22 October 2015
EMA/743698/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Humira

International non-proprietary name: adalimumab

Procedure No. EMEA/H/C/000481/P46 088

Note

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

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Introduction

On 03 August 2015, the MAH submitted the completed paediatric study for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006.

This application concerns the final Clinical Study Report (CSR) for study M04-717 which was completed on 3 February 2015. An interim CSR of the same study was used to support the Type II variation application EMEA/H/C/481/II/134 that was approved in March 2015. This Type II variation included use in paediatric patients (from 4 years of age) with severe chronic plaque psoriasis. The cut-off date for the interim CSR was the date when the last subject completed Period C of the study (2 December 2013).

A short critical expert overview was provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that Study M04-717 is a stand-alone study.

1.2. Information on the pharmaceutical formulation used in the study

Humira 40 mg/0.8 ml solution for injection for paediatric use contains 40 mg of adalimumab. Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report(s) for:

- 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)

1.3.2. Clinical 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)

Description

Study M04-717 consisted of 4 treatment periods, summarised in the table below:

Period	Description	Duration (for an individual subject)
Period A	Primary Treatment Phase: Subjects received treatment via randomization to adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg, or MTX 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Period B	Withdrawal Phase: Responders from Period A were withdrawn from active treatment and monitored for loss of disease control	Up to 36 weeks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)	52 weeks

At the cut-off date for the interim CSR, the vast majority of patients (69 of 90) had already completed the final long-term open label period of the study (Period D). Twenty-four patients had withdrawn from the study at that time. At the completion of the study, 90 patients had completed Period D, and the number of drop-outs from the study remained at 24.

Methods

Objective(s)

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.

Study design

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

Figure. Study design schematic

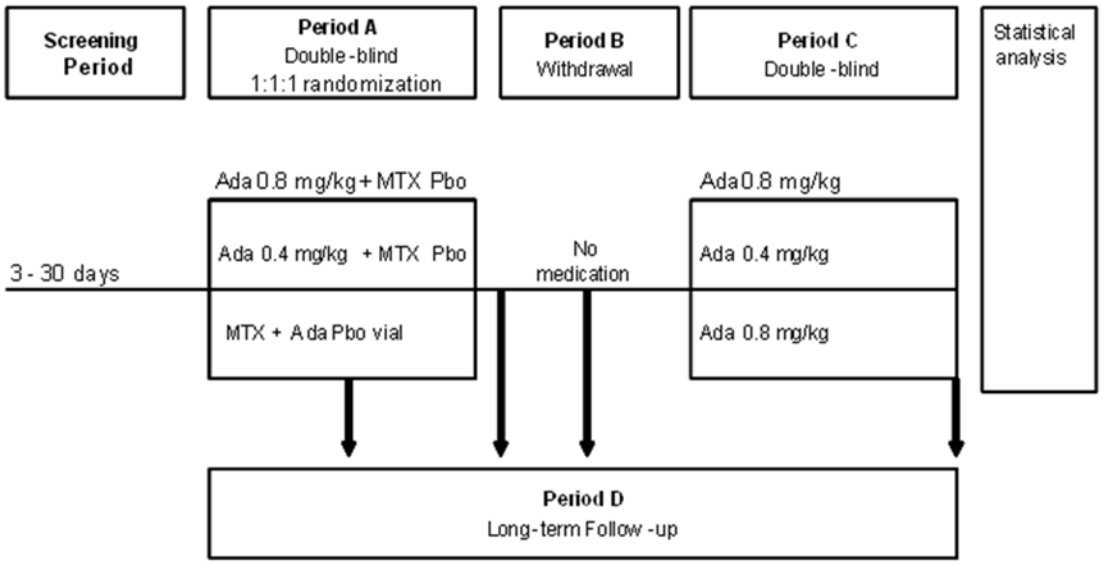


Table. Summary of Study M04-717 design

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.

Study population /Sample size

Treatments

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

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).

CHMP comment

The study design is somewhat complex but has been agreed upon at scientific advice meetings and is considered acceptable.

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).

In addition to the primary and the ranked secondary endpoints, the following efficacy endpoints were to be assessed at the different time points throughout the study:

● Proportion of subjects achieving a PGA of "cleared" or "minimal" (0 or 1).

● Proportion of subjects achieving a PGA of "cleared" (0).

● Proportion of subjects achieving ≥ PASI 50/75/90/100.

● Mean % improvement in PASI score relative to baseline (Week 0A).

- Change from baseline in CDLQI.
- Proportion of subjects with CDLQI = 0.
- Time to PASI 50/75/90/100 response.
- Change from baseline in PedsQL.
- Change from baseline in the CDI:S.

CHMP comment

The design of the study has been agreed upon by the PDCO, and the protocol, including the primary endpoint, has been approved as compliant with the PIP.

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 continous variables. This includes subjects that "early escaped" during the initial 16-week Period A.

CHMP comment

The statistical methods are considered acceptable.

Results

Recruitment

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

Baseline data

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

Table. 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.

CHMP comment

Only two subjects between the age of 4 and 6 were treated, and these subjects were randomized to adalimumab 0.4 mg/kg. Consequently there are no subjects that have received adalimumab 0.8 mg/kg, the dose proposed for marketing in this age group. 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 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. 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)

CHMP comment

The severity of psoriasis was evaluated using the PASI and the PGA scales which are often used scales. According to the Applicant, 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 in the study used cleared, minimal, mild, moderate, marked and severe to define the disease severity of the patients. According to this definition approximately half of the subjects had moderate and half had marked psoriasis, while only a few subjects had a severe form, one a minimal and a few mild psoriasis. The average subject had 28% of the body surface area affected by psoriasis lesions.

The effects of the disease on quality of life was measured using three scales; a life quality index, a pediatric quality of life inventory and a children's depression inventory. All together, the results demonstrate that the quality of life of the children was negatively affected by their disease.

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 on-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. 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

CHMP comment

Considering the disease severity of the subjects included in the study, the previous medications used are as could be expected.

Efficacy results

Primary efficacy endpoints

The results are presented for the two primary efficacy endpoints to compare the adalimimab 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 16_A (Period A).

The results presented for the primary endpoints are 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. Proportion of Subjects Who Achieved a PASI 75 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 above).

CHMP comment

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 was superior to that of methotrexate. The difference in per cent efficacy superior to that efficacy achieved with methotrexate is approximately 26.

The efficacy of adalimumab in adult patients with psoriasis was according to the SmPC section 5.1 evaluated using the same efficacy scores as in the present application. The efficacy results in adults seem overall to be somewhat higher than in children and adolescents. This might have affected the Applicant in designing the responder rates in the sample size calculation. As can be seen earlier in this AR, 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 Applicant 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 it can only be concluded that a less convincing efficacy has been demonstrated in paediatric subjects with psoriasis compared to the adult population. No subjects at the proposed lower age limit for treatment, between 4-6 years, have been exposed to the dose proposed for marketing (**LoQ**) since they were randomised to adalimumab 0.4 mg/kg.

Furthermore, the Applicant has conducted several post-hoc sensitivity analysis in which PASI 75 and PGA 0,1 (cleared or minimal) results were stratified against different factors. Overall, these calculations are considered of limited value.

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.

In the following sections, the efficacy response through the entire study is described and assessed.

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. Clinically Meaningful Improvements in Primary and Ranked Secondary Endpoints

Variable	Initial Randomized Treatment Group				
		Adalimumab			
	MTX	0.4 mg/kg	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 (see table).

No subjects experienced a loss of disease control during the withdrawal period of the study that met the definition of rebound, defined as a rapid and excessive or atypical recurrence of psoriasis following the cessation of therapy, with a PASI score at least 125% above baseline PASI within 90 days of treatment discontinuation.

CHMP comment

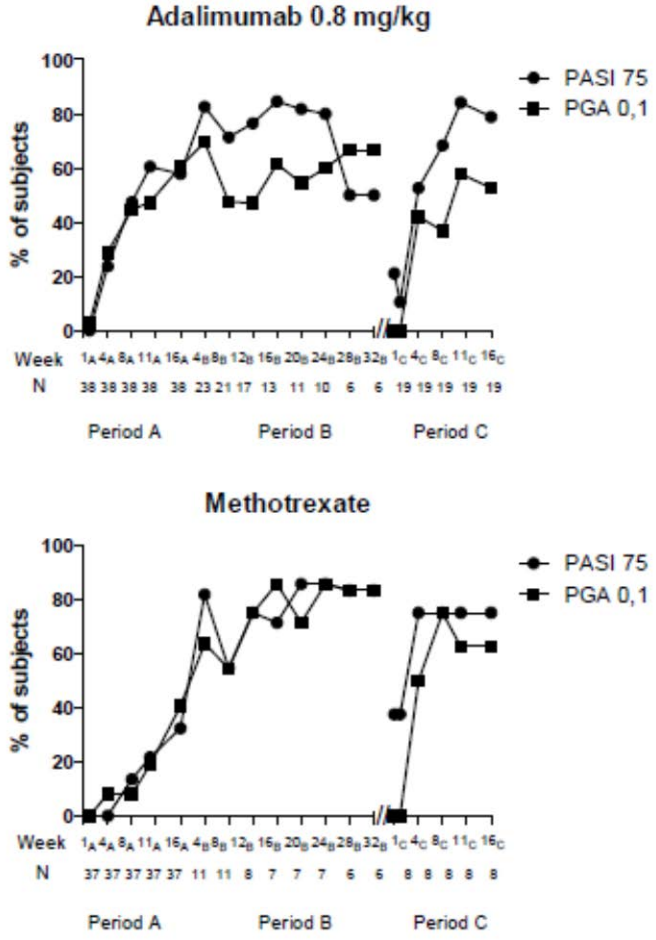
The time to loss of disease control defined as a worsening of PGA scores in comparison to Week 16A by at least 2 grades after treatment withdrawal, was numerically shorter for subjects randomized to adalimumab 0.8 mg/k, than subjects who were randomized to MTX. This finding is assessed as could be anticipated considering the higher responder rates for adalimimab 0.8 mg/kg in PASI scores at week 16A.

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. 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 (see figure below).

Figure. 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 (data not shown).

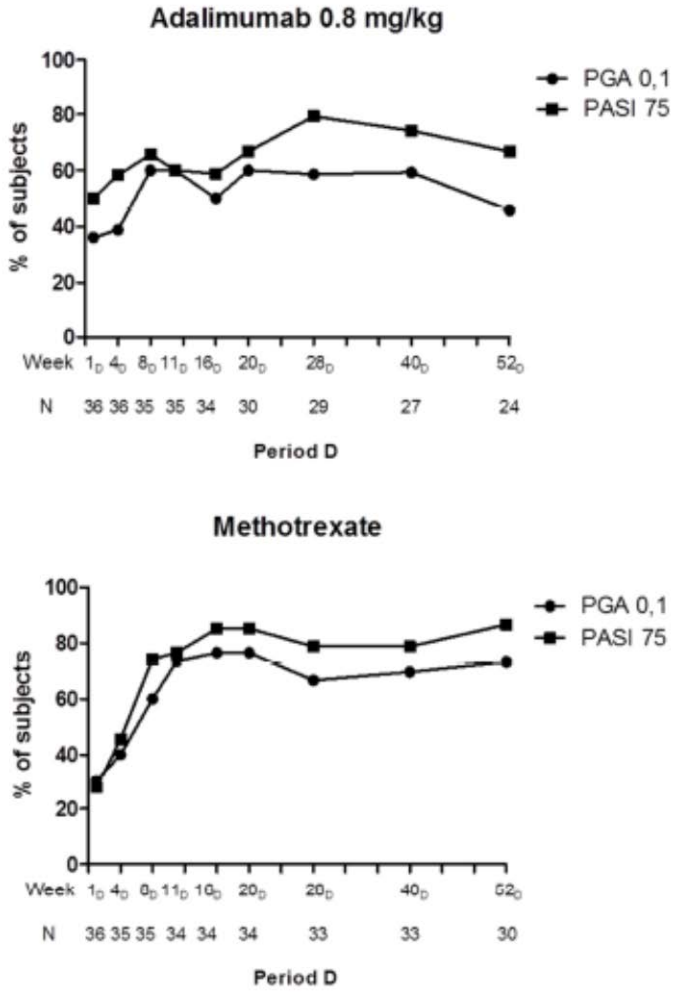
CHMP comment

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. 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.

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. 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 (see figure below)

Figure. 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 was 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 was 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.

CHMP comment

The efficacy of adalimumab 0.8 mg/kg was maintained over the 52 week follow up period, which is reflected also in the CDLQI.

Safety results

Introduktion

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.

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

	Initial Randomized Treatment Group*			
	MTX[a] N = 37	Adalimumab 0.4 mg/kg[b] N = 39	Adalimumab 0.8 mg/kg N = 38	All Adalimumab N = 77
Duration of treatment (days)				
Mean ± SD	434.4 ± 140.59	373.8 ± 174.64	464.1 ± 151.63	418.4 ± 168.83
Median	476.0	474.0.0	477.0	476.0
Min to max	119 to 602	65 to 611	119 to 600	65 to 611

MTX = methotrexate

* Subjects who continued directly from Period A to Period D received open label adalimumab 0.8 mg/kg in Period D. Subjects entering Period B initially randomized to MTX received adalimumab 0.8 mg/kg in Periods C and D. Subjects initially randomized to adalimumab 0.4 mg/kg or 0.8 mg/kg received adalimumab in Periods C and D according to their initial randomized dose. All subjects had a dose increase option to open label 0.8 mg/kg in Period D. Subjects who maintained disease control continued off treatment in Period D.

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

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.

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.

Cross reference: R&D/14/1263 Table 14.1__2.1

CHMP comment

The mean duration of treatment with either dose of adalimumab during Period A was 112 days. The duration of treatment overall to adalimumab 0.4 mg/kg was 374 days and to adalimumab 0.8 mg/kg 464 days. The demographic characteristics, baseline disease measures, prior and concomitant medications were identical as presented earlier in this Assessment report.

In the Updated Rapporteur extension of indication variation AR, is was stated in section 2.5.2 Discussion on clinical safety. The text has been updated with results obtained from the last 21 patients in Period D.

Assessment of paediatric data 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. A total of 114 subjects from 4 through 17 years of age, diagnosed with chronic plaque psoriasis were enrolled in the study. The subjects were randomized 1:1:1 to receive treatment with either adalimumab 0.4 mg/kg, adalimumab 0.8 mg/kg or MTX.

The data presented are from the end of the first 16-week treatment period (Period A) and from the entire study (Period B to Period D). The duration of treatment overall to adalimumab 0.4 mg/kg was 374 days and to adalimumab 0.8 mg/kg 464 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 B-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.

Adverse events occurring in at least 5% of subjects in any treatment group are shown in the table below.

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

SOC MedDRA 17.0 Preferred Term:	Initial Randomized Treatment Group* 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	34 (91.9)	35 (89.7)	36 (94.7)	71 (92.2)	105 (92.1)
GI disorders					
Abdominal pain	5 (13.5)	1 (2.6)	3 (7.9)	4 (5.2)	9 (7.9)
Abdominal pain upper	2 (5.4)	3 (7.7)	3 (7.9)	6 (7.8)	8 (7.0)
Diarrhoea	2 (5.4)	2 (5.1)	3 (7.9)	5 (6.5)	7 (6.1)
Dyspepsia	0	2 (5.1)	0	2 (2.6)	2 (1.8)
Nausea	7 (18.9)	6 (15.4)	7 (18.4)	13 (16.9)	20 (17.5)
Vomiting	2 (5.4)	4 (10.3)	4 (10.5)	8 (10.4)	10 (8.8)
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	3 (8.1)	5 (12.8)	2 (5.3)	7 (9.1)	10 (8.8)
Influenza-like illness	1 (2.7)	1 (2.6)	2 (5.3)	3 (3.9)	4 (3.5)
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)
Pyrexia	3 (8.1)	4 (10.3)	2 (5.3)	6 (7.8)	9 (7.9)
Infections and infestations					
Acute tonsillitis	0	1 (2.6)	2 (5.3)	3 (3.9)	3 (2.6)
Bronchitis	2 (5.4)	1 (2.6)	4 (10.5)	5 (6.5)	7 (6.1)
Folliculitis	2 (5.4)	0	1 (2.6)	1 (1.3)	3 (2.6)
Gastroenteritis	3 (8.1)	2 (5.1)	2 (5.3)	4 (5.2)	7 (6.1)
Herpes zoster	0	2 (5.1)	1 (2.6)	3 (3.9)	3 (2.6)
Influenza	5 (13.5)	1 (2.6)	4 (10.5)	5 (6.5)	10 (8.8)
Nasopharyngitis	12 (32.4)	15 (38.5)	17 (44.7)	32 (41.6)	44 (38.6)
Oral herpes	2 (5.4)	1 (2.6)	2 (5.3)	3 (3.9)	5 (4.4)
Otitis media	0	2 (5.1)	1 (2.6)	3 (3.9)	3 (2.6)

SOC MedDRA 17.0 Preferred Term:	Initial Randomized Treatment Group* 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 (%)
Infections and infestations (continued)					
Pharyngitis[a]	5 (13.5)[a]	1 (2.6)	1 (2.6)	2 (2.6)[a]	7 (6.1)
Rhinitis	3 (8.1)	2 (5.1)	3 (7.9)	5 (6.5)	8 (7.0)
Sinusitis	1 (2.7)	2 (5.1)	1 (2.6)	3 (3.9)	4 (3.5)
Tonsillitis	1 (2.7)	0	3 (7.9)	3 (3.9)	4 (3.5)
Upper respiratory tract infection	10 (27.0)	7 (17.9)	6 (15.8)	13 (16.9)	23 (20.2)
Urinary tract infection	2 (5.4)	0	1 (2.6)	1 (1.3)	3 (2.6)
Viral upper respiratory tract infection	3 (8.1)	1 (2.6)	1 (2.6)	2 (2.6)	5 (4.4)
Injury, poisoning, and procedural complications					
Contusion	2 (5.4)	2 (5.1)	1 (2.6)	3 (3.9)	5 (4.4)
Ligament sprain[b]	3 (8.1)	0	0	0	3 (2.6)
Metabolism and nutrition disorders					
Decreased appetite	2 (5.4)	2 (5.1)	0	2 (2.6)	4 (3.5)
Musculoskeletal					
Arthralgia	4 (10.8)	1 (2.6)	2 (5.3)	3 (3.9)	7 (6.1)
Back pain	1 (2.7)	2 (5.1)	4 (10.5)	6 (7.8)	7 (6.1)
Myalgia	1 (2.7)	2 (5.1)	0	2 (2.6)	3 (2.6)
Neoplasms benign, malignant and unspecified					
Skin papilloma	5 (13.5)	1 (2.6)	2 (5.3)	3 (3.9)	8 (7.0)
Nervous system disorders					
Headache	9 (24.3)	12 (30.8)	15 (39.5)	27 (35.1)	36 (31.6)
Psychiatric disorders					
Agitation	0	2 (5.1)	0	2 (2.6)	2 (1.8)
Renal and urinary disorders					
Haematuria	2 (5.4)	0	0	0	2 (1.8)

SOC MedDRA 17.0 Preferred Term:	Initial Randomized Treatment Group* 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 (%)
Respiratory, thoracic and mediastinal disorders					
Cough[c]	3 (8.1)	9 (23.1)	2 (5.3)	11 (14.3)	14 (12.3)
Dysphonia	2 (5.4)	0	0	0	2 (1.8)
Epistaxis	2 (5.4)	2 (5.1)	0	2 (2.6)	4 (3.5)
Oropharyngeal pain	4 (10.8)	3 (7.7)	4 (10.5)	7 (9.1)	11 (9.6)
Rhinorrhea	1 (2.7)	3 (7.7)	1 (2.6)	4 (5.2)	5 (4.4)
Skin and subcutaneous tissue disorders					
Acne	0	0	3 (7.9)	3 (3.9)	3 (2.6)
Dry skin	2 (5.4)	0	3 (7.9)	3 (3.9)	5 (4.4)
Eczema	5 (13.5)	2 (5.1)	1 (2.6)	3 (3.9)	8 (7.0)
Pruritus	4 (10.8)	3 (7.7)	3 (7.9)	6 (7.8)	10 (8.8)
Psoriasis	3 (8.1)	5 (12.8)	3 (7.9)	8 (10.4)	11 (9.6)
Rash maculo-papular	0	0	2 (5.3)	2 (2.6)	2 (1.8)
Rash papular	0	1 (2.6)	2 (5.3)	3 (3.9)	3 (2.6)
Urticaria[d]	3 (8.1)	1 (2.6)	0	1 (1.3)	4 (3.5)

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

* Subjects who continued directly from Period A to Period D received open label adalimumab 0.8 mg/kg in Period D. Subjects entering Period B initially randomized to MTX received adalimumab 0.8 mg/kg in Periods C and D. Subjects initially randomized to adalimumab 0.4 mg/kg or 0.8 mg/kg received adalimumab in Periods C and D according to their initial randomized dose. All subjects had a dose increase option to open label 0.8 mg/kg in Period D. Subjects who maintained disease control continued off treatment in Period D.

a. Pharyngitis: $P = 0.036$ (all adalimumab – MTX); Fisher's exact test.

b. Ligament sprain: $P = 0.032$ (all adalimumab – MTX); Fisher's exact test.

c. Cough: $P = 0.047$ (adalimumab 0.4 mg/kg – adalimumab 0.8 mg/kg); Fisher's exact test.

d. Urticaria: $P = 0.100$ (all adalimumab – MTX); Fisher's exact test.

Notes: Subjects are presented by treatment group to which they were randomized in Period A.
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 which are in the same system organ class is counted only once in the system organ class total.

Cross reference: R&D/14/1263 Table 14.3__1.3.1

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 assessor. 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. One new SAE was reported in Period D (eye nevus) after the cut-off for the interim report. 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.

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 SmPC, and are not considered a cause for concern.

The new safety data collected from the last 21 subjects who completed the study have not changed the conclusions of the interim safety data base.

Conclusion of 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.

1.3.3. Discussion on clinical aspects

See below section 3. Rapporteur´s overall conclusion and recommendation.

2. Rapporteur's overall conclusion and recommendation

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 adalimimab, the 4 years of age as lower age limit for treatment of children with chronic plaque psoriasis was accepted. The new safety data collected from the last 21 subjects who completed the study have not changed the conclusions of the interim safety data base.

Overall conclusion

The variation application to extend the indication of Humira to treat children with severe chronic plaque psoriasis from the age of 4 was approved in March 2015. The submission of the final report does not change the conclusions drawn from the interim data.

Recommendation

The application is recommended for approval.

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Humira Active substance:Adalimumab

Study title	Study number	Date of completion	Date of submission of final study report
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 M04-717:	3 February 2015	3 August 2015