercept.

***Blinding (masking)***

All the MAH's personnel with direct oversight of the conduct and management of the trial, (with the exception of the MAH's Drug Supply Management Team), the PI, study site personnel, and the subject were to remain blinded to each subject's treatment throughout the blinded period of the study.

**Statistical methods**

All efficacy analyses were based on the ITT population.

The two primary efficacy endpoints were the proportion of subjects achieving a PASI ≥75 response and the proportion of subjects achieving a PGA "cleared" or "minimal" (0 or 1) response at Week 16A. These endpoints were tested in hierarchical order, first PASI then PGA, at a level of significance of 5% to preserve the overall type I error.

Due to the expected small number of subjects per group with prior etanercept treatment, the primary confirmatory analysis was to be done without stratification using a chi-square test or Fisher's exact test if expected cell count was less than 5 at alpha level of 5%. Analysis using a Cochran-Mantel-Haenszel test stratified for prior etanercept use was to be done as sensitivity analysis.

Subjects who did not have PGA or PASI assessments at Week 16A were to be imputed as nonresponders in the primary analysis and using LOCF for continuous variables. This includes subjects that "early escaped" during the initial 16-week Period A.

### *Results*

#### Participant flow

The study disposition in the study overall can be seen in the tables below.

**Table 6. Study disposition**

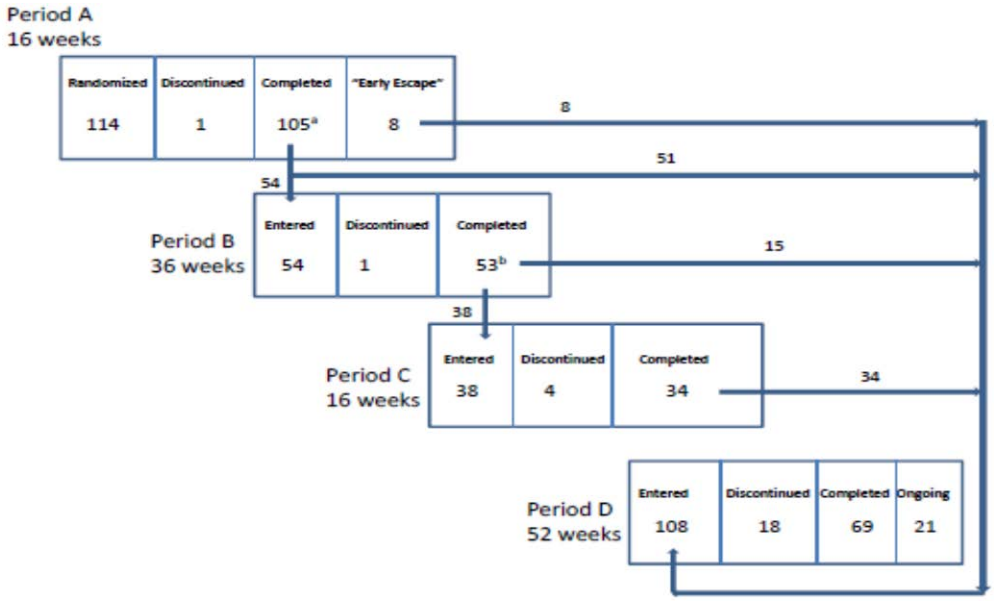
| | Number of Subjects | | | |
|---|---|---|---|---|
| | Initially Randomized Treatment Group | | | |
| | | Adalimumab | | |
| Variable | MTX | 0.4 mg/kg | 0.8 mg/kg | Total |
| Randomized | 37 | 39 | 38 | 114 |
| Completed | 29 | 21 | 19 | 69 |
| Ongoing | 5 | 5 | 11 | 21 |
| Discontinued | 3 | 13 | 8 | 24 |
| Primary reason for discontinuation | | | | |
| Adverse event | 1 | 0 | 1 | 2 |
| Withdrew consent | 0 | 2 | 1 | 3 |
| Lost to follow-up | 0 | 1 | 0 | 1 |
| Lack of efficacy | 1 | 9 | 3 | 13 |
| Other[a] | 1 | 1 | 3 | 5 |

MTX = methotrexate

a. Loss of disease control (1 subject randomized to adalimumab 0.4 mg/kg), inadequate response (1 subject randomized to adalimumab 0.8 mg/kg), almost total clearing of psoriatic lesions (1 subject randomized to MTX), pregnancy (2 subjects randomized to adalimumab 0.8 mg/kg).

Cross reference: Table 14.1__1.1.1, Table 14.1__1.1.2, Table 14.1__1.2.1.1, Appendix 16.2__1.1

**Figure 5. Study disposition in period A through D**




a. 54 subjects entered Period B and 51 subjects entered Period D.
b. 38 subjects entered Period C and 15 subjects entered Period D off-treatment.

### *Recruitment*

A total of 114 subjects were recruited at 38 sites in Canada, the EU, and rest of world (Chile, Mexico, Switzerland, and Turkey).

### *Conduct of the study*

Eleven subjects were judged to have 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:

**Table 7. Protocol Deviations (ITT Set)**

| | Number of Subjects | | | |
|---|---|---|---|---|
| | Initially Randomized Treatment Group | | | |
| | | Adalimumab | | |
| Protocol Deviation Category | MTX N = 37 | 0.4 mg/kg N = 39 | 0.8 mg/kg N = 38 | Total N = 114 |
| Inclusion/Exclusion criteria violated | 1 | 3 | 3 | 7 |
| Received wrong treatment or incorrect dose | 5 | 8 | 3 | 16 |
| Received excluded concomitant treatment | 1 | 1 | 1 | 3 |
| Developed withdrawal criteria, but was not withdrawn | 0 | 0 | 0 | 0 |

MTX = methotrexate

Cross reference: Table 14.1__1.3

### *Baseline data*

The demographic characteristics of patients in Study M04-717 can be seen in the table below.

**Table 8. Demographic characteristics (ITT set)**

| Variable | Initial Randomized Treatment Group | | | |
|---|---|---|---|---|
| | | Adalimumab | | |
| | MTX N = 37 | 0.4 mg/kg N = 39 | 0.8 mg/kg N = 38 | Total N = 114 |
| Age[a], years | | | | |
| 4 | 0 | 0[b] | 0 | 0 |
| 5 | 0 | 2[b] | 0 | 2 |
| 6 | 0 | 4 | 0[c] | 4 |
| 7 | 2 | 2 | 2[c] | 6 |
| 8 | 1 | 1 | 3 | 5 |
| 9 to 18 | 34 | 30 | 33 | 97 |
| Sex, n (%) | | | | |
| Female | 26 (70.3) | 18 (46.2) | 21 (55.3) | 65 (57.0) |
| Male | 11 (29.7) | 21 (53.8) | 17 (44.7) | 49 (43.0) |
| Race, n (%) | | | | |
| White | 34 (91.9) | 34 (87.2) | 35 (92.1) | 103 (90.4) |
| Black | 0 | 0 | 0 | 0 |
| Asian | 2 (5.4) | 2 (5.1) | 1 (2.6) | 5 (4.4) |
| American Indian/ Alaska Native | 0 | 0 | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 | 0 |
| Other | 1 (2.7) | 2 (5.1) | 2 (5.3) | 5 (4.4) |
| Multi Race | 0 | 1 (2.6) | 0 | 1 (0.9) |
| BMI, n(%)[d] | | | | |
| < 5th percentile | 1 (2.7) | 1 (2.6) | 3 (7.9) | 5 (4.4) |
| 5th to < 85th percentile | 22 (59.5) | 25 (64.1) | 21 (55.3) | 68 (59.6) |
| 85th to < 95th percentile | 6 (16.2) | 4 (10.3) | 7 (18.4) | 17 (14.9) |
| > 95th percentile | 8 (21.6) | 9 (23.1) | 7 (18.4) | 24 (21.1) |
| Weight (kg) | | | | |
| Mean ± SD | 53.1 ± 18.69 | 50.2 ± 22.51 | 50.8 ± 19.94 | 51.3 ± 20.34 |
| Median (min – max) | 52.0 (20.0 – 87.0) | 53.0 (15.0 – 108.0) | 48.5 (17.0 – 95.0) | 51.5 (15.0 – 108.0) |
| Height (cm) | | | | |
| Mean ± SD | 153.2 ± 16.44 | 151.1 ± 23.11 | 153.2 ± 19.39 | 152.4 ± 19.74 |
| Median (min – max) | 157.0 (121.0 – 182.0) | 157.0 (103.0 – 183.0) | 156.5 (104.0 – 185.0) | 157.0 (103.0 – 185.0) |

BMI = body mass index; MTX = methotrexate; WHO = World Health Organization

a. Due to privacy laws and rules surrounding collection of personal information for clinical studies, birthdates for all subjects were normalized to January 1 of their birth year.

b. 1 subject was 4 years old when enrolled, but was recorded as 5 years old when normalized by birth year.

c. 1 subject was 6 years old when enrolled, but was recorded as 7 years old when normalized by birth year.

d. Based on age- and sex-specific WHO BMI charts.

Note: Percentages calculated on nonmissing values.

The average subject had been diagnosed with plaque psoriasis for 5 years before participating in this study. The disease was considered severe on the basis of enrolment criteria.

**Table 9. Baseline disease measures (ITT set)**

| | Initial Randomized Treatment Group | | | |
|---|---|---|---|---|
| | | Adalimumab | | |
| Baseline Measure | MTX N = 37 | 0.4 mg/kg N = 39 | 0.8 mg/kg N = 38 | Total N = 114 |
| PASI (0 –72) | | | | |
| Mean ± SD | 19.2 ± 10.02 | 16.9 ± 5.76 | 18.9 ± 10.03 | 18.3 ± 8.78 |
| Median (min – max) | 17.5 (5.0 – 51.4) | 15.6 (6.1 – 29.4) | 15.3 (10.2 – 50.4) | 16.1 (5.0 – 51.4) |
| PGA, n (%) | | | | |
| Cleared | 0 | 0 | 0 | 0 |
| Minimal | 0 | 1 (2.6) | 0 | 1 (0.9) |
| Mild | 1 (2.7) | 3 (7.7) | 3 (7.9) | 7 (6.1) |
| Moderate | 19 (51.4) | 18 (46.2) | 17 (44.7) | 54 (47.4) |
| Marked | 17 (45.9) | 15 (38.5) | 17 (44.7) | 49 (43.0) |
| Severe | 0 | 2 (5.1) | 1 (2.6) | 3 (2.6) |
| CDLQI (0 – 30) | | | | |
| N | 36 | 38 | 38 | 112 |
| Mean ± SD | 11.4 ± 5.58 | 11.6 ± 7.92 | 10.9 ± 6.61 | 11.3 ± 6.74 |
| Median (min – max) | 12.0 (1 – 23) | 10.5 (0 – 27) | 10.0 (1 – 23) | 10.5 (0 – 27) |
| PedsQL (0 – 100) | | | | |
| N | 37 | 38 | 38 | 113 |
| Mean ± SD | 78.8 ± 14.92 | 70.4 ± 21.33 | 70.4 ± 14.19 | 73.1 ± 17.44 |
| Median (min – max) | 84.8 (38.0 – 98.9) | 75.0 (5.4 – 100.0) | 72.3 (41.3 – 93.5) | 77.2 (5.4 – 100.0) |
| CDI:S (39 – 100) | | | | |
| N | 36 | 35 | 36 | 107 |
| Mean ± SD | 48.5 ± 8.16 | 53.0 ± 11.54 | 51.3 ± 8.83 | 50.9 ± 9.69 |
| Median (min – max) | 49 (40 – 70) | 51 (40 – 94) | 49 (40 – 70) | 49 (40 – 94) |

All subjects reported prior topical use of medication for psoriasis. One half of the subjects had previously received phototherapy. Approximately 10% had previously used etanercept and one-third of the subjects had previously used a systemic nonbiologic treatment. The most frequently reported prior psoriasis treatments, reported by >30% of subjects were vitamin D analogue, mid to high potency corticosteroids and ultraviolet B narrow band UVB treatment.

**Table 10. Prior psoriasis medications/non-medication treatments received by > 5% of subjects (ITT set)**

| | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Initial Randomized Treatment Group | | | |
| | | Adalimumab | | |
| Prior Psoriasis Treatment | MTX N = 37 | 0.4 mg/kg N = 39 | 0.8 mg/kg N = 38 | Total N = 114 |
| Any prior psoriasis treatment | 37 (100) | 39 (100) | 38 (100) | 114 (100) |
| Etanercept | 3 (8.1) | 4 (10.3) | 4 (10.5) | 11 (9.6) |
| Systemic nonbiologic treatments | 9 (24.3) | 11 (28.2) | 14 (36.8) | 34 (29.8) |
| Acitretin | 4 (10.8) | 5 (12.8) | 6 (15.8) | 15 (13.2) |
| Cyclosporine | 5 (13.5) | 3 (7.7) | 7 (18.4) | 15 (13.2) |
| Methotrexate | 1 (2.7) | 3 (7.7) | 2 (5.3) | 6 (5.3) |
| Systemic nonbiologic treatment or etanercept | 10 (27.0) | 14 (35.9) | 17 (44.7) | 41 (36.0) |
| Topical treatments | 37 (100) | 39 (100) | 38 (100) | 114 (100) |
| Vitamin D analog | 19 (51.4) | 15 (38.5) | 17 (44.7) | 51 (44.7) |
| Corticosteroids: high potency | 19 (51.4) | 15 (38.5) | 17 (44.7) | 51 (44.7) |
| Corticosteroids: mid potency | 21 (56.8) | 15 (38.5) | 14 (36.8) | 50 (43.9) |
| Corticosteroids: low potency | 7 (18.9) | 10 (25.6) | 15 (39.5) | 32 (28.1) |
| Anthralin | 12 (32.4) | 9 (23.1) | 9 (23.7) | 30 (26.3) |
| Non-medication treatments | 21 (56.8) | 26 (66.7) | 19 (50.0) | 66 (57.9) |
| Phototherapy | 19 (51.4) | 23 (59.0) | 17 (44.7) | 59 (51.8) |
| UVB ± tar, narrow-band UVB | 14 (37.8) | 19 (48.7) | 9 (23.7) | 42 (36.8) |
| Broad-band UVB | 4 (10.8) | 4 (10.3) | 5 (13.2) | 13 (11.4) |
| Oral psoralen + UVA | 5 (13.5) | 2 (5.1) | 5 (13.2) | 12 (10.5) |

MTX = methotrexate; UVA = ultraviolet A; UVB = ultraviolet B
Note: This table includes all psoriasis-related treatments stopped prior to inclusion of the subject into the study.
Cross reference: Study M04-717 CSR Table 17

***Numbers analysed***

114 subjects were randomized and analysed.

***Outcomes and estimation***

Primary efficacy endpoints

The results were presented for the two primary efficacy endpoints to compare the adalimumab 0.8 mg/kg and MTX treatment groups in the proportion of subjects achieving a ≥PASI 75 response and the proportion of subjects achieving a PGA 0,1 (cleared, minimal) response at Week 16A (Period A).

The results presented for the primary endpoints were based on the ITT set. The primary method of handling missing or incomplete data was the nonresponder imputation (NRI) method. Sensitivity analysis included last observation carried forward (LOCF) and observed cases analyses. Results from LOCF and observed cases analyses were similar to NRI.

A statistically significantly higher proportion of subjects randomized to adalimumab 0.8 mg/kg achieved a PASI 75 response at Week 16A than subjects randomized to MTX (57.9% versus 32.4%, p = 0.027) (see table below).

**Table 11. Proportion of Subjects Who Achieved a PASI 75 or PGA 0, 1 Response at Week 16A (NRI) (ITT Set)**

| | n/N[a] (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Initial Randomized Treatment Group | | | | |
| | | Adalimumab | | | |
| Variable | MTX | 0.4 mg/kg | 0.8 mg/kg | 95% CI[b] | *P* Value[c] |
| PASI 75 | 12/37 (32.4) | 17/39 (43.6) | 22/38 (57.9) | –47.2, –3.7 | 0.027 |
| PGA 0,1[d] | 15/37 (40.5) | 16/39 (41.0) | 23/38 (60.5) | –42.2, 2.2 | 0.083 |

MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment of Psoriasis

a. n/N = number of subjects with PASI 75 or PGA 0,1 values out of the total number of subjects in Period A in each treatment group.

b. 95% confidence interval for difference in response rates between MTX and adalimumab 0.8 mg/kg, which is based on normal approximation of the binomial distribution.

c. *P* value compares difference between MTX and adalimumab 0.8 mg/kg and is based on chi-square test or Fisher's exact test, if cells have expected cell count < 5.

d. PGA 0,1 is defined as PGA cleared or minimal.

Cross reference: Study M04-717 CSR Table 22, Table 23, Table 14.2 1.1.1, Table 14.2 2.1.1

The other primary endpoint investigated, the response at Week 16A of PGA 0,1 (cleared, minimal), did not reach statistical significance (see Table 11).

Secondary endpoints

The ranked secondary endpoints provide support for the 2 primary endpoints; however, because the secondary ranked primary endpoint (PGA 0.1 [cleared, minimal]) did not achieve statistical significance, none of the secondary ranked endpoints can be interpreted as confirmatory.

*Initial response (Period A)*

Period A was a 16-week period of initial treatment in which subjects were randomized to adalimumab 0.4 mg/kg, adalimumab 0.8 mg/kg, or MTX.

A higher proportion (20% to 39%) of subjects randomized to adalimumab 0.8 mg/kg achieved PASI 50/75/90 and PGA 0,1 responses than subjects randomized to MTX. Statistical significance was observed as early as Week 4A for PASI 50/75 and as early as Week 8A for PASI 90. No statistical significance was observed for any of the timepoints in PASI 100 responses.

At Week 16A, an improvement in the mean CDLQI and PedsQL scores was greater for subjects randomized to adalimumab 0.8 mg/kg than subjects randomized to MTX (see table below). The change from baseline in PedsQL at Week 16A was statistically significant.

**Table 12. Clinically Meaningful Improvements in Primary and Ranked Secondary Endpoints**

| Variable | Initial Randomized Treatment Group: MTX | Adalimumab: 0.4 mg/kg | Adalimumab: 0.8 mg/kg | MTX – Ada 0.8 (95% CI)[a] | *P* Value |
|---|---|---|---|---|---|
| **Initial Treatment (Period A)** | | | | | |
| PASI 75 (Week $16_A$), n/N (%) | 12/37 (32.4) | 17/39 (43.6) | 22/38 (57.9) | −25.5 (−47.2, −3.7) | 0.027 |
| PGA 0,1 (Week $16_A$), n/N (%) | 15/37 (40.5) | 16/39 (41.0) | 23/38 (60.5) | −20.0 (−42.2, 2.2) | 0.083 |
| PASI 90 (Week $16_A$), n/N (%) | 8/37 (21.6) | 12/39 (30.8) | 11/38 (28.9) | −7.3 (−26.9, 12.3) | 0.466[b] |
| PASI 100 (Week $16_A$) n/N (%) | 1/37 (2.7) | 4/39 (10.3) | 7/38 (18.4) | −15.7 (−29.1, −2.3) | 0.056[b] |
| CDLQI change from baseline (Week $16_A$)[c] | −5.0 ± 7.11 (N = 36) | −4.9 ± 6.16 (N = 38) | −6.6 ± 6.22 (N = 38) | 1.61 (−1.48, 4.70) | 0.304[d] |
| PedsQL change from baseline (Week $16_A$)[c] | 1.9 ± 10.41 (N = 37) | 9.5 ± 12.25 (N = 38) | 10.8 ± 15.38 (N = 38) | −8.88 (−14.94, −2.82) | 0.005[d] |
| **Treatment Withdrawal (Period B)[e]** | | | | | |
| Loss of disease control, n/N (%) | 9/13 (69.2) | 12/18 (66.7) | 19/23 (82.6) | | |
| Time to loss of disease control (median), days | 184 | 217 | 118 | 1.58[f] (0.70, 3.54)[g] | 0.262[h] |
| | | | | 1.65[i] (0.75, 3.61)[j] | 0.204[h] |
| **Re-Treatment (Period C)** | | | | | |
| PGA 0,1 (Week $16_C$) n/N (%) | 5/8 (62.5) | 3/11 (27.3) | 10/19 (52.6) | −28.3 (−60.6, 4.0)[k] | 0.113[l] |

Ada = adalimumab; CDLQI = Children's Dermatology Life Quality Index; MTX = methotrexate; PASI = Psoriasis Area and Severity Index; PedsQL = Pediatric Quality of Life Inventory; PGA = Physician's Global Assessment of Psoriasis

a. 95% confidence interval for difference between MTX and adalimumab 0.8 mg/kg.
b. *P* values for differences between adalimumab 0.8 mg/kg and MTX were based on chi-square test or Fisher's exact test, if cells have expected cell count < 5.
c. Only subjects with both baseline and visit values are shown.
d. *P* values for difference between adalimumab 0.8 mg/kg and MTX from 1-way ANOVA.
e. Loss of disease control is defined as the worsening of PGA in comparison to Week $16_A$ by at least 2 grades.
f. Hazard ratio of adalimumab 0.8 mg/kg versus MTX.
g. 95% confidence interval for hazard ratio of adalimumab 0.8 mg/kg versus MTX.
h. *P* value for differences between adalimumab 0.8 mg/kg and MTX from log-rank test.
i. Hazard ratio of adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg.
j. 95% confidence interval for hazard ratio of adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg.
k. 95% confidence interval for difference between adalimumab 0.4 mg/kg and combined adalimumab 0.8 mg/kg + MTX groups.
l. *P* value compares the difference between the combined adalimumab 0.8 mg/kg + MTX groups and the adalimumab 0.4 mg/kg group.

Note: n/N = number of subjects with measured value out of total number of subjects in each treatment group.

*Loss of response (Period B)*

Subjects who achieved both a PASI 75 and a PGA 0,1 (cleared, minimal) response after 16 weeks of initial treatment in Period A had their treatment withdrawn for up to 36 weeks in Period B.

The time to loss of disease control, defined as a worsening of PGA scores in comparison to Week 16A by at least 2 grades after treatment withdrawal, was numerically shorter for subjects randomized to adalimumab 0.8 mg/kg than subjects who were randomized to MTX.

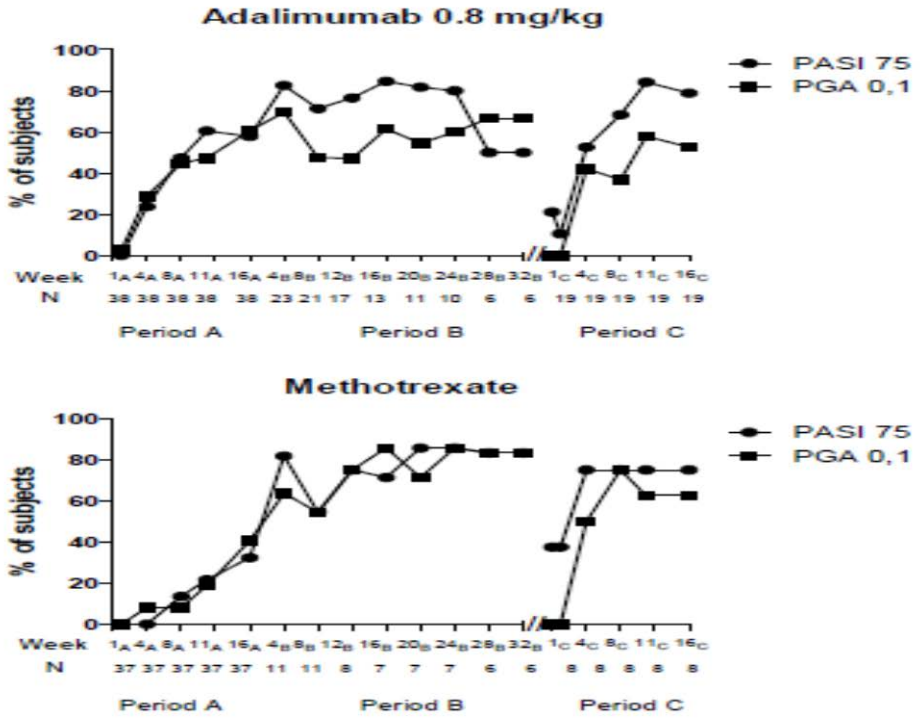
No subjects experienced a loss of disease control during the withdrawal period of the study that met the definition of rebound, defined as a PASI score at least 125% above baseline PASI within 90 days of treatment discontinuation.

*Retreatment (Period C)*

In Period C, subjects who lost disease control during Period B were re-treated for 16 weeks with their initially randomized adalimumab dose regimen or, if they were initially randomized to MTX, with adalimumab 0.8 mg/kg. PASI 75 and PGA 0,1 (cleared, minimal) responses at Week 16C for subjects initially randomized to MTX, therefore, are a result from exposure to both MTX (during initial treatment in Period A) and adalimumab 0.8 mg/kg (during re-treatment in Period C).

For subjects randomized to adalimumab 0.8 mg/kg, the PASI 75 and PGA 0,1 (cleared, minimal) response rates during initial treatment and re-treatment were similar (PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects)). For subjects randomized to MTX, the response rate to adalimumab 0.8 mg/kg in Period C was higher and occurred faster than the response rate to MTX in Period A (Figure 6).

**Figure 6. Comparison of PASI 75 and PGA 0,1 (Cleared, Minimal) Response Rates Between Initial Treatment in Period A and Re-Treatment in Period C for Subjects Initially Randomized to Adalimumab 0.8 mg/kg or Methotrexate (NRI) (ITT Set)**




Notes: Week $16_A$ = Week $0_B$.
Week $0_C$ data shown, but not labeled.

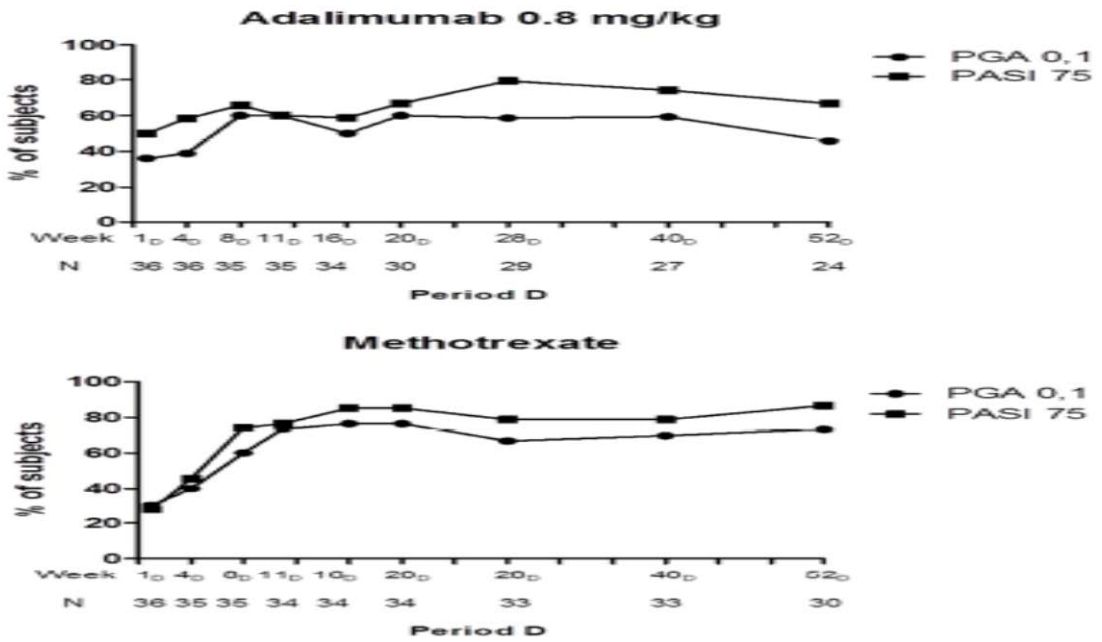
Subjects randomized to adalimumab 0.8 mg/kg or to MTX, who were re-treated with adalimumab 0.8 mg/kg, also had an improvement in mean CDLQI and mean PedsQL values.

*Maintenance (Period D)*

Period D is a 52-week long-term follow-up period during which subjects continued to receive adalimumab 0.4 mg/kg or adalimumab 0.8 mg/kg or continued to be observed off-treatment, if their disease remained under control after treatment withdrawal in Period B. At the time of data cut-off for the Study M04-717 interim CSR (02 December 2013), 21 subjects (18.4%) were still ongoing in the study.

PASI 75 and PGA 0,1 (cleared, minimal) response rates for subjects initially randomized to adalimumab 0.8 mg/kg or MTX were retained through at least Week 40D (Figure 7).

**Figure 7. PASI 75 and PGA 0,1 (Cleared, Minimal) Response Rates During Treatment Maintenance in Period D for Subjects Initially Randomized to Adalimumab 0.8 mg/kg or Methotrexate and Receiving Adalimumab 0.8 mg/kg in Period D (NRI) (ITT Set)**




For subjects initially randomized to adalimumab 0.8 mg/kg, who achieved an adequate clinical response in Period A, lost disease control in Period B, and re-achieved an adequate clinical response in Period C, PASI 75 and PGA 0,1 (cleared, minimal) response rates appeared to be maintained for the full 52 weeks in Period D. In addition, PASI 50/75/90/100 response rates were generally as high or higher at Week 52D than at Week 16A.

The improvement in CDLQI that was achieved at Week 16A appeared to be maintained with adalimumab 0.8 mg/kg throughout Period D and the proportion of subjects who achieved CDLQI scores of 0 at Week 16A generally increased with adalimumab 0.8 mg/kg treatment throughout Period D. Subjects randomized to MTX and treated with adalimumab 0.8 mg/kg in Period D showed an approximate 5-fold increase in mean change from baseline in PedsQL at Week 52D, as compared to Week 16A.

***Ancillary analyses***

*Nonresponders*

Subjects who did not achieve a PASI 75 and PGA 0,1 (cleared, minimal) response by Week 16A were considered nonresponders. These subjects continued directly to Period D, where they received open-label adalimumab 0.8 mg/kg for 52 weeks. A total of 51 subjects met the definition of nonresponder (19 subjects randomized to MTX, 18 subjects randomized to adalimumab 0.4 mg/kg, and 14 subjects randomized to adalimumab 0.8 mg/kg).

In a subgroup analysis of nonresponders from Period A, who entered Period D directly and received adalimumab 0.8 mg/kg, the PASI 75 and PGA 0,1 response rates during Period D were similar to the response rates for subjects who achieved PASI 75 and PGA 0,1 (cleared, minimal) responses in Period A (for subjects randomized to adalimumab 0.8 mg/kg) and Period C (for subjects randomized to adalimumab 0.8 mg/kg and subjects initially randomized to MTX, but receiving adalimumab 0.8 mg/kg)

The majority of nonresponders who were initially randomized to MTX and who continued directly to Period D achieved a PASI 75 and PGA 0,1 (cleared, minimal) response with adalimumab 0.8 mg/kg after 16 weeks and sustained this response to the end of the study at Week 52D.

All nonresponders, whether initially randomized to adalimumab or MTX, had an improvement in their mean CDLQI and PedsQL values after treatment with adalimumab 0.8 mg/kg for 52 weeks in Period D.

*Dose-response discussions*

Final results for Period A through Period C of this study suggest that adalimumab, at a dose of 0.8 mg/kg, was more effective than adalimumab 0.4 mg/kg in the treatment of the subject population. A substantially higher proportion of subjects treated with adalimumab 0.8 mg/kg achieved clinical response (by PASI 75 or PGA 0,1 [cleared, minimal]), as compared with subjects treated with adalimumab 0.4 mg/kg. The differences in PASI 75 and PGA 0,1 (cleared, minimal) response rates between the 2 adalimumab dose groups were not statistically significant.

In Period A, after 16 weeks of initial treatment, PASI 75 and PGA 0,1 (cleared, minimal) response rates were approximately 15 to 20 percentage points higher for subjects randomized to adalimumab 0.8 mg/kg than subjects randomized to adalimumab 0.4 mg/kg. Additionally, at Week 16A, results from the CDLQI showed a greater mean decrease (improvement) for subjects randomized to adalimumab 0.8 mg/kg than subjects randomized to adalimumab 0.4 mg/kg.

Following treatment withdrawal, re-treatment for 16 weeks (Period C) showed a 28.3% difference in PGA response rates between subjects re-treated with adalimumab 0.8 mg/kg (i.e., subjects from the randomized adalimumab 0.8 mg/kg and MTX groups) and subjects re-treated with adalimumab 0.4 mg/kg. A similar treatment difference (25.3%) was observed when the response rates for re-treatment of subjects randomized to adalimumab 0.8 mg/kg was compared to the response rate for re-treatment of subjects randomized to adalimumab 0.4 mg/kg.

During the long-term maintenance period (Period D), subjects treated with adalimumab 0.8 mg/kg had higher PASI 75 and PGA 0,1 (cleared, minimal) response rates overall than subjects treated with adalimumab 0.4 mg/kg (20% to 25% for PASI 75 and up to 12% for PGA 0,1 [cleared, minimal]).

### ***Summary of main study***

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 1. Summary of Efficacy for trial**

| | | | |
|---|---|---|---|
| **Title:** A Multicenter, Randomized, Double-Dummy, Double-Blind Study Evaluating Two Doses of Adalimumab versus Methotrexate (MTX) in Pediatric Subjects with Chronic Plaque Psoriasis (Ps) | | | |
| Study identifier | M04-717 | | |
| Design | Multicenter, Phase 3, double-dummy, double-blind active-controlled study to assess the short and long-term safety and efficacy of adalimumab versus MTX in pediatric subjects with severe chronic plaque Ps. Interim results from the double blind, withdrawal, and re-treatment periods were submitted with the current application. Data on patients in Period D (long-term follow up) were also included in the current application, up to the time when the last subject had completed the re-treatment period. Final data from Period D have not been submitted yet. | | |
| | Duration of main phase:<br><br><br><br>Duration of run-in phase:<br>Duration of extension phase: | | Period A (double blind): 16 weeks<br>Period B (withdrawal): up to 36 weeks<br>Period C (retreatment): 16 weeks<br>Not applicable<br>Period D: 52 weeks |
| Hypothesis | Superiority<br>The a priori defined order of the statistical hypotheses is:<br>1. Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a ≥ PASI 75 response at Week 16A.<br>2. Superiority of adalimumab 0.8 mg/kg versus MTX, regarding the proportion of subjects achieving a PGA "cleared" or "minimal" (0 or 1) at Week 16, Period A. | | |
| Treatment groups | ADA 0.8 mg/kg | | Adalimumab 0.8 mg/kg: 16 weeks (Period A); single SC dose of 0.8 mg/kg (maximum 40 mg) at Week 0, then 0.8 mg/kg every other week (eow) beginning Week 1. N=38. |
| | ADA 0.4 mg/kg | | Adalimumab 0.4 mg/kg: 16 weeks (Period A); single SC dose of 0.4 mg/kg (maximum 20 mg) at Week 0, then 0.4 mg/kg eow beginning Week 1 . N=39. |
| | MTX | | Methotrexate (MTX): 16 weeks (Period A); single dose of 0.1 mg/kg at Week 0 (maximum 7.5 mg), then weekly MTX dosing up to 0.4 mg/kg (maximum dose of 25 mg/week) if there were no tolerability issues. N=37. |
| Endpoints and definitions | Primary endpoint | PASI 75 | The proportion of subjects achieving a ≥ PASI 75 response at Week 16, Period A, adalimumab 0.8 mg/kg versus MTX. |
| | Primary endpoint | PGA 0 or 1 | The proportion of subjects achieving a PGA "cleared" or "minimal" (0 or 1) at Week 16, Period A, adalimumab 0.8 mg/kg versus MTX. |
| | Secondary Endpoint | PASI 90 | The proportion of subjects achieving a PASI 90 at Week 16, Period A, adalimumab 0.8 mg/kg versus MTX |

| | | | |
|---|---|---|---|
| | Secondary Endpoint | PASI 100 | The proportion of subjects achieving a PASI 100 at Week 16, Period A, adalimumab 0.8 mg/kg versus MTX |
| | Secondary Endpoint | CDLQI | Change from baseline in the CDLQI scores at Week16, Period A, adalimumab 0.8 mg/kg versus MTX |
| | Secondary Endpoint | PedsQL | Change from baseline in the PedsQL scores at Week16, Period A, adalimumab 0.8 mg/kg versus MTX |
| | Secondary Endpoint | PGA 0 or 1 (Period C) | The proportion of subjects achieving PGA "cleared" or "minimal" (0 or 1) upon completion of re-treatment (Period C), according to the original randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg). |
| | Secondary Endpoint | Time to loss of disease control (Period B) | Time to loss of disease control (Period B), according to the original randomized group assignment in Period A (adalimumab 0.8 mg/kg versus adalimumab 0.4 mg/kg and MTX) |
| Database lock | Last Subject Last Visit for interim report: 2 December 2013 (Week 16, Period C visit completed for last subject) | | |
| **Results and analysis** | | | |
| **Analysis description** | **Primary analysis** | | |
| Analysis population and time point description | Intent to Treat (ITT, defined as all randomized subjects) at week 16A (NRI for categorical endpoints, LOCF for continuous endpoints) | | |

| Descriptive statistics and estimate variability | Treatment group | ADA 0.8 mg/kg | ADA 0.4 mg/kg | MTX |
|---|---|---|---|---|
| | Number of subjects | 38 | 39 | 37 |
| | PASI75 (%) | 57.9 | 43.6 | 32.4 |
| | | | | |
| | PGA 0 or 1 (%) | 60.5 | 41.0 | 40.5 |
| | | | | |
| | PASI 90 (%) | 28.9 | 30.8 | 21.6 |
| | | | | |
| | PASI 100 (%) | 18.4 | 10.3 | 2.7 |
| | | | | |

| | | | | |
|---|---|---|---|---|
| | CDLQI (mean change from baseline) | -6.6 | -4.9 | -5.0 |
| | SD | 6.22 | 6.16 | 7.11 |
| | PedsQL (mean change from baseline) | 10.8 | 9.5 | 1.9 |
| | SD | 15.38 | 12.25 | 10.41 |
| | PGA 0 or 1 (Period C) (%) | 52.6 | 27.3 | 62.5 |
| | | | | |
| | Time to loss of disease control (Period B) median (days) | 118 | 217 | 184 |
| | | | | |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint PASI75 | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | | |
| | | Difference | –25.5 |
| | | 95% CI | (–47.2, –3.7) |
| | | P-value | 0.027 |
| | Primary endpoint PGA 0,1 | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | Difference | –20.0 |
| | | 95% CI | (–42.2, 2.2) |
| | | P-value | 0.083 |
| | Secondary endpoint PASI 90 | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | Difference | –7.3 |
| | | 95% CI | (–26.9, 12.3) |
| | | P-value | 0.466 |
| | Secondary endpoint PASI 100 | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | Difference | –15.7 |
| | | 95% CI | (–29.1, –2.3) |
| | | P-value | 0.056 |
| | Secondary endpoint CDLQI | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | Change from baseline | 1.61 |
| | | 95% CI | (–1.48, 4.70) |
| | | P-value | 0.304 |
| | Secondary endpoint PedsQL | Comparison groups | MTX vs ADA 0.8 mg/kg |
| | | Change from baseline | –8.88 |
| | | 95% CI | (–14.94, –2.82) |
| | | P-value | 0.005 |

| | | | |
|---|---|---|---|
| | Secondary endpoint PGA 0 or 1 (Period C) | Comparison groups | ADA 0.8 mg/kg vs ADA 0.4 mg/kg) |
| | | Difference | –28.3 |
| | | 95% CI | (–60.6, 4.0) |
| | | P-value between the combined adalimumab 0.8 mg/kg + MTX groups and adalimumab 0.4 mg/kg group. | 0.113 |
| | Secondary endpoint Time to loss of disease control (Period B) | Comparison groups | ADA 0.8 mg/kg vs ADA 0.4 mg/kg |
| | | Hazard ratio | 1.65 |
| | | 95% CI | (0.75, 3.61) |
| | | P-value | 0.204 |
| | Secondary endpoint Time to loss of disease control (Period B) | Comparison groups | ADA 0.8 mg/kg vs MTX |
| | | Hazard ratio | 1.58 |
| | | 95% CI | (0.70, 3.54) |
| | | P-value | 0.262 |

## 2.4.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

In support of the present application, to extend the indication of Humira to treat not only adults, but children from the age of 4 years old and adolescents with chronic plaque psoriasis, the MAH has submitted a Phase 3, randomized, 4-period, double-blind, double-dummy, multicentre clinical trial. The study design is somewhat complex but has been agreed upon at scientific advice meetings and is accepted. The study is not yet completed; the long-term follow up period was on-going at the time of submission of the variation application (as described in the RMP).

114 subjects were randomized to receive adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or methotrexate (MTX) in a 1:1:1 ratio, respectively.

The statistical methods used in the study are considered acceptable. 16 out of 114 subjects received the wrong medication which is considered a fairly large number. The MAH clarified that the incidence of the error ”wrong medication” occurred at single time points in the study and the MAH’s view that the overall study result would not have changed due to these errors is endorsed by the CHMP.

The demographic characteristics demonstrated that only two subjects between the age of 4 and 6 were exposed to adalimumab, and these subjects were randomized to adalimumab 0.4 mg/kg. Consequently there are no subjects below the age of 6 that have received adalimumab 0.8 mg/kg, the dose proposed for marketing. The numbers of subjects at the age of 6, 7 and 8 years of age were approximately 5 in every age group, while the majority of subjects were 9-18 years of age. It was a slight majority for girls in the study, as could be expected considering the gender distribution of the disease. The vast majority of participating subjects was white and of normal height according to their age. The weight was somewhat on the higher level, as could be expected in subjects with psoriasis.

The severity of psoriasis was evaluated using the PASI and the PGA scales which are often used psoriasis scales. According to the MAH, the subjects included in the study had severe psoriasis, which partly can be agreed upon. In the PASI scale, moderate to severe psoriasis has a score between 10 and 20, while

severe psoriasis has a score above 20. The average score in the study was 18.3. The PGA scale used cleared, minimal, mild, moderate, marked and severe to define the disease severity of the patients. During the procedure the MAH clarified that severity of psoriasis assessment for inclusion in Study M04-717 was based not only on the PASI and PGA scores, but also on the thickness, distribution, and location of the lesions, with thicker lesions or lesions affecting functionally and socially important locations, such as the hands, feet, face, and genitals, conferring higher severity. The Physician's Global Assessment (PGA) of disease severity was defined as the degree of overall lesion severity at the time of the physician's evaluation of the subject. The PGA was based on definitions for different degrees of scaling, erythema, and induration. The protocol specified that each site should make every attempt to have the same individual (i.e., efficacy assessor) conduct a patient's assessment throughout Period A. The protocol also specified that the PGA is static and refers to the subject's disease state at the time of the assessment and is not a comparison to the subject's previous disease state, whether at Screening, Baseline, or any other previous visits. When using these subdivisions, approximately half of the subjects had moderate and half had marked psoriasis, while only a few subjects had a severe form, one subject had a minimal and a few subjects had mild psoriasis. The average subject had 28% of the body surface area affected by psoriasis lesions.

According to the proposed SmPC, the dosing of adalimumab is different in paediatric patients compared to adults, who start with a bolus dose. The MAH clarified that the different dosing in paediatric patients compared to adults who start with a bolus dose of adalimumab resulted in comparable serum adalimumab concentrations. Moreover, comparable efficacy results, measured as PASI scores, were obtained in paediatric and adult subjects although the initial dose differed. Thus, there appears to be no impact of the difference in initial adalimumab dose for paediatric and adult patients. This was agreed by the CHMP.

The proposed recommended dose in Paediatric plaque psoriasis is 0.8 mg per kg body weight reflecting the regimen that was used in Study M04-717. In the current Humira product information, dosing for the approved pediatric indications of JIA and ERA is determined by body surface area. The MAH clarified that that the difference in dosing recommendations between JIA and psoriasis should not confusing for the dermatologists who would be prescribing Humira for pediatric patients with plaque psoriasis as there is clear separation of the dosing recommendations according to indication in the product information and the recommended dosing recommendations for each indication is clearly presented. Additionally, a comparison of body weight versus body surface area dosing regimens demonstrated that the proposed dosing regimen would, in general, be within a similar range as that already in the Humira label and would not result in significant over dosing or under dosing if the incorrect dosing table was referenced. Finally, the steady-state serum adalimumab concentrations for pediatric patients with plaque psoriasis who received the proposed recommended dose of 0.8 mg/kg bodyweight eow are similar to the steady-state serum adalimumab concentrations for patients with polyarticular JIA who received the recommended dose of 24 mg/m$^2$ body surface area (for patients 2 to <4 and 4 to 12 years of age) administered eow. The CHMP agreed with this rationale and was reassured that if a physician should follow the dosing table for JIA, instead of psoriasis, or vice-versa, the systemic exposure of adalimumab is likely to be very similar to that which would be obtained if the correct dosing table had been followed.

**Efficacy data and additional analyses**

The results following 16 weeks of treatment (Period A) demonstrated that the efficacy of adalimumab 0.8 mg/kg, measured as per cent subjects reaching PASI 75, seems to be higher than that of adalimumab 0.4 mg/kg. The dose proposed for marketing in subjects with paediatric psoriasis is 0.8 mg/kg. Moreover, treatment with adalimumab 0.8 mg/kg seems to be higher than that of methotrexate (PASI 75: 57.9% vs. 32.4% p=0.027; PGA: 60.5%vs. 40.5% p=0.083). The difference in per cent efficacy superior to that efficacy achieved with methotrexate is approximately 26 (for PASI 75).

The efficacy of adalimumab in adult patients with psoriasis was according to the approved product information evaluated using the same efficacy scores as in the present application. The efficacy results in in children and adolescents seem overall to be less convincing than in adults. This might have affected the MAH in designing the responder rates in the sample size calculation. The postulated responder rate in PASI 75 was 69% responder rate for adalimumab 0.8 mg/kg, while the outcome was 57%.

The second primary endpoint, the response at Week 16A of PGA 0,1 (cleared, minimal), did not reach statistical significance. A tendency of efficacy was obtained, while statistical significance using this endpoint has been obtained in adult psoriasis patients. The MAH concluded that the lack of statistical significance might be due to the limited sample size and power of the study or to an imbalance of exposure to prior nonbiologic treatment or etanercept. This might be the case. However, the CHMP can only conclude that a less convincing efficacy has been demonstrated in paediatric subjects with psoriasis compared to the adult population.

The CHMP also noted that no subjects at the proposed lower age limit for treatment, between 4-6 years, have been exposed to the dose proposed for marketing since they were randomised to adalimumab 0.4 mg/kg. During the procedure the MAH argued that the clinical features of plaque psoriasis are essentially the same among younger and older subjects within the paediatric population. In addition, the pharmacokinetic data in the submitted study M04-717 and PK data in other paediatric indication, particular in polyarticular JIA where Humira is approved from 2 years of age, demonstrate that the PK and exposure of adalimumab are similar between subjects 4 to 6 years of age and 6 to 17 years of age when dosed at 0.8 mg/kg. Finally the safety of Humira was overall similar in the paediatric population compared to the adult population.

Considering both the PK and safety profile of adalimumab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis is accepted by the CHMP.

Subjects who achieved both a PASI 75 and a PGA 0,1 (cleared, minimal) response after 16 weeks of initial treatment in Period A had their treatment withdrawn for up to 36 weeks in Period B and the time to loss of disease control was investigated. The time to loss of disease control, defined as a worsening of PGA scores in comparison to Week 16A by at least 2 grades after treatment withdrawal, was numerically shorter for subjects randomized to adalimumab 0.8 mg/kg, than subjects who were randomized to MTX. This finding could be anticipated considering the higher responder rates for adalimumab 0.8 mg/kg in PASI scores at week 16A.

In Period C, subjects who lost disease control during Period B were re-treated for 16 weeks with their initially randomized adalimumab dose regimen or, if they were initially randomized to MTX, with adalimumab 0.8 mg/kg. The efficacy of adalimumab 0.8 mg/kg (PASI 75 and PGA 0,1 (cleared, minimal) response rates) was similar following the 16 week retreatment period C in subjects that previously (period A) had been randomized to adalimumab 0.8 mg/kg (PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects)). Subjects that had been initially treated with MTX, and in Period C treated with adalimumab 0.8 mg/kg, demonstrated a higher and faster response rate to adalimumab than to MTX in Period A.

Period D is a 52-week long-term follow-up period during which subjects continued to receive adalimumab 0.4 mg/kg or adalimumab 0.8 mg/kg or continued to be observed off-treatment, if their disease remained under control after treatment withdrawal in Period B. At the time of data cut-off for the Study M04-717 interim CSR (02 December 2013), 21 subjects (18.4%) were still ongoing in the study. The efficacy of adalimumab 0.8 mg/kg seems to be maintained over the 52 week follow up period which is reflected also in the CDLQI.

Ancillary analysis was performed on nonresponders, defined as subjects who did not achieve a PASI 75 and PGA 0,1 (cleared, minimal) response by Week 16A. These subjects continued directly to Period D,

where they received open-label adalimumab 0.8 mg/kg for 52 weeks. The PASI 75 and PGA 0,1 response rates during Period D were similar to the response rates for subjects who achieved PASI 75 and PGA 0,1 (cleared, minimal) responses in Period A (for subjects randomized to adalimumab 0.8 mg/kg) and Period C (for subjects randomized to adalimumab 0.8 mg/kg and subjects initially randomized to MTX, but receiving adalimumab 0.8 mg/kg). The majority of nonresponders who were initially randomized to MTX and who continued directly to Period D achieved a PASI 75 and PGA 0,1 (cleared, minimal) response with adalimumab 0.8 mg/kg after 16 weeks and sustained this response to the end of the study at Week 52D.

During the procedure, and in order to increase the flexibility of each treatment center to decide on the phototherapy treatment, the CHMP requested the MAH to amend the indication as follows:

"Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies".
This was agreed by the MAH.

## 2.4.4. Conclusions on the clinical efficacy

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis who were inadequately controlled with topical therapy and heliotherapy or phototherapy. Patients received Humira 0.8mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4mg/kg eow or MTX.

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

The second primary endpoint, the response at Week 16 of PGA 0,1 (cleared, minimal), did not reach statistical significance. However, a tendency for clinical efficacy was demonstrated also in this endpoint. Taken together, a fairly convincing efficacy of adalimumab 0.8 mg/kg has been demonstrated in children and adolescents.

The CHMP also noted that no subjects at the proposed lower age limit for treatment, between 4-6 years, have been exposed to the dose proposed for marketing since they were randomised to adalimumab 0.4 mg/kg. However, considering both the PK and safety profile of adalimumab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis is accepted by the CHMP.

## *2.5. Clinical safety*

**Introduction**

The safety of adalimumab in subjects with paediatric psoriasis was determined using data from one Phase 3 clinical trial. Study M04-717 is a randomized, 4-period, double-blind, double-dummy, multicenter,

clinical trial conducted in pediatric subjects from 4 through 17 years of age with severe chronic plaque psoriasis.

The data presented is from all subjects that completed Period C, and all data accumulated in Period D up to the cut-off data of 02 December 2013.

AEs representing identified and potential risks of tumor necrosis factor (TNF) inhibitor therapy are of special interest and were examined separately by category.

**Patient exposure**

A total of 114 subjects from 4 through 17 years of age who were diagnosed with chronic plaque psoriasis and whose disease was considered severe on the basis of enrolment criteria were enrolled in the study. In Period A, these subjects were randomized 1:1:1 to either adalimumab 0.4 mg/kg, adalimumab 0.8 mg/kg or MTX.

The duration of treatments can be seen in the tables below.

**Table 13. Duration of Treatment with Study Drug – Period A (Safety Set)**

| | Initial Randomized Treatment Group | | | |
|---|---|---|---|---|
| | MTX N = 37 | Adalimumab 0.4 mg/kg N = 39 | Adalimumab 0.8 mg/kg N = 38 | All Adalimumab N = 77 |
| **Duration of treatment (days)** | | | | |
| Mean ± SD | 104.1 ± 25.11 | 110.2 ± 21.88 | 114.7 ± 14.86 | 112.4 ± 18.76 |
| Median | 112.0 | 118.0 | 119.0 | 118.0 |
| Min to max | 29 to 122 | 25 to 124 | 28 to 123 | 25 to 124 |
| **Duration of exposure, n (%)** | | | | |
| 0 to 28 days | 0 | 2 (5.1) | 1 (2.6) | 3 (3.9) |
| 29 to 56 days | 4 (10.8) | 0 | 0 | 0 |
| 57 to 84 days | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) |
| 85 to 112 days | 15 (40.5) | 12 (30.8) | 9 (23.7) | 21 (27.3) |
| 113 to 140 days | 17 (45.9) | 24 (61.5) | 28 (73.7) | 52 (67.5) |
| > 140 days | 0 | 0 | 0 | 0 |

MTX = methotrexate

Notes: Adalimumab exposure in Period A is calculated as follows:

Date of last dose of study drug – date of first dose of study drug + 14 (d), if the subject did not enter any other study period.

Date of first dose of study drug in Period D – date of first dose of study drug in Period A, if the subject continued from Period A directly to Period D.

Date of last dose of study drug in Period A – date of first dose of study drug + 14 (d), if the subject continued from Period A to Period B.

MTX exposure in Period A = date of last dose of oral study drug – date of first dose of oral study drug + 7 (d).

**Table 14. Duration of Treatment with Injectable Study Drug – Cumulative Exposure (Safety Set)**

| | Initial Randomized Treatment Group | | | |
|---|---|---|---|---|
| | MTX N = 37 | Adalimumab 0.4 mg/kg[a] N = 39 | Adalimumab 0.8 mg/kg N = 38 | All Adalimumab N = 77 |
| **Duration of treatment (days)** | | | | |
| Mean ± SD | 414.9 ± 147.92 | 348.1 ± 168.53 | 412.1 ± 135.40 | 379.7 ± 155.45 |
| Median | 476.0 | 392.0 | 475.5 | 436.0 |
| Min to max | 118 to 602 | 65 to 611 | 119 to 600 | 65 to 611 |

MTX = methotrexate

a. Exposure to adalimumab 0.4 mg/kg includes subjects who went from Period A directly to Period D, where they received adalimumab 0.8 mg/kg and subjects who went from Period A to Period B to Period C to Period D, where they had the option to switch from blinded adalimumab 0.4 mg/kg to OL adalimumab 0.8 mg/kg.

b. Exposure in MTX group includes placebo injections during Period A.

Notes: Cumulative adalimumab exposure is the sum of days of exposure in Period A + Period C + Period D.
Cumulative MTX exposure is the days of exposure in Period A.

**Adverse events**

TEAEs in period A and in the overall study are presented below.

*Period A*

In Period A, 84 of 114 subjects (73.7%) reported at least 1 AE (Table 15). The incidence of AEs was similar across all treatment groups. The incidence of AEs at least possibly related to adalimumab was 33.8% for subjects randomized to adalimumab (similar incidence between both dose groups) and 27.0% for subjects randomized to MTX.

**Table 15. Overview of Number and Percentage of Subjects with Treatment-Emergent Adverse Events – Period A (Safety Set)**

| | Initial Randomized Treatment Group | | | | |
|---|---|---|---|---|---|
| Subjects with: | MTX N = 37 n (%) | Adalimumab 0.4 mg/kg N = 39 n (%) | Adalimumab 0.8 mg/kg N = 38 n (%) | All Adalimumab N = 77 n (%) | Total N = 114 n (%) |
| Any AE | 28 (75.7) | 30 (76.9) | 26 (68.4) | 56 (72.7) | 84 (73.7) |
| Any AE at least possibly related[a] to | | | | | |
| Adalimumab | 10 (27.0) | 13 (33.3) | 13 (34.2) | 26 (33.8) | 36 (31.6) |
| MTX | 13 (35.1) | 11 (28.2) | 9 (23.7) | 20 (26.0) | 33 (28.9) |
| Study drug | 13 (35.1) | 15 (38.5) | 13 (34.2) | 28 (36.4) | 41 (36.0) |
| Any severe AE | 2 (5.4) | 5 (12.8) | 1 (2.6) | 6 (7.8) | 8 (7.0) |
| Any serious AE | 0 | 3 (7.7) | 0 | 3 (3.9) | 3 (2.6) |
| Any SAE at least possibly related[a] to | | | | | |
| Adalimumab | 0 | 0 | 0 | 0 | 0 |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug[b] | 0 | 0 | 0 | 0 | 0 |
| Any AE leading to discontinuation of | | | | | |
| Adalimumab | 0 | 0 | 0 | 0 | 0 |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug | 0 | 0 | 0 | 0 | 0 |
| Study | 0 | 0 | 0 | 0 | 0 |
| AEs leading to death | 0 | 0 | 0 | 0 | 0 |
| Deaths[c] | 0 | 0 | 0 | 0 | 0 |
| AEs of special interest | | | | | |
| All infections | 20 (54.1) | 22 (56.4) | 18 (47.4) | 40 (51.9) | 60 (52.6) |
| Serious infections | 0 | 1 (2.6) | 0 | 1 (1.3) | 1 (0.9) |
| Allergic reactions, incl. angioedema, anaphylaxis | 2 (5.4) | 1 (2.6) | 0 | 1 (1.3) | 3 (2.6) |
| Worsening and new onset of psoriasis | 1 (2.7) | 1 (2.6) | 1 (2.6) | 2 (2.6) | 3 (2.6) |
| Hematologic disorders, incl. pancytopenia | 0 | 1 (2.6) | 0 | 1 (1.3) | 1 (0.9) |
| Injection site reactions | 3 (8.1) | 3 (7.7) | 4 (10.5) | 7 (9.1) | 10 (8.8) |

AE = adverse event, MTX = methotrexate

a. As assessed by the investigator.

b. All AEs that were at least possibly related to 1 of the 2 study drugs (oral or injectable). Since investigators ticked related to oral and related to injectable study drug for some AEs, the number of subjects with events related to study drug is smaller than the sum of the number of subjects with events related to adalimumab plus the number of subjects with events related to MTX.

c. Includes non-treatment-emergent deaths.

Note: For AEs of special interest, subcategories with no events reported are not shown, including malignancies and autoimmune diseases.

*Number and Percentage of Subjects with TEAEs – Overall Study*

Overall, 104 of 114 subjects (91.2%) reported at least 1 AE during the study (Table 16). The incidence of AEs was similar across all treatment groups. The incidence of AEs considered by the investigator to be at least possibly related to adalimumab was 42.9% among subjects in the adalimumab groups, and 40.5% among subjects randomized to MTX.

**Table 16. Overview of Number and Percentage of Subjects with Adverse Events – Overall (Safety Set)**

| | Initial Randomized Treatment Group | | | | |
|---|---|---|---|---|---|
| Subjects with: | MTX N = 37 n (%) | Adalimumab 0.4 mg/kg N = 39 n (%) | Adalimumab 0.8 mg/kg N = 38 n (%) | All Adalimumab N = 77 n (%) | Total N = 114 n (%) |
| Any AE | 33 (89.2) | 35 (89.7) | 36 (94.7) | 71 (92.2) | 104 (91.2) |
| Any AE at least possibly related[a] to | | | | | |
| Adalimumab | 15 (40.5) | 17 (43.6) | 16 (42.1) | 33 (42.9) | 48 (42.1) |
| MTX | 13 (35.1) | 11 (28.2) | 9 (23.7) | 20 (26.0) | 33 (28.9) |
| Study drug[b] | 17 (45.9) | 18 (46.2) | 16 (42.1) | 34 (44.2) | 51 (44.7) |
| Any severe AE | 5 (13.5) | 7 (17.9) | 5 (13.2) | 12 (15.6) | 17 (14.9) |
| Any serious AE | 1 (2.7) | 3 (7.7) | 3 (7.9) | 6 (7.8) | 7 (6.1) |
| Any serious AE at least possibly related[a] to | | | | | |
| Adalimumab | 0 | 0 | 0 | 0 | 0 |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug | 0 | 0 | 0 | 0 | 0 |
| Any AE leading to discontinuation of | | | | | |
| Adalimumab | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| Study | 1 (2.7) | 1 (2.6) | 1 (2.6) | 2 (2.6) | 3 (2.6) |
| AEs leading to death | 0 | 0 | 1 (2.6) | 1 (1.3) | 1 (0.9) |
| Deaths[c] | 0 | 0 | 1 (2.6) | 1 (1.3) | 1 (0.9) |
| AEs of special interest | | | | | |
| All infections | 27 (73.0) | 28 (71.8) | 30 (78.9) | 58 (75.3) | 85 (74.6) |
| Serious infections | 0 | 1 (2.6) | 0 | 1 (1.3) | 1 (0.9) |
| AEs of special interest (continued) | | | | | |
| TB conversion[d] | 0 | 1 (2.6) | 1 (2.6) | 2 (2.6) | 2 (1.8) |
| Parasitic infection | 1 (2.7) | 0 | 0 | 0 | 1 (0.9) |
| Allergic reactions, incl. angioedema, anaphylaxis | 5 (13.5) | 2 (5.1) | 0 | 2 (2.6) | 7 (6.1) |
| Worsening and new onset psoriasis | 3 (8.1) | 5 (12.8) | 3 (7.9) | 8 (10.4) | 11 (9.6) |
| Hematologic disorders, incl. pancytopenia | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| Injection site reactions | 4 (10.8) | 4 (10.3) | 6 (15.8) | 10 (13.0) | 14 (12.3) |

AE = adverse event; MTX = methotrexate; TB = tuberculosis

a. As assessed by the investigator.

b. All AEs that were at least possibly related to 1 of the 2 study drugs (oral or injectable). Since investigators ticked related to oral and related to injectable study drug for some AEs, the number of subjects with events related to study drug is smaller than the sum of the number of subjects with events related to adalimumab plus the number of subjects with events related to MTX.

c. Includes non-treatment-emergent deaths.

d. No subjects had active TB during the study. Both subjects with TB conversion had a negative baseline TB PPD skin test and no signs of TB at screening. Adalimumab was interrupted and oral isoniazid 100 mg QD was given.

Note: Subjects are presented by treatment group to which they were randomized in Period A.
For AEs of special interest, subcategories with no events reported are not shown.

*Common adverse events*

*Period A*

Adverse events occurring in at least 5% of subjects in any treatment group can be seen in Table 17. Eighty-four of 114 subjects (73.7%) reported at least 1 AE in Period A. The most frequently reported events were in the Infections and Infestations SOC, reported by 60 of 114 subjects (52.6%). Upper respiratory tract infections occurred in 7.8% of subjects randomized to adalimumab (10.3% of subjects randomized to adalimumab 0.4 mg/kg, and 5.3% of subjects randomized to adalimumab 0.8 mg/kg) and 16.2% of subjects randomized to MTX. Rhinitis was reported in 5.2% of subjects randomized to adalimumab (2.6% of subjects randomized to adalimumab 0.4 mg/kg and 7.9% of subjects randomized to adalimumab 0.8 mg/kg) and 2.7% of subjects randomized to MTX. Two events of herpes zoster were reported by subjects randomized to adalimumab (1 event in each dose group).

Events in the Gastrointestinal Disorders SOC were more frequently reported among MTX subjects than adalimumab subjects (24.3% versus 18.2%, respectively). The most commonly reported gastrointestinal events were nausea, vomiting, abdominal pain, and abdominal pain upper, which are events commonly associated with MTX.

**Table 17. AEs Reported by at Least 5% of Subjects in Any Treatment Group by Primary SOC and PT – Period A (Safety Set)**

| SOC<br>MedDRA 16.0<br>Preferred Term | Initial Randomized Treatment Group<br>MTX<br>N = 37<br>n (%) | Adalimumab<br>0.4 mg/kg<br>N = 39<br>n (%) | Adalimumab<br>0.8 mg/kg<br>N = 38<br>n (%) | All<br>Adalimumab<br>N = 77<br>n (%) | Total<br>N = 114<br>n (%) |
|---|---|---|---|---|---|
| Any AE | 28 (75.7) | 30 (76.9) | 26 (68.4) | 56 (72.7) | 84 (73.7) |
| Gastrointestinal disorders | | | | | |
| Abdominal pain | 4 (10.8) | 1 (2.6) | 1 (2.6) | 2 (2.6) | 6 (5.3) |
| Abdominal pain upper | 0 | 2 (5.1) | 1 (2.6) | 3 (3.9) | 3 (2.6) |
| Dyspepsia | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| Nausea | 4 (10.8) | 3 (7.7) | 2 (5.3) | 5 (6.5) | 9 (7.9) |
| Vomiting | 0 | 3 (7.7) | 1 (2.6) | 4 (5.2) | 4 (3.5) |
| General disorders and administration site conditions | | | | | |
| Asthenia | 1 (2.7) | 2 (5.1) | 0 | 2 (2.6) | 3 (2.6) |
| Chest pain | 2 (5.4) | 0 | 0 | 0 | 2 (1.8) |
| Fatigue | 2 (5.4) | 4 (10.3) | 0 | 4 (5.2) | 6 (5.3) |
| Injection site pain | 3 (8.1) | 1 (2.6) | 3 (7.9) | 4 (5.2) | 7 (6.1) |
| Injection site reaction | 0 | 1 (2.6) | 2 (5.3) | 3 (3.9) | 3 (2.6) |
| Pyrexia | 1 (2.7) | 3 (7.7) | 1 (2.6) | 4 (5.2) | 5 (4.4) |
| Infections and infestations | | | | | |
| Gastroenteritis | 3 (8.1) | 0 | 2 (5.3) | 2 (2.6) | 5 (4.4) |
| Nasopharyngitis | 7 (18.9) | 10 (25.6) | 8 (21.1) | 18 (23.4) | 25 (21.9) |
| Rhinitis | 1 (2.7) | 1 (2.6) | 3 (7.9) | 4 (5.2) | 5 (4.4) |
| Upper respiratory tract infection | 6 (16.2) | 4 (10.3) | 2 (5.3) | 6 (7.8) | 12 (10.5) |
| Musculoskeletal | | | | | |
| Arthralgia | 2 (5.4) | 1 (2.6) | 1 (2.6) | 2 (2.6) | 4 (3.5) |
| Back pain | 0 | 1 (2.6) | 2 (5.3) | 3 (3.9) | 3 (2.6) |
| Nervous system disorders | | | | | |
| Headache | 4 (10.8) | 7 (17.9) | 6 (15.8) | 13 (16.9) | 17 (14.9) |
| Respiratory, thoracic and mediastinal disorders | | | | | |
| Cough | 1 (2.7) | 4 (10.3) | 1 (2.6) | 5 (6.5) | 6 (5.3) |
| Oropharyngeal pain | 2 (5.4) | 1 (2.6) | 2 (5.3) | 3 (3.9) | 5 (4.4) |
| Skin and subcutaneous tissue disorders | | | | | |
| Dry skin | 1 (2.7) | 0 | 3 (7.9) | 3 (3.9) | 4 (3.5) |
| Eczema | 0 | 2 (5.1) | 1 (2.6) | 3 (3.9) | 3 (2.6) |
| Pruritus | 1 (2.7) | 3 (7.7) | 1 (2.6) | 4 (5.2) | 5 (4.4) |

AE = adverse event; MTX = methotrexate

Note: The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports two or more different preferred terms which are in the same system organ class is counted only once in the system organ class total.

*Overall study*

104 of 114 subjects (91.2%) reported at least 1 AE during the study (Table 18). The incidence of AEs was similar across all treatment groups.

**Table 18. Overview of Number and Percentage of Subjects with Adverse Events – Overall (Safety Set)**

| | Initial Randomized Treatment Group | | | | |
|---|---|---|---|---|---|
| Subjects with: | MTX N = 37 n (%) | Adalimumab 0.4 mg/kg N = 39 n (%) | Adalimumab 0.8 mg/kg N = 38 n (%) | All Adalimumab N = 77 n (%) | Total N = 114 n (%) |
| Any AE | 33 (89.2) | 35 (89.7) | 36 (94.7) | 71 (92.2) | 104 (91.2) |
| Any AE at least possibly related[a] to | | | | | |
| Adalimumab | 15 (40.5) | 17 (43.6) | 16 (42.1) | 33 (42.9) | 48 (42.1) |
| MTX | 13 (35.1) | 11 (28.2) | 9 (23.7) | 20 (26.0) | 33 (28.9) |
| Study drug[b] | 17 (45.9) | 18 (46.2) | 16 (42.1) | 34 (44.2) | 51 (44.7) |
| Any severe AE | 5 (13.5) | 7 (17.9) | 5 (13.2) | 12 (15.6) | 17 (14.9) |
| Any serious AE | 1 (2.7) | 3 (7.7) | 3 (7.9) | 6 (7.8) | 7 (6.1) |
| Any serious AE at least possibly related[a] to | | | | | |
| Adalimumab | 0 | 0 | 0 | 0 | 0 |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug | 0 | 0 | 0 | 0 | 0 |
| Any AE leading to discontinuation of | | | | | |
| Adalimumab | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| MTX | 0 | 0 | 0 | 0 | 0 |
| Study drug | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| Study | 1 (2.7) | 1 (2.6) | 1 (2.6) | 2 (2.6) | 3 (2.6) |

| | Initial Randomized Treatment Group | | | | |
|---|---|---|---|---|---|
| Subjects with: | MTX N = 37 n (%) | Adalimumab 0.4 mg/kg N = 39 n (%) | Adalimumab 0.8 mg/kg N = 38 n (%) | All Adalimumab N = 77 n (%) | Total N = 114 n (%) |
| AEs leading to death | 0 | 0 | 1 (2.6) | 1 (1.3) | 1 (0.9) |
| Deaths[c] | 0 | 0 | 1 (2.6) | 1 (1.3) | 1 (0.9) |
| AEs of special interest | | | | | |
| All infections | 27 (73.0) | 28 (71.8) | 30 (78.9) | 58 (75.3) | 85 (74.6) |
| Serious infections | 0 | 1 (2.6) | 0 | 1 (1.3) | 1 (0.9) |
| TB[d] | 0 | 1 (2.6) | 1 (2.6) | 2 (2.6) | 2 (1.8) |
| TB conversion | 0 | 1 (2.6) | 1 (2.6) | 2 (2.6) | 2 (1.8) |
| Parasitic infection | 1 (2.7) | 0 | 0 | 0 | 1 (0.9) |
| Allergic reactions, incl. angioedema, anaphylaxis | 5 (13.5) | 2 (5.1) | 0 | 2 (2.6) | 7 (6.1) |
| Worsening and new onset psoriasis | 3 (8.1) | 5 (12.8) | 3 (7.9) | 8 (10.4) | 11 (9.6) |
| Hematologic disorders, incl. pancytopenia | 1 (2.7) | 1 (2.6) | 0 | 1 (1.3) | 2 (1.8) |
| Injection site reactions | 4 (10.8) | 4 (10.3) | 6 (15.8) | 10 (13.0) | 14 (12.3) |

AE = adverse event; MTX = methotrexate; TB = tuberculosis

a. As assessed by the investigator.

b. All AEs that were at least possibly related to 1 of the 2 study drugs (oral or injectable). Since investigators ticked related to oral and related to injectable study drug for some AEs, the number of subjects with events related to study drug is smaller than the sum of the number of subjects with events related to adalimumab plus the number of subjects with events related to MTX.

c. Includes non-treatment-emergent deaths.

d. No subjects had active TB during the study.

Notes: Subjects are presented by treatment group to which they were randomized in Period A.
For AEs of special interest, subcategories with no events reported are not shown.

*Adverse events assessed as possibly or probably related to study drug*

Adverse events that were assessed as possibly or probably related to study drug in Period A and the study overall can be seen in the tables below.

*Period A*

**Table 19. AEs Reported in More than one Subject in Any Treatment Group and Assessed as Possibly or Probably Related to Study Drug – Period A (Safety Set)**

| SOC<br>MedDRA 16.0<br>Preferred Term: | Initial Randomized Treatment Group<br>MTX<br>N = 37<br>n (%) | Adalimumab 0.4 mg/kg<br>N = 39<br>n (%) | Adalimumab 0.8 mg/kg<br>N = 38<br>n (%) | All Adalimumab<br>N = 77<br>n (%) | Total<br>N = 114<br>n (%) |
|---|---|---|---|---|---|
| Any AE | 13 (35.1) | 15 (38.5) | 13 (34.2) | 28 (36.4) | 41 (36.0) |
| GI disorders | | | | | |
| Abdominal pain upper | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| Dyspepsia | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| Nausea | 3 (8.1) | 3 (7.7) | 2 (5.3) | 5 (6.5) | 8 (7.0) |
| Vomiting | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| General disorders and administration site conditions | | | | | |
| Fatigue | 2 (5.4) | 4 (10.3) | 0 | 4 (5.2) | 6 (5.3) |
| Injection site pain | 3 (8.1) | 1 (2.6) | 3 (7.9) | 4 (5.2) | 7 (6.1) |
| Injection site reaction | 0 | 1 (2.6) | 2 (5.3) | 3 (3.9) | 3 (2.6) |
| Infections and infestations | | | | | |
| Nasopharyngitis | 2 (5.4) | 1 (2.6) | 3 (7.9) | 4 (5.2) | 6 (5.3) |
| Upper respiratory tract infection | 3 (8.1) | 2 (5.1) | 0 | 2 (2.6) | 5 (4.4) |
| Nervous system disorders | | | | | |
| Headache | 2 (5.4) | 3 (7.7) | 1 (2.6) | 4 (5.2) | 6 (5.3) |

AE = adverse event; GI = gastrointestinal; MTX = methotrexate

Note: The sum of the total number of subjects reporting each of the preferred terms should be greater than or equal to the system organ class total. A subject who reports 2 or more different preferred terms that are in the same system organ class is counted only once in the system organ class total.

*Overall study*

**Table 20. Adverse Events Reported in More than one Subject in Any Treatment Group and Assessed as Possibly or Probably Related to Study Drug – Overall (Safety Set)**

| SOC<br>MedDRA 16.0<br>Preferred Term: | Initial Randomized Treatment Group<br>MTX<br>N = 37<br>n (%) | Adalimumab 0.4 mg/kg<br>N = 39<br>n (%) | Adalimumab 0.8 mg/kg<br>N = 38<br>n (%) | All Adalimumab<br>N = 77<br>n (%) | Total<br>N = 114<br>n (%) |
|---|---|---|---|---|---|
| Any AE | 17 (45.9) | 18 (46.2) | 16 (42.1) | 34 (44.2) | 51 (44.7) |
| GI disorders | | | | | |
| Abdominal pain upper | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| Dyspepsia | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| Nausea | 3 (8.1) | 4 (10.3) | 2 (5.3) | 6 (7.8) | 9 (7.9) |
| Vomiting | 0 | 2 (5.1) | 0 | 2 (2.6) | 2 (1.8) |
| General disorders and administration site conditions | | | | | |
| Fatigue | 2 (5.4) | 5 (12.8) | 1 (2.6) | 6 (7.8) | 8 (7.0) |
| Injection site pain | 3 (8.1) | 2 (5.1) | 3 (7.9) | 5 (6.5) | 8 (7.0) |
| Injection site reaction | 0 | 1 (2.6) | 3 (7.9) | 4 (5.2) | 4 (3.5) |
| Infections and infestations | | | | | |
| Bronchitis | 2 (5.4) | 1 (2.6) | 0 | 1 (1.3) | 3 (2.6) |
| Herpes zoster | 0 | 2 (5.1) | 1 (2.6) | 3 (3.9) | 3 (2.6) |
| Nasopharyngitis | 4 (10.8) | 3 (7.7) | 6 (15.8) | 9 (11.7) | 13 (11.4) |
| Upper respiratory tract infection | 4 (10.8) | 4 (10.3) | 2 (5.3) | 6 (7.8) | 10 (8.8) |
| Musculoskeletal and connective tissue disorders | | | | | |
| Back pain | 0 | 2 (5.1) | 1 (2.6) | 3 (3.9) | 3 (2.6) |
| Nervous system disorders | | | | | |
| Headache | 3 (8.1) | 3 (7.7) | 2 (5.3) | 5 (6.5) | 8 (7.0) |

AE = adverse event; GI = gastrointestinal; MTX = methotrexate

Note: Subjects are presented by treatment group to which they were randomized in Period A.

**Serious adverse event / deaths / other significant events**

*Deaths*

There was one death reported during the study. A 17-year-old white male randomized to adalimumab 0.8 mg/kg died from an accidental fall. The fall occurred 11 days after the last dose in Period D, but before the last scheduled Period D visit. The event was assessed by the investigator as not related to study drug.

*Other serious adverse event*

Seven of 114 subjects (6.1%) reported 8 treatment-emergent SAEs, and 1 subject reported a non-treatment-emergent SAE. A listing of all treatment-emergent SAEs is presented in Table 21.

**Table 21. Listing of Treatment-Emergent Serious Adverse Events by Study Period (Safety Set)**

| Subject Number | Initial Randomized Treatment Group | Age/ Sex/ Race | Period[b]/ Day | Rx Day Onset[c] | SAE PT | Duration | Severity | Relation[d] to: ADA/MTX | Other Cause of Event | Action Taken |
|---|---|---|---|---|---|---|---|---|---|---|
| 10800108 | Adalimumab 0.4 mg/kg | 18/ male/ white | A/65 | 65 | Hand fracture | 30 days | Severe | Not/Not | Upper right extremity trauma | Other: right hand metacarpal bone wiring surgery |
| | | | D/112 | 224 | Tendon injury | 45 days | Severe | Not/Not | Right hand injury | Other: secondary reconstruction of IV finger extensor |
| 10200506 | Adalimumab 0.8 mg/kg | 17/ male/ white | D/726 (Post/11) | 726 | Fall* | 1 days | Severe | Not/Not | Accidental fall causing death | Discontinued study |
| 10700202 | Adalimumab 0.8 mg/kg | 15/ female/ Hispanic | B/52 | 164 | Haemorrhagic ovarian cyst | 4 days | Severe | Probably not/ Probably not | Irregular menstrual cycles | Treated with medication |
| 10400504 | Adalimumab 0.4 mg/kg | 18/ female/ white | A/7 | 7 | GI infection | 4 days | Moderate | Not/Not | Food poisoning | Interruption of study drug |
| 10500304 | MTX | 16/ female/ white | D/23 | 135 | Chest pain | 46 days | Severe | Probably not/ Probably not | Not evaluated/ intensive sport activity leading to muscle strain | None |
| 10800203 | Adalimumab 0.8 mg/kg | 15/ female/ white | D/110 | 224 | Rash maculo-papular | 9 days | Moderate | Probably not/ Not | Probably drug reaction after phenoxymethyl-penicillin or mononucleosis | Treated with medication |
| 1100103 | Adalimumab 0.4 mg/kg | 17/ female/ white | A/23 | 23 | Agitation | 12 hours | Moderate | Probably not/ Probably not | Single episode of alcohol overtake | Treated with medication |

Ada = adalimumab; GI = gastrointestinal; MTX = methotrexate; PT = preferred term; SAE = serious adverse event

* Fatal event that occurred 11 days after the last dose of adalimumab 0.8 mg/kg, but before the last Period D visit.

a. Treatment to which subject was initially randomized in Period A.

b. Period A = double-blind period; Period B = withdrawal period; Period C = retreatment period; Period D = follow-up period; Post = post follow-up period.

c. Relative to the first dose of study drug.

d. As assessed by the investigator.

*Adverse events of special interest*

<u>Infections</u>

Infectious AEs were reported in a total of 74.6% of subjects overall. 29 subjects (25.4%) experienced infectious AEs of special interest which were assessed by the investigator as possibly or probably related to study drug. These were respiratory infections (13 subjects [11.4%] with nasopharyngitis, 10 subjects

[8.8%] with upper respiratory tract infections, 3 subjects [2.6%] each with bronchitis and herpes zoster, and 1 subject each with viral upper respiratory tract infection, influenza, pharyngitis streptococcal, rhinitis, and tonsillitis).

Tuberculosis

Two subjects tested positive for TB conversion, both during Period D.

- One subject who was randomized to adalimumab 0.8 mg/kg, reported an AE of tuberculin test positive on Day 270 of Period D that was considered by the investigator to be probably related to adalimumab. The subject's baseline TB PPD skin test was negative and there were no signs of TB at screening. Adalimumab was interrupted and the subject treated with oral isoniazid 100 mg QD. The event was ongoing after 83 days.
- One subject who was randomized to adalimumab 0.4 mg/kg, tested positive for TB on Day 225 of Period D. Mild latent TB was reported as an AE, which was considered by the investigator to be possibly related to adalimumab. The subject's baseline TB PPD test was negative and there were no signs of TB at screening. The subject was treated with oral isoniazide 100 mg QD. The event was ongoing after 142 days.

Parasitic infections

One subject had a parasitic infestation (lice) assessed as not related to study drug.

Herpes Zoster

In addition to two subjects (1 each in the 0.4 mg/kg and 0.8 mg/kg adalimumab groups) with herpes zoster in Period A, one additional subject had a possibly drug-related herpes zoster infection while receiving adalimumab in Period D.

Allergic reactions

Allergic reactions were reported for 7 subjects. There were 4 events of urticaria (1 subject receiving MTX in Period A, 2 subjects receiving adalimumab in Period A or D, and 1 subject 3 days after the last adalimumab treatment in Period D). There were 2 events of pruritus generalized (both receiving adalimumab in Period C or D), and 1 event of dyspnea (subject receiving MTX in Period A). One event of severe urticaria in a subject randomized to MTX, but receiving adalimumab 0.8 mg/kg in Period C, led to discontinuation of adalimumab and discontinuation from the study.

One event of pruritus and 1 event of urticaria were assessed by the investigator as probably related to adalimumab. All of the events resolved with the exception of one case of pruritus, which was ongoing after 25 days.

Haematological disorders

Two subjects reported 3 haematological AEs, while receiving adalimumab.

- A subject initially randomized to MTX, but receiving adalimumab 0.8 mg/kg, reported an event of mild leukopenia on Day 2 of Period C that lasted 6 days. The event was considered by the investigator to be possibly related to study drug. The subject had several events of upper respiratory tract infection during Period A and Period B that may have contributed to the low WBC counts. On Day 1 of Period D, the subject also reported an event of mild neutropenia that lasted 107 days. The event was considered by the investigator to be possibly related to adalimumab.
- A Subject randomized to adalimumab 0.4 mg/kg had an event of mild leukopenia on Day 30. The event was assessed by the investigator as probably not related to adalimumab.

Injection site reactions

Fourteen of 114 subjects (12.3%) on study M04-717 reported events of injection site reactions. Ten subjects randomized to adalimumab (4 subjects randomized to adalimumab 0.4 mg/kg and 6 subjects randomized to adalimumab 0.8 mg/kg) and 4 subjects randomized to MTX reported a total of 20 injection site reaction-related AEs, including 7 injection site reactions, 9 events of injection site pain, and 1 event each of pruritus, rash, swelling, and hematoma. Almost all injection site AEs were assessed by the investigator as possibly or probably related to adalimumab and not related to MTX. The majority of injection sites AEs were mild and most resolved without treatment. The only severe injection site-related event (injection site pain) was reported in Period A by a subject randomized to MTX, but receiving placebo injection.

Worsening and new onset of psoriasis

Eleven subjects (5 subjects randomized to adalimumab 0.4 mg/kg and 3 subjects each randomized to adalimumab 0.8 mg/kg or MTX) reported 12 events of worsening or new onset of psoriasis. Three events were reported during Period A, 1 event during Period B, 4 events during Period D, and 4 events during the post-treatment period following Period D. The majority of these events were mild to moderate in severity and 2 events were considered to be severe. These severe events were reported by subjects randomized to adalimumab 0.4 mg/kg (1 event occurred in Period A and 1 event in the post-treatment period following Period D). All of these events were due to a worsening of psoriasis, with the exception of 1 subject who had a new onset of the psoriasis variant, psoriasis inversa, which occurred during treatment withdrawal in Period B.

**Laboratory findings**

*Haematology*

In Period A, analysis of mean changes in haematology values from baseline to final visit showed a few statistically significant pairwise differences between treatment groups. The differences were by the MAH not considered clinically meaningful.

*Clinical chemistry*

Analysis of mean changes in chemistry values from baseline to final visit also showed few statistically significant pairwise differences between treatment groups. These differences were not considered clinically meaningful. In Period A and overall, no subjects randomized to adalimumab experienced shifts in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin from normal or low at baseline to high (≥ 1.5 × the upper limit of normal [ULN]) at final. One subject had shifts in ALT and AST from normal at baseline to ≥ 1.5 - <3 × ULN at final visit. This subject was randomized to MTX and entered Period D directly from Period A.

Liver function tests were examined for clinical significance according to the following criteria: ≥ 2.5 × ULN for ALT, AST, and alkaline phosphatase and ≥ 1.5 × ULN for total bilirubin:

- A subject randomized to MTX, had 3 occurrences of ALT elevation. On Day 1 and Day 113 of Period D, during which the subject was receiving adalimumab 0.8 mg/kg, ALT values increased to 68 U/L and 49 U/L, respectively (ULN = 48 U/L). On Day 5 of the post-treatment period following Period D, the subject's ALT value was further increased to 146 U/L and the AST value was elevated to 68 U/L (ULN = 42 U/L). An AE of hepatic enzyme increased was reported on Post-treatment Day 5 and assessed by the investigator as possibly related to adalimumab.

Post-study follow-up visits were planned, but no further information on results of retesting is available.

- A subject randomized to adalimumab 0.8 mg/kg, had an elevated ALT value of 174 U/L (ULN = 48 U/L) and an elevated AST value of 121 U/L (ULN = 42 U/L) on Day 106 of Period D. The total bilirubin value was normal on that day and the subject was asymptomatic. Both tests were within the normal range by Day 14 of the post-treatment period following Period D.
- A subject randomized to adalimumab 0.4 mg/kg, had total bilirubin values ≥ 1.5 × ULN at all study visits from Pretreatment Day - 27 through Day 28 of Period D. The highest total bilirubin value was reported on Day 1 of Period D when the total bilirubin value was 50 µmol/L (ULN = 22 µmol/L).

*Urinalysis*

There were no statistically significant between-group differences in mean changes from baseline to final visit in continuous urinalysis values (pH and specific gravity).

**Safety in special populations**

The use of adalimumab during pregnancy and lactation is not recommended. No change in the Humira prescribing information is recommended at this time.

**Discontinuation due to adverse events**

No AEs led to discontinuation from the study during Period A or Period B. One subject, who was initially randomized to MTX, but received adalimumab 0.8 mg/kg in Period C, reported an event of severe urticaria that led to discontinuation from treatment.

- The subject randomized to MTX, but receiving adalimumab 0.8 mg/kg in Period C, reported a severe event of urticaria on Day 209 that was assessed by the investigator as probably related to adalimumab. The subject was discontinued from study drug and from the study and was treated with a single application twice a-day (BID) of betamethasone valerate for 7 days. The event was considered resolved on Day 213.

In Period D, 1 subject randomized to adalimumab 0.8 mg/kg died from an accidental fall that occurred 11 days after the last dose, assessed by the investigator as not related to study drug. One subject randomized to adalimumab 0.4 mg/kg and concurrently receiving adalimumab 0.8 mg/kg had an AE of moderate flare of Ps that led to discontinuation from adalimumab.

- The subject randomized to adalimumab 0.4 mg/kg, reported an event of moderate Ps flare are on Day 57 of Period D that was assessed by the investigator as not related to study drug. The subject was discontinued from adalimumab and from the study and was treated with a single application once-a-day (QD) of topical betamethasone with calcipotriol and betamethasone + salicylic acid. The event was ongoing as of Day 223. No further information was provided.

**Post marketing experience**

Adalimumab was first approved for treatment of rheumatoid arthritis on 31 December 2002. As of 31 December 2013, adalimumab has been evaluated in 42,568 subjects with rheumatoid arthritis, juvenile idiopathic arthritis, pediatric enthesitis related arthritis, PsA, Crohn's disease, pediatric CD, Psoriasis, pediatric Ps, ulcerative colitis, ankylosing spondylitis, spondyloarthritis, non-radiographic axial SpA, hidradenitis suppurativa, uveitis, and intestinal Behçet's disease. The estimated cumulative postmarketing patient exposure since the IBD through 31 December 2013 is 2.9 million PYs and for juvenile idiopathic arthritis and Crohn's disease patients <18 years of age since the IBD through 31

December 2013 is 38,421 PYs worldwide.

### 2.5.1. Discussion on clinical safety

The safety of adalimumab in subjects with paediatric psoriasis was determined using data from study M04-717, a randomized, 4-period, double-blind, double-dummy, multicenter, clinical trial. The data presented are from the end of the first 16-week treatment period (Period A) and from the entire study (Period A to Period D). The duration of treatment overall to adalimumab 0.4 mg/kg was 348 days and to adalimumab 0.8 mg/kg 412 days.

During Period A, the incidence of adverse events was approximately 35% in subjects dosed with either dose of adalimumab or MTX. In the study overall (Period B to Period D), the incidence of AEs was also similar across all treatment groups. The incidence of AEs considered by the investigator to be at least possibly related to adalimumab was 42.9% among subjects in the adalimumab groups, and 40.5% among subjects randomized to MTX.

The most frequently reported adverse events in Period A were in the Infections and Infestations SOC. Upper respiratory tract infections occurred in 7.8% of subjects randomized to adalimumab (10.3% in subjects randomized to adalimumab 0.4 mg/kg, and 5.3% in subjects randomized to adalimumab 0.8 mg/kg) and in 16.2% of subjects randomized to MTX. Rhinitis was reported in 5.2% of subjects randomized to adalimumab (2.6% adalimumab 0.4 mg/kg and 7.9% adalimumab 0.8 mg/kg) and 2.7% of subjects randomized to MTX. Occasionally, there is more adverse event noted among subjects treated with 0.4 mg/kg adalimumab compared to 0.8 mg/kg, which is assessed as a chance finding. 0.8 mg/kg of adalimumab is the dose proposed for use in paediatric psoriasis patients.

Adverse events in the gastrointestinal tract were more frequently reported among MTX subjects than adalimumab subjects (24.3% versus 18.2%, respectively). The most commonly reported gastrointestinal events were nausea, vomiting, abdominal pain, and abdominal pain upper, which are adverse events commonly associated with MTX.

In the study overall (Period A-Period D), the incidence of adverse events was similar among the treatment groups, with infections as the most frequently seen adverse event. Among the adverse events reported in more than one subject in any treatment group and by the investigator assessed as possibly or probably related to study drug, infections, injections site pain and injections site reactions, nausea and headache dominated in the overall safety data set.

One death occurred during the study, a 17-year-old white male randomized to adalimumab 0.8 mg/kg, who died from an accidental fall. The death was by the investigator assessed as not related to study drug, an opinion which is endorsed by the CHMP. All treatment-emergent SAEs (hand fracture tendon injury, fall, haemorrhagic ovarian cyst, GI infection, chest pain, rash, agitation) were assessed by the investigator as not related or probably not related to study drug. No malignancies were detected during the study.

Adverse events of special interest followed during the study were infections, tuberculosis, parasitic infections, herpes zoster, allergic reactions, haematological disorders, injections site reactions, and worsening and new onset of psoriasis. Three subjects had herpes zoster, assessed as a fairly large number. The MAH has presented the incidences of herpes zoster in paediatric clinical trials overall including the paediatric psoriasis study. The event rate was slightly higher in the pediatric psoriasis study. It is however acknowledged that the number of events is small (n=3) and a few subjects have so far been exposed, compared to larger clinical trials in other indication. The overall rate of herpes zoster infection in paediatric subjects (2.7% – 3.1%) is was considered by the CHMP consistent with the current adalimumab label of ≥ 1/100 to < 1/10.

Respiratory infections with nasopharyngitis were the most common observed infection during the study. Two subjects tested positive for TB conversion and one subject had a parasitic infection assessed as not related to study drug. Three subjects had herpes zoster and allergic reactions (urticarial and pruritus) were reported for 7 subjects. Two subjects reported three haematological adverse events (mild leukopenia and mild neutropenia). Injection site AEs were observed in 12% of subjects in the study M04-717. The majority were mild and most resolved without treatment. Eleven subjects reported worsening of new onset of psoriasis; three events were reported during Period A, one event during Period B, four events during Period D, and four events during the post-treatment period following Period D.

Occasional elevations of ALT were noted during the study. Elevated liver enzymes are included as a very common adverse event in the product information, and are not considered a cause for concern by the CHMP.

One significant adverse event that led to study discontinuation was severe urticarial in a 10-years old white male receiving adalimumab 0.8 mg/kg in Period C, assessed by the investigator as probably related to adalimumab. This opinion is endorsed by the CHMP.

In Period D, 13-year-old white male got a moderate flare of psoriasis, which could be related to treatment, although assessed by the MAH as not related. This opinion is endorsed by the CHMP.

The safety of Humira was overall similar in the paediatric population compared to the adult population. During the procedure the MAH has addressed the safety of Humira in patients 4 to 17 years of age with polyarticular JIA and patients 2 to <4 years of age with polyarticular JIA. The safety of adalimumab was comparable despite the differences in the age groups receiving treatment. The view of the MAH that the safety profile in younger children with plaque psoriasis (lower age limit of 4 years) would be consistent with the safety profile in younger patients with polyarticular JIA is endorsed.

### 2.5.2. Conclusions on clinical safety

No new safety concerns have emerged in the present study performed in paediatric patients with psoriasis. The adverse events noted have been seen in adult patients with psoriasis and in clinical trials with Humira in other paediatric indications.

Based on the data provided by the MAH the CHMP concluded that safety profile in younger children with plaque psoriasis (lower age limit of 4 years) would be consistent with the safety profile in younger patients with polyarticular JIA and therefore that the proposed lower age limit for treatment, between 4-6 years has been justified.

### 2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

## *2.6. Risk management plan*

The PRAC considered that the risk management plan version 11.2 could be acceptable if the applicant implemented the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report. The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 11.2.1 with the following content:

***Safety concerns***

Table 22: Summary of the Safety Concerns

| Summary of Safety Concerns | |
|---|---|
| Important identified risks | Serious infections including diverticulitis and opportunistic infection, e.g., invasive fungal infections, parasitic infections, legionellosis and tuberculosis (TB);<br>Reactivation of hepatitis B;<br>Pancreatitis;<br>Lymphoma;<br>Hepatosplenic T-cell lymphoma (HSTCL);<br>Leukemia;<br>Non-melanoma skin cancer (NMSC);<br>Melanoma;<br>Merkel Cell Carcinoma (Neuroendocrine carcinoma of the skin);<br>Demyelinating disorders (including multiple sclerosis [MS], Guillain-Barré syndrome [GBS] and optic neuritis);<br>Immune reactions (including lupus-like reactions and allergic reactions);<br>Sarcoidosis;<br>Congestive heart failure (CHF);<br>Myocardial infarction (MI);<br>Cerebrovascular Accident (CVA);<br>Interstitial lung disease (ILD);<br>Pulmonary embolism;<br>Cutaneous vasculitis;<br>Stevens-Johnson syndrome (SJS) and erythema multiforme;<br>Worsening and new onset of Psoriasis (Ps);<br>Haematologic disorders;<br>Intestinal perforation;<br>Intestinal stricture in Crohn's disease (CD);<br>Liver failure and Other Liver Events;<br>Elevated Alanine aminotransferase (ALT) levels;<br>Autoimmune Hepatitis; and<br>Medication errors and maladministration. |

| Summary of Safety Concerns | |
|---|---|
| Important potential risks | Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma);<br>Vasculitis (non-cutaneous);<br>Progressive multifocal leukoencephalopathy (PML);<br>Reversible posterior leukoencephalopathy syndrome (RPLS);<br>Amyotrophic Lateral Sclerosis (ALS);<br>Colon cancer in ulcerative colitis (UC) patients;<br>Infections in infants exposed to adalimumab in utero;<br>Medication errors with paediatric vial; and<br>Off-label use. |
| Missing information | • Subjects with immune-compromised conditions either due to underlying conditions (i.e., diabetes, renal or liver failure, HIV infection, alcohol or illicit drug abuse) or due to medications (post cancer chemotherapy, anti-rejection drugs for organ transplant) may have increased known risks of infection or other unknown risks related to the condition or to the concomitant medications.<br>• Long-term safety information in the treatment of children aged from 4 years to less than 18 years with Ps and from 6 years to less than 18 years with CD and pedERA;<br>• Pregnant and lactating women;<br>• Remission-withdrawal-retreatment nr-axSpA data and episodic treatment in Ps, CD, UC, and juvenile idiopathic arthritis (JIA). |

***Pharmacovigilance plan***

## Overview of Ongoing and Planned Pharmacovigilance Actions

| Actions | Milestone/ Exposure | Milestones/ Calendar Time | Study Status |
|---|---|---|---|
| **Ongoing Pharmacovigilance Actions** | | | |
| Long-Term PedERA Data (OL Extension Period of Study M11-328) | Up to 204 weeks | September 2016 | Ongoing |
| Annual interim data from Registry for CD patients (Study P06-134) | -- | Reporting February through 2015 | Ongoing |
| Registry for CD patients (Study P06-134) | 6 years | Final report August 2016 | Ongoing |
| Annual interim data from Registry for pedCD patients (Study P11-292) | -- | Reporting August through 2023 | Ongoing |
| Registry for pedCD patients (Study P11-292) | 10 years | TBD | Ongoing |
| Annual interim data from Registry for Ps patients (Study P10-023) | -- | Reporting February through 2022 | Ongoing |
| Registry for Ps patients (Study P10-023) | 10 years | Final Report February 2023 | Ongoing |
| Evaluation of treatment interruptions with the Ps registry (Study P10-023) | 10 years | February 2023 | Ongoing |
| Annual interim data from Registry for JIA patients (Study P10-262) | -- | Reporting August through 2024 | Ongoing |
| Registry for JIA patients (Study P10-262) | 10 years | Final Report December 2024 | Ongoing |
| Evaluation of treatment interruptions with the JIA registry (Study P10-262) | 10 years | December 2024 | Ongoing |
| Support Rheumatoid Arthritis National Registry in Germany (RABBIT) until the end of 2017 (Biannual summary report) | NA | Reporting February through 2017 (Biannually) | Ongoing |
| Support Rheumatoid Arthritis National Registry in Germany (RABBIT) until the end of 2017 | NA | TBD | Ongoing |
| Support Rheumatoid Arthritis National Registry in United Kingdom (BSRBR) until 2013 | NA | TBD | Ongoing |
| Support Rheumatoid Arthritis National Registry in Sweden (ARTIS) until 2011 | NA | TBD | Ongoing |

| | | | |
|---|---|---|---|
| Progress report for Registry for UC (Study P11-282) | -- | August 2013 | Planned |
| Annual Interim data from Registry for UC (Study P11-282) | -- | Reporting August through 2019 | Planned |
| Biannual Interim data from Registry for UC (Study P11-282) | -- | Reporting August from 2019 through 2023 | Planned |
| Registry for UC patients (Study P11-282) | 10 years | TBD | Planned |
| Long-term pedPs data (52-week follow-up phase of Study M04-717) | -- | No later than 03 August 2015 | Ongoing |

***Risk minimisation measures***

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important Identified Risk** | | |
| Serious infections including diverticulitis and opportunistic infections, e.g., invasive fungal infections, parasitic infections, legionellosis, and TB | Labelling. | To educate prescribers and patients about the risk of serious infections associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Reactivation of hepatitis B | Labelling. | None proposed. |
| Pancreatitis | Labelling. | None proposed. |
| Lymphoma | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| HSTCL | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Leukemia | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| NMSC | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important Identified Risk (continued)** | | |
| Melanoma | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Merkel cell carcinoma (Neuroendocrine carcinoma of the skin) | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Demyelinating disorders | Labelling. | To educate prescribers and patients about the risk of demyelinating disorders associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Immune reactions (including lupus-like reactions and allergic reactions) | Labelling. | None proposed. |
| Sarcoidosis | Labelling. | None proposed. |
| CHF | Labelling. | To educate prescribers and patients about the risk of CHF associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| MI | Labelling. | None proposed. |
| Cerebrovascular accident | Labelling. | None proposed. |
| Interstitial lung disease | Labelling. | None proposed. |
| Pulmonary embolism | Labelling. | None proposed. |

| Safety Concern | Routine Risk Minimisation Measures | Additional Risk Minimisation Measures |
|---|---|---|
| **Important Identified Risk (continued)** | | |
| Cutaneous vasculitis | Labelling. | None proposed. |
| SJS | Labelling. | None proposed. |
| Erythema multiforme | Labelling. | None proposed. |
| Worsening and new onset of Ps | Labelling. | None proposed. |
| Haematologic disorders | Labelling. | None proposed. |
| Intestinal perforation | Labelling. | None proposed. |
| Intestinal stricture in CD | Labelling. | None proposed. |
| Liver failure and other liver events | Labelling. | None proposed. |
| Elevated ALT levels | Labelling. | None proposed. |
| Autoimmune hepatitis | Labelling. | None proposed. |
| Medication errors and maladministration | Labelling | None proposed. |
| **Important Potential Risks** | | |
| Other malignancies (except lymphoma, HSTCL, leukemia, NMSC, and melanoma) | Labelling. | To educate prescribers and patients about the risk of malignancies associated with the use of Humira:<br>• Patient Alert Card<br>• HCP Educational Material. |
| Vasculitis (non-cutaneous) | The SmPC currently contains no text regarding vasculitis (non-cutaneous). | None proposed. |
| Progressive multifocal leukoencephalopathy (PML) | The SmPC currently contains no text regarding PML. | None proposed. |
| Reversible posterior leukoencephalopathy syndrome (RPLS) | The SmPC currently contains no text regarding reversible posterior leukoencephalopathy syndrome. | None proposed. |
| Amyotrophic lateral sclerosis (ALS) | The SmPC currently contains no text regarding reversible ALS. | None proposed. |
| Colon cancer in UC patients | Labelling. | None proposed. |

## *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*

**Paediatric plaque psoriasis**

**Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.**

*Section 4.2*

**Paediatric plaque psoriasis**

**The recommended Humira dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered subcutaneously weekly for the first two doses and every other week thereafter. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.**

**If retreatment with Humira is indicated, the above guidance on dose and treatment duration should be followed.**

**The safety of Humira in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.**

**There is no relevant use of Humira in children aged less than 4 years in this indication.**

**The volume for injection is selected based on the patients' weight (Table 2).**

**Table 2: Humira Dose in Milliliters (mL) by Weight for Patients with Pediatric Psoriasis**

| Body Weight (kg) | Paediatric Psoriasis Dose |
|---|---|
| 13 – 16 | 0.2 mL (10 mg) |
| 17 – 22 | 0.3 mL (15 mg) |
| 23 – 28 | 0.4 mL (20 mg) |
| 29 – 34 | 0.5 mL (25 mg) |
| 35 – 40 | 0.6 mL (30 mg) |
| 41 – 46 | 0.7 mL (35 mg) |
| 47+ | 0.8 mL (40 mg) |

Method of administration

Humira is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.

**A 40 mg pen and a 40 mg prefilled syringe are also available for patients to administer a full 40 mg dose.**

*Section 4.8*

Humira was studied in ~~8,198~~ **8,308** 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, 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 pivotal controlled studies involved ~~5,343~~ **5,420** patients receiving Humira and ~~3,148~~ **3,185** patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 6.**0**~~1~~% for patients taking Humira and 5.7% for control treated patients

Injection site reactions

In the pivotal controlled trials in adults and children, 13.**5**~~6~~% of patients treated with Humira developed injection site reactions …

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.5**1** ~~2~~ per patient year in the Humira treated patients and 1.4**4** ~~5~~ per patient year in the placebo and active control-treated patients.

Malignancies and lymphoproliferative disorders

No malignancies were observed in 249 paediatric patients with an exposure of 655.6 patient years during Humira trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis). 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**. No malignancies were observed in 77 paediatric patients with an exposure of 80.0 patient years during a Humira trial in paediatric patients with chronic plaque psoriasis.**

Hepato-biliary events

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.

**No ALT elevations ≥3 X ULN occurred in the Phase 3 trial of Humira in paediatric patients with plaque psoriasis.**

*Section 5.1*

**Paediatric plaque psoriasis**

**The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or PASI ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.**

**Patients received Humira 0.8mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4mg/kg eow or MTX.**

**Table 15: Paediatric Plaque Psoriasis Efficacy Results at 16 Weeks**

| | MTX[a] N=37 | Humira 0.8mg/kg eow N=38 |
|---|---|---|
| PASI 75[b] | 12 (32.4%) | 22 (57.9%) |
| PGA: Clear/minimal[c] | 15 (40.5%) | 23 (60.5%) |
| [a] MTX = methotrexate<br>[b] P=0.027, Humira 0.8 mg/kg versus MTX<br>[c] P=0.083, Humira 0.8 mg/kg versus MTX | | |

**Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2**

**grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).**

**In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.**

*Section 5.2*

**Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/mL (79% CV).**

### *2.8. Significance of paediatric studies*

The CHMP is of the opinion that the paediatric clinical studies (M04-717, DE038, M06-806, M10-444 and M11-328) of adalimumab which are contained in the agreed Paediatric Investigation Plan P/0324/2013 and completed after 26 January 2007 are significant. The assessment criteria for significance of studies as defined in Section III, Title 4.2 of the Europe Commission Communication - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01) has been fulfilled, taking into account the study type of the above-mentioned study:

(1) Comparative efficacy studies (randomized/ active control or placebo): The pivotal study M04-717 is a Phase 3, randomized, 4-period, double-blind, double-dummy, multicentre clinical trial conducted in paediatric subjects from 4 through 17 years of age with severe chronic plaque psoriasis

(2) Prospective clinical safety studies: as the pivotal study M04-717 is a randomized, 4-period, double-blind, double-dummy, multicentre clinical trial, adverse events (AEs), laboratory data, physical examinations, and vital signs were assessed throughout the study.

Furthermore studies DE038, M06-806, M10-444 and M11-328 provide meaningful pharmacokinetic information as per criteria (e) of the above mentioned Guideline which is supporting the claimed indication.

# 3. Benefit-Risk Balance

**Benefits**

**Beneficial effects**

The efficacy of adalimumab 0.8 mg/kg seems to be higher than that of adalimumab 0.4 mg/kg and methotrexate. Adalimumab 0.8 mg/kg reached statistical significance in one of the primary endpoints used; per cent subjects reaching PASI 75. The second primary endpoint, the response at Week 16 of PGA 0,1 (cleared, minimal), did not reach statistical significance. However, a tendency for clinical efficacy was demonstrated also in this endpoint. Taken together, a fairly convincing efficacy of adalimumab 0.8 mg/kg

has been demonstrated in children and adolescents. The efficacy of adalimumab was similar during a retreatment period following a withdrawal phase, and was also maintained during a 52 week period.

**Uncertainty in the knowledge about the beneficial effects**

No subjects at the proposed lower age limit for treatment, between 4-6 years, have been exposed to the dose proposed for marketing (0.8 mg/kg) since they were randomised to the lower dose of adalimumab (0.4 mg/kg). However the data showed that that the PK and exposure of adalimumab are similar between subjects 4 to 6 years of age and 6 to 17 years of age when dosed at 0.8 mg/kg. Furthermore, safety in polyarticular JIA, approved from 2 years of age demonstrated no additional cause for concern due to young age. To conclude, considering both the PK and safety profile of adalimumab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis is accepted.

**Risks**

**Unfavourable effects**

No new safety concerns have emerged in the present study. The adverse events noted have been seen in adult patients with psoriasis, and in clinical trials with adalimumab in other paediatric indications.

**Uncertainty in the knowledge about the unfavourable effects**

Long-term safety data beyond 52 weeks are lacking in the target population. As described in the RMP, there are already two ongoing non-interventional studies registries in paediatric Crohn's disease and juvenile idiopathic arthritis, which are considered sufficient to follow the long-term safety in paediatric patients treated with adalimumab.

***Benefit-Risk Balance***

**Importance of favourable and unfavourable effects**

A fairly convincing efficacy of adalimumab 0.8 mg/kg has been demonstrated in children and adolescents with severe plaque psoriasis.

Considering both the PK and safety profile of adalimumab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis is accepted.

***Benefit-risk balance***

**Discussion on the Benefit-Risk Balance**

The efficacy of Humira was assessed in a randomised, double-blind, controlled study of 114 paediatric patients from 4 years of age with severe chronic plaque psoriasis who were inadequately controlled with topical therapy and heliotherapy or phototherapy. Patients received Humira 0.8mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomised to Humira 0.8 mg/kg had positive efficacy responses (e.g., PASI 75) than those randomised to 0.4mg/kg eow or MTX.

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for loss of disease control (i.e. a worsening of PGA by at least 2 grades). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and response rates observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

The second primary endpoint, the response at Week 16 of PGA 0,1 (cleared, minimal), did not reach statistical significance. However, a tendency for clinical efficacy was demonstrated also in this endpoint. Taken together, a fairly convincing efficacy of adalimumab 0.8 mg/kg has been demonstrated in children and adolescents.

The CHMP also noted that no subjects at the proposed lower age limit for treatment, between 4-6 years, have been exposed to the dose proposed for marketing since they were randomised to adalimumab 0.4 mg/kg. However, considering both the PK and safety profile of adalimumab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis is accepted by the CHMP.

During the procedure, and in order to increase the flexibility of each treatment center to decide on the phototherapy treatment, the CHMP requested the MAH to amend the indication as follows:

"Humira is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies". This was agreed by the MAH.

The benefit-risk balance of adalimumab for the severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies is considered positive.

# 4. Recommendations

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

Extension of Indication to include the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet.

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

***Paediatric data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0324/2013and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed

paediatric investigation plan P/0324/2013 have been completed after the entry into force of that Regulation.

# 5. EPAR changes

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

***Scope***

Extension of Indication to include the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet.

***Summary***

Please refer to the scientific discussion Humira EMEA/H/C/0481/II/0134 for further information

# Attachments/annexes

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 26 February 2015
2. Rapporteurs initial Assessment Report dated 15 September 2014
3. PRAC Rapporteur's initial Assessment Report dated 18 September 2014
4. PRAC Rapporteur's Assessment Report endorsed by PRAC on 9 October 2014
5. Rapporteurs updated Assessment Report dated 17 October 2014
6. CHMP Request for supplementary information as agreed by the CHMP on 23 October 2014
7. Rapporteur's Assessment Report on the responses provided by the MAH, dated 26 January 2015
8. PRAC Rapporteur's Assessment Report on the responses provided by the MAH, dated 26 January 2015
9. PRAC Rapporteur's updated Assessment Report on the responses provided by the MAH, dated 12 February 2015
10. PRAC Rapporteur's Assessment Report on the responses provided by the MAH endorsed by PRAC on 12 February 2015
11. Rapporteur's updated assessment report on the MAH's responses circulated on 20 February 2015