10 November 2016
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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

adalimumab

Procedure no: EMEA/H/C/000481/P46/093

Note

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

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Introduction

On 22 June 2016, the MAH submitted the completed paediatric study M11-328 for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This submission also fulfils the MAH obligation listed in the Humira Risk Management Plan to submit the final CSR for Study M11-328, as a required additional pharmacovigilance activity, by July 2016.

A short clinical overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that Study M11-328 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

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for M11-328: "*A Double-Blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Adalimumab in Pediatric Subjects with Enthesitis Related Arthritis*"

Study M11-328 was a Phase 3, double-blind (DB), placebo-controlled, multicenter study with an open-label (OL) period conducted in Canada, Mexico, and Europe in paediatric subjects with enthesitis-related arthritis (ERA), who were at least 6 years but less than 18 years of age at Baseline. Approximately 45 paediatric patients with ERA were planned to be enrolled.

An interim CSR with a data cut-off of 29 November 2012 (Week 52 visits were complete for all subjects) was previously written and submitted in December 2013; this CSR was the basis for approval of the variation (EMEA/H/C/000481/II/0127) to extend the indication for adalimumab for the treatment of paediatric subjects with ERA, 6 years of age and older, who have had an inadequate response to, or are intolerant of, conventional therapy in September 2014.

The final CSR for the study is provided with the current submission and contains additional safety data up to Week 204 and additional efficacy data up to Week 156.

1.3.2. Clinical study

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

Description

This was a Phase 3, double-blind (DB), placebo-controlled, multicenter study with an open-label (OL) period in paediatric subjects with ERA.

Methods

Objective(s)

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

Study design

The study included a 30-day Screening period, a 12-week DB placebo controlled treatment period with an early escape option, and an OL adalimumab eow treatment period with a maximum duration of 192 weeks, and a follow-up phone call 70 days after the last dose of adalimumab.

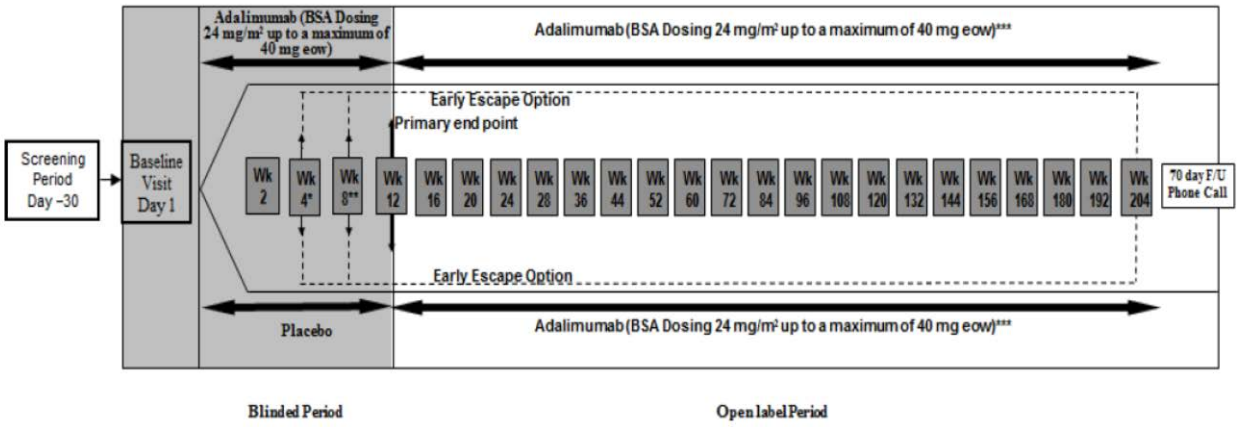
Subjects who met enrollment criteria were randomized in a 2:1 ratio to receive either adalimumab (body surface area [BSA] dosing 24 mg/m2 up to a maximum of 40 mg) eow or matching placebo via SC injection. An early escape option at Weeks 4 and 8 was provided for subjects who either experienced a worsening of disease or failed to improve.

The option for early escape was available in case a subject experienced a decline in disease status, defined as an increase in the number of active joints by ≥30% with a minimum of at least 2 additional active joints compared with Baseline, at the Week 4 visit or had failed to improve, as defined as <30% improvement in the number of active joints compared with Baseline, at the Week 8 visit.

For subjects who completed the blinded period, the OL period began at the Week 12 visit.

For subjects who met the criteria for early escape, the OL period began at the Week 4 or Week 8 visit (depending on when the criteria were met). During the OL period, each subject received OL adalimumab eow for a maximum of 192 weeks. The OL period continued until Week 204 or until a subject completed 108 weeks of treatment (from Baseline) and adalimumab received country and local (if applicable) regulatory approval for ERA and all applicable local reimbursement procedures were completed. All subjects not continuing on adalimumab after the end of the study had a 70-day follow-up phone call to obtain follow-up information on any new or ongoing adverse events (AEs).

Figure 1: Study design schematic



* Subjects fulfilling protocol defined criteria for worsening of ERA may have early escaped into the OL period.

** Subjects who failed to demonstrate improvement in ERA may have early escaped into the OL period.

*** Each subject received a maximum of 192 weeks of OL adalimumab. The OL period continued until Week 204 or until a subject completed 108 weeks of treatment (from Baseline) and adalimumab received country and local (if applicable) regulatory approval for ERA, whichever occurred first.

Study population /Sample size

Approximately 45 paediatric subjects 6 to <18 years of age with ERA who met all inclusion criteria and none of the exclusion criteria were eligible for participation in this study. The specific subject population chosen was selected on the basis of knowledge that tumor necrosis factor (TNF) is involved in the pathogenesis of enthesitis.

Inclusion criteria (selected)

- Age ≥6 to <18 years at Baseline
- Diagnosis of ERA as defined by the ILAR prior to subject's sixteenth birthday
- Subjects must have had disease activity as defined by the fulfillment of the following conditions:
    - At least 3 active joints (swelling not due to deformity or joints with LOM + pain and/or tenderness) AND
    - Evidence of enthesitis in at least one location (either documented in the past or present at Baseline)
- Inadequate response or intolerance to at least one NSAID. In addition, subject must also have had inadequate response or intolerance to at least 1 disease-modifying anti-rheumatic drug (DMARD), either sulfasalazine (SSZ) or methotrexate (MTX). Subjects who had a contraindication to SSZ or MTX use could be enrolled in the study.

Exclusion criteria (selected)

- Subjects fulfilling a diagnosis of any ILAR JIA (juvenile idiopathic arthritis) subtype other than ERA
- Psoriasis (Ps) or a history of Ps in the subject or first-degree relative
- Presence of IgM RF
- Presence of systemic JIA
- History of inflammatory bowel disease
- Previous biologic therapy, including anti-TNF therapy with a potential impact on paediatric ERA
- Diagnosis of acute inflammatory joint disease not associated with ERA
- Known hypersensitivity to adalimumab or its excipients
- Subject had received intra-articular joint injections with corticosteroids within 28 days prior to Baseline
- Joint surgery within 2 months prior to Baseline
- If entering the study on concomitant MTX or SSZ at Screening/Baseline, subject was not on stable dose of MTX (≤15 mg/m2 with a maximum dose of 25 mg/week) or SSZ (≤50 mg/m2 with a maximum dose of 3 g/day) for 28 days prior to Baseline
- Subject was on concomitant DMARDs other than MTX or SSZ within 28 days prior to Baseline
- If entering the study on concomitant prednisone (and/or prednisone equivalents), subject was not on a stable dose (≤10 mg/day or 0.2 mg/km body weight, whichever was lower) for 14 days prior to Baseline

Treatments

Study drug (adalimumab or placebo) was provided as a sterile, preservative-free solution for SC injection contained in 0.8 mL single-use vials. Study drug was to be administered SC by subject, parent or legal guardian, or qualified designee eow at approximately the same time of day.

Outcomes/endpoints

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

The efficacy of adalimumab compared to placebo was evaluated using the following secondary (ranked) variables at Week 12:

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

The OL period began at the Week 12 visit for subjects who completed the DB period. For subjects who met the criteria for early escape, the OL period began either at Week 4 or Week 8 (depending on when the criteria were met).

In addition to the Week 12 visit, subjects were to visit the study site at Weeks 16, 20, 24, 28, 36, 44, 52, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, and 204 (Final Study Completion Visit), or if they terminated early from the study.

Assessor's comment:

No efficacy data was collected beyond Week 156.

Efficacy variables (other than the primary and secondary efficacy endpoints at Week 12) included the following (Table 1 below):

Table 1: Non-ranked secondary efficacy variables analysed by category

Category	Variable
Reduction of Signs and Symptoms	Number of active joints with arthritis (swelling not due to deformity or joints with LOM + pain and/or tenderness) [0 – 72] including changes and percent changes from Baseline (excluding Week 12)
	Number of sites of enthesitis (excluding Week 12)
	SPARCC enthesitis index
	MASES
	TJC for 72 joints (excluding Week 12)
	SJC for 68 joints (excluding Week 12)
	Number of joints with LOM (component of ACR Pedi30)
	Number of digits with dactylitis
	ACR Pedi30/50/70 responses (excluding Week 12)
	BASDAI
	Inflammation (mean of BASDAI items 5 and 6)
	BASDAI50
	PGA (component of ACR Pedi30)
	Patient's assessment of total back pain
	Parent's assessment of subject's pain
	hs-CRP (component of ACR Pedi30)
	Parent's global assessment of subject's overall well-being (component of ACR Pedi30)
Health-Related QoL	CHAQ
	Parent's Assessment of Subject's Eye Disease
	Parent's Assessment of Subject's School Attendance

Statistical Methods

The analysis of all data through the Week 52 visit (DB period plus the first 40 weeks of the OL period) was conducted after all ongoing subjects in the study completed Week 52 and the data were cleaned. This efficacy and safety analysis was the only and final analysis of data from this time period.

Efficacy analyses were to be conducted on the intent-to-treat (ITT) analysis set. Missing or incomplete data were handled using the nonresponder imputation (NRI) method, as observed cases, and the last observation carried forward (LOCF) methods as appropriate. The safety analysis was to be conducted on the safety analysis set.

OL period

Analysis of results from the 192-week OL period is descriptive. Results in the OL period were reported stratified by the treatment the subject was randomized to in the DB period and overall.

Assessor's comment:
The data through the Week 52 visit (DB period plus the first 40 weeks of the OL period) has been reported and assessed previously as part of the approval procedure to extend the indication for adalimumab for the treatment of paediatric subjects with ERA (see EMEA/H/C/481/II/127).

Long term effectiveness of adalimumab during the OL period was analyzed. This is further discussed below. Key results from the DB and early OL part of the study will be included for reference.

Results

Recruitment / Number analysed

A total of 46 paediatric subjects with ERA were randomized at 16 study sites located in Canada, France, Germany, Italy, Mexico, Poland, Spain, Sweden, and Switzerland.

Seventeen subjects discontinued from the study, all during the OL period; 4 of these subjects discontinued due to sustained remission. Seven subjects (3 randomized to placebo, 4 randomized to adalimumab) early escaped from the DB period to the OL period. See Table 2 below.

Table 2: Disposition of subjects

	Subjects by Randomization Group		
Subject Status	**Placebo N = 15**	**Adalimumab N = 31**	**Total N = 46**
Subjects randomized, n	15	31	46
Completed Week 12 (DB period) and entered OL (ITT), n	12	27	39
Early escaped at Week 4 and entered OL, n	1	2	3
Early escaped at Week 8 and entered OL, n	2	2	4
Discontinued in DB period (up to Week 12) (ITT), n	0	0	0
Discontinued in OL period (ITT), n (%)[a]	5 (33.3)	12 (38.7)	17 (37.0)
Primary reason for discontinuation during OL period (ITT, n [%])			
AE	2 (13.3)	4 (12.9)	6 (13.0)
Withdrew consent	1 (6.7)	3 (9.7)	4 (8.7)
Lack of efficacy	0	2 (6.5)	2 (4.3)
Other[b]	2 (13.3)	3 (9.7)	5 (10.9)

a. Subjects discontinuing the study after Week 108 but prior to Week 204 due to regulatory approval were considered as having completed the study.

b. "Other" reasons for discontinuation included remission (4 subjects) and irregular compliance (1 subject).

Note: Subjects who discontinued study drug are counted under each reason given for discontinuation; therefore, the sum of the counts given for the reasons may be greater than the overall number of discontinuations.

Table 3: Number of subjects by analysis set

	Number of Subjects by Randomization Group		
Subject Status	**Placebo**	**Adalimumab**	**Total**
Subjects randomized	15	31	46
ITT	15	31	46
PP	14	27	41
Safety	15	31	46
Any adalimumab	--	--	46

Baseline data

The majority of subjects in the ITT analysis set were male (67.4%) and white (76.1%); mean age was 12.9±2.9 years. Subjects reported having had symptoms of ERA for a mean of 2.6 years and had been diagnosed with ERA for a mean of 1.9 years prior to Baseline. A total of 91.3% of subjects previously used DMARDs for their ERA, 100.0% previously used NSAIDs, and 56.5% previously used corticosteroids. No statistically significant differences were observed between treatment groups.

PK results

PK results and conclusions have been presented previously in a separate PK report (R&D/13/011).

Assessor's comment:

Adalimumab trough levels were obtained at Baseline, Weeks 2, 4, 8, 12, 24, 36, and 52; see EMEA/H/C/481/II/127. PK data in children with ERA was considered to be similar to children with polyarticular juvenile arthritis. Similarly, data on immunogenicity was collected up to Week 52 and assessed previously. These data will not be further discussed here.

Efficacy results

Primary efficacy variable

Table 4: Percent change from Baseline at Week 12 in number of active joints with arthritis (ITT and PP)

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

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

Table 5: Sensitivity analyses for percent change from Baseline at Week 12 in number of active joints with arthritis using non-parametric testing (ITT and PP)

	Placebo				Adalimumab				
Week 12	N	Mean ± SD	Median (Q1, Q3)	Mean Wilcoxon Score	N	Mean ± SD	Median (Q1, Q3)	Mean Wilcoxon Score	*P* value[a]
ITT (LOCF)	15	–11.6 ± 100.50	–50.0 (–76.2, 66.7)	29.67	31	–62.6 ± 59.53	–88.9 (–100.0, –55.0)	20.52	0.025
PP (LOCF)	14	–30.2 ± 72.38	–58.3 (–76.2, 25.0)	26.21	27	–66.0 ± 57.29	–90.9 (–100.0, –66.7)	18.30	0.038

a. *P* value from exact two-sample Wilcoxon test.

Assessor's comment:

The primary efficacy variable was in favour of adalimumab (mean percent decrease of –62.6% in subjects in the adalimumab group compared to –11.6% in subjects in the placebo group (P = 0.039; LOCF). This finding was supported by sensitivity analyses using as observed data, as well as non-parametric methods and numerically improvement observed in the PP analysis set (for details see EMEA/H/C/481/II/127).

Ranked secondary variables

Results for number of sites of enthesitis, TJC, SJC, ACR Pedi30 response, and ACR Pedi50 response were numerically superior in favour of adalimumab; Results for the 6th ranked secondary efficacy variable, ACR Pedi70 response, reached statistical significance at Week 12.

Assessor's comment:

The ranked secondary variables were tested in hierarchical order for statistical significance between the groups at Week 12. That is, statistically significant results (P value ≤ 0.05) must be achieved for a comparison in the higher rank in order to initiate the next comparison in the lower rank. As illustrated by the table, the key secondary endpoints did not reach statistical significance even though the adalimumab group tended to show improvement of variable size (see Table 6 below).

During the approval procedure for this indication (EMEA/H/C/481/II/127), it was considered that the greater difference between the treated and placebo group observed for ACR Pedi50 and 70 as compared to Pedi30 pointed towards a true treatment effect with adalimumab compared to placebo, and this was considered supportive of the primary endpoint. In this regard, it should be noted that the final CSR states the following:

"After the blind break, it was discovered that the statistical conventions for calculation of ACR Pedi30/50/70 responses specified in the SAP were inconsistent with the published methodology and expert opinion for calculation of the response rates. Specifically, the following convention was noted in the SAP Amendment 1:

If hs-CRP values at both Baseline and comparison visits are within the normal reference range, hs-CRP values will not be used to evaluate ACR Pediatric response.

Additionally, handling of baseline values of "0" was not described in the SAP. Thus, ACR Pedi30/50/70 response rates presented in this report were re-calculated:

- The hs-CRP was handled as a continuous variable, regardless of whether or not it was within normal limits at both Baseline and comparison visits.

- A change of "0" was reported as a percent change of "0" regardless of the baseline value.

In addition to the analyses defined in the final SAP, an additional sensitivity analysis was performed removing a subject from the PP analysis. During preparation for the final database lock, an additional protocol deviation with potential impact on the primary endpoint was identified for this subject."

Consequently, the ACR Pedi30/50/70 response data were recalculated and therefore slightly differ (and are numerically somewhat more in favour of adalimumab) as compared to the previously reported results (through Week 52 only) in EMEA/H/C/481/II/127.

However, these changes are not considered to have impact on the B/R.

Table 6: Mean change from baseline and responder status at Week 12 for ranked secondary variables (ITT)

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

Ranked Variables 4 through 6 (NRI)						
	N	Responder	Non-Responder	Difference[b]	95% CI[e]	*P* value[f]
4. ACR Pedi30						
Placebo	15	9 (60.0)	6 (40.0)	--	--	--
Adalimumab	31	22 (71.0)	9 (29.0)	11.0	−18.5, 40.5	0.514
5. ACR Pedi50						
Placebo	15	6 (40.0)	9 (60.0)	--	--	--
Adalimumab	31	21 (67.7)	10 (32.3)	27.7	−2.0, 57.5	0.111
6. ACR Pedi70						
Placebo	15	3 (20.0)	12 (80.0)	--	--	--
Adalimumab	31	17 (54.8)	14 (45.2)	34.8	8.1, 61.6	0.031

a. Only subjects with both Baseline and visit values are shown.
b. Difference of adalimumab minus placebo.
c. 95% CI for difference of adalimumab minus placebo.
d. *P* value for differences between treatment groups from 1-way ANOVA.
e. 95% CI based on normal approximation.
f. *P* value for differences between treatment groups from Fisher's exact test.

OL period

- **Number of active joints with arthritis**

Decreases in the mean percent change from Baseline in the number of active joints with arthritis continued through Week 156, with an average of only 0.9 active joints with arthritis at Week 156 as compared to 7.8 at Baseline (see Table 7 below).

Table 7: Percent change from baseline in number of active joints with arthritis (ITT; LOCF)

Visit Week		Baseline	Visit	% Change from Baseline[b]		Between Group Difference		
Treatment Group	N	Mean[a] ± SD	Mean[a] ± SD	Mean ± SD	Median (Min to Max)	Difference[c]	95% CI	*P* value[d]
DB Period								
Week 12								
Placebo	15	6.7 ± 5.29	4.2 ± 3.59	−11.6 ± 100.50	−50.0 (−100 to 250.0)	--	--	--
Adalimumab	31	8.4 ± 7.12	4.0 ± 8.17	−62.6 ± 59.53	−88.9 (−100 to 100.0)	−51.05	(−98.62, −3.49)	0.036
OL Period								
Week 24								
Placebo	15	6.7 ± 5.29	1.1 ± 1.28	−80.0 ± 30.24	−95.2 (−100 to 0.0)	--	--	--
Adalimumab	31	8.4 ± 7.12	1.6 ± 4.99	−87.7 ± 19.21	−100 (−100 to −22.2)			
Total	46	7.8 ± 6.57	1.4 ± 4.14	−85.2 ± 23.32	−100 (−100 to 0.0)	−7.70	(−22.47, 7.06)	0.299
Week 52								
Placebo	15	6.7 ± 5.29	0.6 ± 1.12	−87.7 ± 23.96	−100 (−100 to −20.0)	--	--	--
Adalimumab	31	8.4 ± 7.12	0.8 ± 2.32	−89.1 ± 27.45	−100 (−100 to 33.3)			
Total	46	7.8 ± 6.57	0.7 ± 1.99	−88.7 ± 26.10	−100 (−100 to 33.3)	−1.44	(−18.17, 15.29)	0.863

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	% Change from Baseline[b] Mean ± SD	 Median (Min to Max)	Between Group Difference Difference[c]	 95% CI	 *P* value[d]
Week 108								
Placebo	15	6.7 ± 5.29	0.3 ± 1.05	−92.4 ± 21.80	−100 (−100 to −20.0)			
Adalimumab	31	8.4 ± 7.12	1.0 ± 3.04	−89.6 ± 27.57	−100 (−100 to 33.3)			
Total	46	7.8 ± 6.57	0.8 ± 2.57	−90.5 ± 25.62	−100 (−100 to 33.3)	2.86	(−13.54, 19.27)	0.726
Week 156								
Placebo	15	6.7 ± 5.29	0.4 ± 1.12	−90.2 ± 25.93	−100 (−100 to −20.0)			
Adalimumab	31	8.4 ± 7.12	1.2 ± 3.11	−87.4 ± 28.91	−100 (−100 to 33.3)			
Total	46	7.8 ± 6.57	0.9 ± 2.64	−88.3 ± 27.72	−100 (−100 to 33.3)	2.85	(−14.89, 20.60)	0.748

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

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

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

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

Note: Results in the OL period are shown by randomized treatment group even though all subjects received OL adalimumab.

Assessor's comment:

As noted by the MAH, a step down procedure was used to handle multiplicity regarding the primary and the ranked (key) secondary endpoints (i.e. at Week 12). All other comparisons were to be considered as exploratory analyses.

Results beyond Week 12 reflect the switch from placebo to OL adalimumab. Results for observed cases were similar (Table 14.2_2.1.2.2 in the final CSR); at Week 156 (the last visit for collection of efficacy data, 12 of the 15 placebo patients (80%) and 26 of the 31 adalimumab patients (84%) had remained in the study.

- **Number of sites of enthesitis**

During the DB period, numerically (not statistically significant) larger decreases from Baseline were seen at Week 12 in the number of sites of enthesitis for subjects randomized to the adalimumab group compared to placebo using the LOCF approach (ITT). During the OL period, decreases in the number of enthesitis sites continued to be seen to Week 156 in subjects with any exposure to adalimumab, with an average of only 2.1 active sites of enthesitis at Week 156 compared to 8.1 at Baseline.

Table 8: Change from Baseline in number of sites of enthesitis (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline Mean ± SD	 Median (Min to Max)	Between Group Difference Difference[b]	 95% CI	 *P* value[c]
DB Period								
Week 12								
Placebo	15	7.8 ± 7.49	5.1 ± 8.92	−2.7 ± 4.98	−4.0 (−12.0 to 11.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	3.9 ± 6.60	−4.4 ± 6.20	−3.0 (−22.0 to 12.0)	−1.62	(−5.32, 2.08)	0.382
OL Period								
Week 24								
Placebo	15	7.8 ± 7.49	1.3 ± 2.61	−6.5 ± 5.68	−4.0 (−22.0 to −2.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	1.4 ± 2.85	−6.9 ± 8.11	−3.0 (−32.0 to −1.0)			
Total	46	8.1 ± 8.38	1.4 ± 2.74	−6.8 ± 7.35	−4.0 (−32.0 to −1.0)	−0.44	(−5.14, 4.27)	0.853
Week 52								
Placebo	15	7.8 ± 7.49	2.3 ± 7.21	−5.5 ± 5.84	−4.0 (−24.0 to 2.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	1.2 ± 3.27	−7.1 ± 8.39	−4.0 (−35.0 to 1.0)			
Total	46	8.1 ± 8.38	1.5 ± 4.85	−6.6 ± 7.62	−4.0 (−35.0 to 2.0)	−1.56	(−6.43, 3.30)	0.520

Visit Week / Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
Week 108								
Placebo	15	7.8 ± 7.49	2.9 ± 7.40	−4.9 ± 5.89	−4.0 (−23.0 to 2.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	1.4 ± 3.43	−6.9 ± 7.92	−4.0 (−35.0 to 1.0)			
Total	46	8.1 ± 8.38	1.9 ± 5.04	−6.3 ± 7.32	−4.0 (−35.0 to 2.0)	−2.07	(−6.72, 2.58)	0.375
Week 156								
Placebo	15	7.8 ± 7.49	3.9 ± 8.84	−3.9 ± 6.96	−4.0 (−24.0 to 9.0)	--	--	--
Adalimumab	31	8.3 ± 8.89	1.3 ± 3.38	−7.0 ± 7.99	−4.0 (−35.0 to 1.0)			
Total	46	8.1 ± 8.38	2.1 ± 5.79	−6.0 ± 7.73	−4.0 (−35.0 to 9.0)	−3.17	(−8.03, 1.70)	0.196

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

b. Change from Baseline in adalimumab treated subjects minus change from Baseline in placebo treated subjects.

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

Note: Results in the OL period are shown by randomized treatment group even though all subjects received OL adalimumab.

- **Tender joint count (TJC)**

During the DB period, a numerically, but not statistically significantly greater decrease in mean change from Baseline in TJC was seen at Week 12 in subjects randomized to the adalimumab group compared to the placebo group using the LOCF approach (ITT). During the OL period, decreases in mean change in number of joints with pain/tenderness continued to be seen through Week 156, with greater than 85% mean improvement from Baseline in subjects with any exposure to adalimumab.

Table 9: Change from Baseline in TJC (ITT; LOCF)

Visit Week / Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline		Between Group Difference		
				Mean ± SD	Median (Min to Max)	Difference[b]	95% CI	*P* value[c]
DB Period								
Week 12								
Placebo	15	11.9 ± 9.34	7.5 ± 8.06	−4.5 ± 8.97	−7.0 (−19.0 to 13.0)			
Adalimumab	31	13.4 ± 10.49	5.5 ± 8.77	−7.9 ± 8.25	−6.0 (−28.0 to 8.0)	−3.40	(−8.78, 1.97)	0.209
OL Period								
Week 24								
Placebo	15	11.9 ± 9.34	2.2 ± 3.21	−9.7 ± 9.33	−8.0 (−29.0 to 6.0)			
Adalimumab	31	13.4 ± 10.49	2.9 ± 6.37	−10.4 ± 8.01	−8.0 (−30.0 to 1.0)			
Total	46	12.9 ± 10.05	2.7 ± 5.51	−10.2 ± 8.36	−8.0 (−30.0 to 6.0)	−0.69	(−6.04, 4.67)	0.798
Week 52								
Placebo	15	11.9 ± 9.34	1.9 ± 5.71	−10.0 ± 9.31	−8.0 (−30.0 to 5.0)			
Adalimumab	31	13.4 ± 10.49	2.2 ± 3.89	−11.1 ± 9.68	−8.0 (−40.0 to 3.0)			
Total	46	12.9 ± 10.05	2.1 ± 4.50	−10.8 ± 9.47	−8.0 (−40.0 to 5.0)	−1.13	(−7.19, 4.93)	0.709
Week 108								
Placebo	15	11.9 ± 9.34	2.5 ± 6.01	−9.5 ± 8.69	−8.0 (−28.0 to 5.0)			
Adalimumab	31	13.4 ± 10.49	2.0 ± 5.03	−11.4 ± 9.75	−6.0 (−33.0 to 3.0)			
Total	46	12.9 ± 10.05	2.2 ± 5.30	−10.7 ± 9.36	−7.0 (−33.0 to 5.0)	−1.89	(−7.86, 4.09)	0.527
Week 156								
Placebo	15	11.9 ± 9.34	2.7 ± 6.02	−9.3 ± 8.53	−7.0 (−28.0 to 5.0)			
Adalimumab	31	13.4 ± 10.49	1.8 ± 4.06	−11.5 ± 9.37	−8.0 (−33.0 to 3.0)			
Total	46	12.9 ± 10.05	2.1 ± 4.73	−10.8 ± 9.07	−7.5 (−33.0 to 5.0)	−2.25	(−8.02, 3.52)	0.437

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

b. Change from Baseline in adalimumab treated subjects minus change from Baseline in placebo treated subjects.

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

Note: Results in the OL period are shown by randomized treatment group even though all subjects received OL adalimumab.

- **Swollen joint count (SJC)**

During the DB period a numerically, but not statistically significantly greater decrease in mean change from Baseline in SJC was seen at Week 12 in subjects randomized to the adalimumab group compared to the placebo group using the LOCF approach (ITT).

During the OL period, decreases in mean change from Baseline in the number of joints with swelling continued to be seen through Week 156 with greater than 85% mean improvement from Baseline in subjects with any exposure to adalimumab.

Table 10: Change from Baseline in SJC (ITT; LOCF)

Visit Week Treatment Group	N	Baseline Mean[a] ± SD	Visit Mean[a] ± SD	Change from Baseline Mean ± SD	 Median (Min to Max)	Between Group Difference Difference[b]	 95% CI	 *P* value[c]
DB Period								
Week 12								
Placebo	15	5.2 ± 3.69	2.8 ± 2.83	–2.4 ± 4.66	–3.0 (–11.0 to 5.0)			
Adalimumab	31	6.7 ±7.30	3.2 ± 7.27	–3.5 ± 5.61	–3.0 (–19.0 to 9.0)	–1.12	(–4.49, 2.26)	0.509
OL Period								
Week 24								
Placebo	15	5.2 ± 3.69	0.8 ± 1.21	–4.4 ± 4.01	–3.0 (–14.0 to 1.0)			
Adalimumab	31	6.7 ± 7.30	1.1 ± 4.31	–5.6 ± 5.08	–4.0 (–19.0 to 0.0)			
Total	46	6.2 ± 6.35	1.0 ± 3.59	–5.2 ± 4.75	–3.5 (–19.0 to 1.0)	–1.21	(–4.23, 1.81)	0.423
Week 52								
Placebo	15	5.2 ± 3.69	0.5 ± 0.92	–4.7 ± 3.94	–4.0 (–15.0 to –1.0)			
Adalimumab	31	6.7 ± 7.30	0.6 ± 2.08	–6.1 ± 7.14	–4.0 (–30.0 to 4.0)			
Total	46	6.2 ± 6.35	0.6 ± 1.77	–5.7 ± 6.27	–4.0 (–30.0 to 4.0)	–1.40	(–5.39, 2.60)	0.485
Week 108								
Placebo	15	5.2 ± 3.69	0.3 ± 0.80	–4.9 ± 3.84	–4.0 (–15.0 to –1.0)			
Adalimumab	31	6.7 ± 7.30	0.7 ± 2.63	–6.1 ± 6.47	–4.0 (–24.0 to 4.0)			
Total	46	6.2 ± 6.35	0.5 ± 2.20	–5.7 ± 5.73	–4.0 (–24.0 to 4.0)	–1.13	(–4.79, 2.52)	0.536
Week 156								
Placebo	15	5.2 ± 3.69	0.3 ± 0.90	–4.9 ± 3.93	–4.0 (–15.0 to 0)			
Adalimumab	31	6.7 ± 7.30	0.9 ± 2.79	–5.8 ± 6.53	–4.0 (–24.0 to 4.0)			
Total	46	6.2 ± 6.35	0.7 ± 2.34	–5.5 ± 5.78	–4.0 (–24.0 to 4.0)	–0.97	(–4.67, 2.72)	0.599

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

b. Change from Baseline in adalimumab treated subjects minus change from Baseline in placebo treated subjects.

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

Note: Results in the OL period are shown by randomized treatment group even though all subjects received OL adalimumab.

- **ACR Pedi30/50/70**

During the DB period using the NRI approach on the ITT analysis set, statistically significant results were observed for the more stringent ACR Pedi70 response in favour of the adalimumab treatment group. Responses for ACR Pedi30 and ACR Pedi50 responses were numerically superior in favor of adalimumab; however, no statistically significant differences were observed between the proportion of subjects randomized to the adalimumab group or the placebo group at Week 12. During the first 12 weeks of the OL period (Week 24), the percentages of ACR Pedi30/50/70 responders increased and then were maintained through Week 156 with over 75% of subjects achieving ACR Pedi30/50/70 responses at Week 156 (Tables 11-13 below).

Table 11: ACR Pedi30/50/70 Responses (ITT; NRI)

Visit Week Treatment Group	N	Responder	Non-Responder	Between Group Difference		
				Difference[a]	95% CI[b]	*P* value[c]
ACR Pedi30						
DB Period						
Week 12						
Placebo	15	9 (60.0)	6 (40.0)			
Adalimumab	31	22 (71.0)	9 (29.0)	11.0	−18.5, 40.5	0.514
OL Period						
Week 24						
Placebo	15	13 (86.7)	2 (13.3)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	40 (87.0)	6 (13.0)	0.4	−20.4, 21.3	1.000
Week 52						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	39 (84.8)	7 (15.2)	7.1	−16.3, 30.5	0.667
Week 108						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	26 (83.9)	5 (16.1)			
Total	46	38 (82.6)	8 (17.4)	3.9	−20.2, 27.9	1.000
Week 156						
Placebo	15	11 (73.3)	4 (26.7)			
Adalimumab	31	25 (80.6)	6 (19.4)			
Total	46	36 (78.3)	10 (21.7)	7.3	−19.0, 33.7	0.706

Table 11: ACR Pedi30/50/70 Responses (ITT; NRI) (continued)

Visit Week Treatment Group	N	Responder	Non-Responder	Between Group Difference		
				Difference[a]	95% CI[b]	*P* value[c]
ACR Pedi50						
DB Period						
Week 12						
Placebo	15	6 (40.0)	9 (60.0)			
Adalimumab	31	21 (67.7)	10 (32.3)	27.7	–2.0, 57.5	0.111
OL Period						
Week 24						
Placebo	15	13 (86.7)	2 (13.3)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	40 (87.0)	6 (13.0)	0.4	–20.4, 21.3	1.000
Week 52						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	27 (87.1)	4 (12.9)			
Total	46	39 (84.8)	7 (15.2)	7.1	–16.3, 30.5	0.667
Week 108						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	26 (83.9)	5 (16.1)			
Total	46	38 (82.6)	8 (17.4)	3.9	–20.2, 27.9	1.000
Week 156						
Placebo	15	11 (73.3)	4 (26.7)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	35 (76.1)	11 (23.9)	4.1	–22.7, 30.9	1.000

Table 11: ACR Pedi30/50/70 Responses (ITT; NRI) (continued)

Visit Week / Treatment Group	N	Responder	Non-Responder	Between Group Difference: Difference[a]	95% CI[b]	*P* value[c]
ACR Pedi70						
DB Period						
Week 12						
Placebo	15	3 (20.0)	12 (80.0)			
Adalimumab	31	17 (54.8)	14 (45.2)	34.8	8.1, 61.6	0.031
OL Period						
Week 24						
Placebo	15	10 (66.7)	5 (33.3)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	34 (73.9)	12 (26.1)	10.8	–17.3, 38.8	0.488
Week 52						
Placebo	15	11 (73.3)	4 (26.7)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	35 (76.1)	11 (23.9)	4.1	–22.7, 30.9	1.000
Week 108						
Placebo	15	12 (80.0)	3 (20.0)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	36 (78.3)	10 (21.7)	–2.6	–27.6, 22.4	1.000
Week 156						
Placebo	15	11 (73.3)	4 (26.7)			
Adalimumab	31	24 (77.4)	7 (22.6)			
Total	46	35 (76.1)	11 (23.9)	4.1	–22.7, 30.9	1.000

a. Difference of adalimumab minus placebo.

b. 95% confidence interval based on normal approximation.

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

Note: Results in the OL period are shown by randomized treatment group even though all subjects received OL adalimumab.

Assessor's comment:

As noted previously, also in the previous assessment, the study is limited by its small sample size. However, it appears that the improvements and trends towards improvements observed for adalimumab during the DB period and the early open-label period generally were maintained. The tables above summarize the ITT set using LOCF but results were similar for observed case only data.

Safety results

Mean duration of treatment with adalimumab was 78.5 days during the DB period and 1147.1 days for subjects who received adalimumab at any time during the study.

During the DB period, a greater percentage of subjects who received adalimumab (21/31, 67.7%) reported at least 1 AE compared with subjects who received placebo (8/15, 53.3%) (Table 12 below). The most frequently reported AEs (reported by ≥2 subjects in any treatment group) included upper respiratory tract infection, headache, gastroenteritis, injection site pain, nausea, alanine aminotransferase (ALT) increased, abdominal pain upper, and syncope (Table 13 below).

All AEs were considered mild or moderate in severity by the Investigator and most subjects (n = 16) reported AEs that were considered by the Investigator to be not related or probably not related to study drug. Nine subjects in the adalimumab treatment group reported possibly or probably related AEs compared to 4 subjects in the placebo group. Two serious AEs (SAEs) were reported by 1 subject in the adalimumab treatment group (abdominal pain upper and headache).

Table 12: N (%) subjects with TEAEs during DB and OL treatment (any adalimumab)

	DB Period			
Subjects with:	**Placebo N = 15**	**Adalimumab N = 31**	**Total N = 46**	**Any Adalimumab N = 46**
Any AE	8 (53.3)	21 (67.7)	29 (63.0)	46 (100)
Any AE at least possibly drug-related[a]	4 (26.7)	9 (29.0)	13 (28.3)	29 (63.0)
Any severe AE	0	0	0	7 (15.2)
Any serious AE	0	1 (3.2)	1 (2.2)	10 (21.7)
Any AE leading to discontinuation of study drug	0	0	0	7 (15.2)
Death[b] or any fatal AE	0	0	0	0

a. As assessed by the Investigator.

b. Includes non-treatment-emergent.

Table 13: Most frequently reported TEAEs (≥2 subjects in any treatment group) – DB period (Safety analysis set)

	DB Period		
MedDRA 18.0 PT	Placebo N = 15	Adalimumab N = 31	Total N = 46
Subjects with any AE	8 (53.3)	21 (67.7)	29 (63.0)
Upper respiratory tract infection	2 (13.3)	3 (9.7)	5 (10.9)
Headache	0	4 (12.9)	4 (8.7)
Injection site pain	1 (6.7)	3 (9.7)	4 (8.7)
Nausea	1 (6.7)	2 (6.5)	3 (6.5)
ALT increased	0	3 (9.7)	3 (6.5)
Abdominal pain upper	1 (6.7)	2 (6.5)	3 (6.5)
Gastroenteritis	0	2 (6.5)	2 (4.3)
Syncope[a]	0	2 (6.5)	2 (4.3)

a. Neither event of syncope was considered by the Investigator to be related to study drug (Appendix 16.2__7.1).

When including the OL period, all subjects who received at least 1 dose of adalimumab at any time during the study experienced at least 1 AE. The most frequently reported AEs (reported by ≥ 15% of subjects) included upper respiratory tract infection, nasopharyngitis, headache, diarrhea, gastroenteritis, juvenile idiopathic arthritis (JIA) (worsening of ERA), pharyngitis, and pharyngotonsillitis.

Seven subjects in the any adalimumab set reported at least 1 severe AE (disseminated tuberculosis; latent TB; pustular psoriasis; JIA [worsening of ERA]; second degree burns and third degree burns [in the same subject]; blood pressure increased and weight increased [in the same subject]; and diffuse vasculitis, pneumonia, and JIA [worsening of ERA, in the same subject]).

Twenty-nine subjects reported AEs that were considered possibly or probably related to study drug by the Investigator. Related events that were reported by more than 2 subjects were nasopharyngitis, pharyngotonsillitis, and injection site erythema (3 subjects each); otitis media and upper respiratory tract infection (4 subjects each); and injection site pain (5 subjects).

No deaths were reported. Overall, 6 SAEs in 5 subjects were considered by the Investigator possibly or probably related to the study drug (upper abdominal pain and headache [in the same subject], disseminated TB, appendicitis, urinary tract infection, and diffuse vasculitis).

Assessor's comment:

Ten subjects reported a total of 19 SAEs. One subject reported a SAE of active TB (disseminated TB) during the OL period, which led to discontinuation of study drug and was considered as probably related to study drug by the Investigator. Two subjects reported treatment emergent latent TB in the OL period. One event was a nonserious event of latent TB that was considered probably related to study drug by the Investigator. The other event was an SAE of positive tuberculin test that was considered to be probably not related to study drug. One subject developed an SAE of diffuse vasculitis on Day 433 and subsequently developed progressive respiratory distress, congestive heart failure and pneumonia. Study drug was discontinued as a causal relationship with study drug could not be ruled out.

None of the following events of special interest were reported during the study:

Legionella infection, reactivation of hepatitis B, opportunistic infection, oral candidiasis; progressive multifocal leukoencephalopathy (PML), malignancies (including lymphoma,

NMSC, melanoma, hepatosplenic T-cell lymphoma [HSTCL], and leukemia), lupus-like syndrome, demyelinating disease, hematologic events, diverticulitis, intestinal perforation, intestinal stricture, pulmonary embolism, interstitial lung disease, adalimumab error related events and maladministration, Stevens-Johnson Syndrome (SJS), erythema multiforme, pancreatitis, sarcoidosis, autoimmune hepatitis, reversible posterior leukoencephalopathy syndrome (RPLS), or amyotrophic lateral sclerosis (ALS).

Seven subjects prematurely discontinued due to AEs, all during or following OL treatment (disseminated TB; Ps; JIA [worsening of ERA] and pain; dermatitis allergic; pustular Ps, injection site pain and injection site pruritus; and diffuse vasculitis and congestive heart failure).

Assessor's comment:

All AEs leading to discontinuation were considered by the Investigator to be possibly or probably related to the study drug, with the exception of the 2 events leading to the discontinuation of a subject (JIA [worsening of ERA] and pain).

During the DB period changes from Baseline in laboratory parameters were small and not clinically significant in both treatment groups. For subjects who received at least 1 dose of adalimumab at any time during the study the majority of hematology parameters demonstrated infrequent shifts from Baseline to the Week 204 visit with the exception of platelets which demonstrated a shift from high to normal values in 13 subjects and eosinophils from high to normal values in 7 subjects.

Shifts in clinical chemistry parameters were infrequent and not considered clinically meaningful in the DB period. For subjects who received at least 1 dose of adalimumab at any time, the majority of clinical chemistry parameters demonstrated infrequent shifts from Baseline to the Week 204 visit with the exception of creatinine which demonstrated a shift from low to normal in 14 subjects, BUN, from high to normal in 10 subjects, and albumin from high to normal in 10 subjects.

Seventeen subjects had at least 1 potentially clinically significant liver function test (LFT) value.

Assessor's comment:

This was defined as ALT, AST and/or alkaline phosphatase ≥2.5 x ULN or total bilirubin ≥1.5 x ULN. Elevated liver enzymes are listed as common ADRs in the current SmPC.

Three subjects experienced elevations in ALT and/or AST > 5 × ULN that improved to only mild elevation or normalized at the last visit value for this final report. All other subjects had mildly elevated and mostly transient elevations in LFTs.

- One Subject (randomized to adalimumab) had mildly elevated ALT values at almost every visit, with maximum ALT elevation of 6.36 × ULN occurring at Day 57 at which time AST was also elevated at 4.29 × ULN. ALT was mildly elevated (1.23 × ULN) at the final visit (Day 1415, 14 days posttreatment). Slightly elevated alkaline phosphatase values were also observed at almost every visit beginning at the Screening visit with all values < 1.5 × ULN.
- One Subject (randomized to adalimumab) had transient elevations in ALT (maximum 2.83 × ULN on Day 168 [Day 83 of the OL period] and AST (maximum 6 × ULN on Day 852 [Day 767 of the OL period]) that normalized by the last visit (Day 1428, 1 day posttreatment). Mild elevations in alkaline phosphatase values (all < 2 × ULN) were observed at 17 consecutive visits beginning at Screening; the values normalized by Day 852 (Day 767 of the OL period) and remained as such by the last visit (Day 1428, 1 day posttreatment).
- One Subject (randomized to placebo) had a single elevated value for both ALT (6.83 × ULN) and AST levels (5.43 × ULN) on Day 673 (Day 589 of the OL period). Study drug was not interrupted and the subject continued on OL therapy. ALT and AST levels returned to normal at the next visit and remained normal through the final visit (Day 1423; 6 days posttreatment).

Overall, while 6 subjects had CTCAE toxicity grade ≥ 3 hematology or clinical chemistry value during the study, all were considered not clinically meaningful, and with the exception of 1 subject who continued to have mildly elevated ALT, all resolved by the last visit for each subject.

1.3.3. Discussion on clinical aspects

The MAH submitted the completed paediatric study M11-328 for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This submission also fulfils the MAH obligation listed in the Humira Risk Management Plan to submit the final CSR, as a required additional pharmacovigilance activity. M11-328 was a Phase 3, double-blind (DB), placebo-controlled, multicenter study with an open-label (OL) period. The initial data through the Week 52 visit (a 12-week DB period plus the first 40 weeks of the OL period) has been reported and assessed previously as part of the approval procedure to extend the indication for adalimumab for the treatment of paediatric subjects with ERA (EMEA/H/C/481/II/127).

The primary efficacy variable was mean percent change from Baseline to Week 12 in the number of active joints with arthritis, which was achieved in favour of adalimumab with mean percent decrease of –62.6% in subjects in the adalimumab group compared to – 11.6% in subjects in the placebo group (P = 0.039; last observation carried forward [LOCF]). This finding was supported by a number of sensitivity analyses using as observed data, non-parametric methods and numerically, but not statistically significant improvement observed in the PP analysis set. Results for the ranked secondary efficacy variables (number of sites of enthesitis, TJC, SJC, ACR Pedi 30, Pedi50, and Pedi70 response) were numerically superior in favour of adalimumab but none reached statistical significance at Week 12. However, they were considered to be supportive of the primary endpoint and observed to be sustained or improving further during the OL period through Week 52.

The final CSR provided with the current submission contained additional safety data up to Week 204 and additional efficacy data up to Week 156.

As noted previously, the interpretation of the study is limited by its small sample size. Most patients were retained in the study, however. At Week 156 (the last visit for collection of efficacy data, 12 of

the 15 placebo patients (80%) and 26 of the 31 adalimumab patients (84%) had remained in the study.

Reviewing the additional OL efficacy data, it can be concluded that the improvements observed for adalimumab during the DB period and the early OL period (through Week 52) were generally maintained during the remainder of the open-label period. Improvement in number of active joints with arthritis was maintained during the OL period through Week 156 of the study. Similarly, improvement in secondary endpoints such as number of sites of enthesitis, TJC, SJC, Pediatric ACR 50 response, and Pediatric ACR 70 response was generally maintained.

In the final CSR, the MAH reported that the statistical conventions for calculation of ACR Pedi30/50/70 responses specified in the SAP were inconsistent with the published methodology and expert opinion for calculation of the response rates. Consequently, the ACR Pedi30/50/70 response data had been recalculated (numerically somewhat more in favour of adalimumab) as compared to the previously reported results in EMEA/H/C/481/II/127. This is not considered to have impact on the overall outcome of the study.

In light of the findings, it is considered appropriate to amend Section 5.1 of the SmPC as follows:

Enthesitis-related arthritis

The safety…….Improvement in number of active joints with arthritis was maintained during the OL period through Week ~~52~~ **156** ~~of the study~~ **for the 26 of 31 (84%) patients in the Humira group who remained in the study**.

From a safety perspective, the pattern of adverse events observed during this small study was consistent with previous data and is considered sufficiently covered by the existing product information. No new safety signals were observed.

In summary, the results from the finalized CSR for study M11-328 are consistent with previous conclusions. The Benefit-Risk for Humira is unchanged.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The results from the finalized CSR for study M11-328 are consistent with previous conclusions. The Benefit-Risk for Humira is unchanged.

Recommendation

☒ Fulfilled:

The MAH is requested to submit a variation to amend the product information as follows:

Section 5.1

Enthesitis-related arthritis

The safety…….Improvement in number of active joints with arthritis was maintained during the OL period through Week ~~52~~ **156** ~~of the study~~ **for the 26 of 31 (84%) patients in the Humira group who remained in the study**.