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Committee for Medicinal Products for Human Use (CHMP)

Humira

(adalimumab)

Procedure No. EMEA/H/C/000481/A46/076

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

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

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Rapporteur's Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

P46 076

Submission of Clinical Study Report for Study M10-240 of the Safety, Efficacy, and Pharmacokinetics of adalimumab in Japanese Children with Polvarticular Juvenile Rheumatoid Arthritis

Humira (adalimumab)

EMEA/H/C/481

Marketing Authorisation Holder:

Abbott Laboratories Limited

Rapporteur:	Kristina Dunder

I. INTRODUCTION

On June 26, 2012, the MAH submitted a completed paediatric study for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided. The MAH stated that the submitted paediatric study does not influence the benefit risk for Humira and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the study

Prefilled syringes, 20 mg/0.4 ml and 40 mg/0.8 ml

II.2 Clinical aspects

1. Introduction

The MAH submitted a clinical study report on the paediatric Juvenile Idiopathic Arthritis Study MI0-240 *(R&D/11/1153*) and the pharmacokinetic report of the same study (*R&D/I0/1036*).

2. Clinical study

Study M10-240: A Multicenter, Open-label Study of the Safety, Efficacy, and Pharmacokinetics of the Human Anti- TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Rheumatoid Arthritis

- **Description**

Study M10-240 was a single-arm, open-label safety, efficacy, and pharmacokinetics study designed to evaluate the efficacy of subcutaneous adalimumab 20 mg or 40 mg every other week (eow), dependent on body weight below or above/equal to 30 kg (20 mg adalimumab eow in subjects weighing < 30 kg or 40 mg adalimumab eow in subjects weighing ≥ 30 kg), in Japanese paediatric subjects between the ages of 4 and 17 (inclusive) years with active polyarticular Juvenile Rheumatoid Arthritis. In addition the study was designed to confirm the similarity between the data obtained from this study and those from study DE038 conducted in Western subjects with juvenile idiopathic arthritis (JIA). Study drug administration was to be completed on the approval day, and the study was to be completed after 70 days follow-up period.

- **Methods**

  - Objective(s)

The primary objective of this study was to evaluate the safety, efficacy and pharmacokinetics including immunogenicity (measured as anti-adalimumab antibody (AAA) of fixed dose

adalimumab eow in Japanese subjects with polyarticular JRA. The secondary objective of this study was to confirm the similarity between the data obtained from this study and those from study DE038 conducted in western subjects with JRA.

- Study population /Sample size

Subjects were enrolled who could not control disease activity by conventional therapy including methotrexate (MTX) or lost response/were intolerant to conventional therapy Active disease was defined as ≥ 5 swollen joints (not due to deformity) and ≥ 3 joints with limitation of passive motion (LOM) with pain by passive motion or/and pain by pressure (tenderness). Planned number of subjects was MTX 20, non-MTX 5, total 25.

- Treatments

Subjects weighing less than 30 kg were to be injected with 20 mg of adalimumab every other week (eow). Subjects weighing 30 kg or more were to be injected with 40 mg of adalimumab eow. Adalimumab dose was not changed from Day1 to Week 14 regardless of body weight gain or loss. After Week 16, it was to be administered, based on body weight measured at Week 16 and every 12 weeks.

Study drug was to be administered subcutaneously in the abdomen, upper arms, or thighs.

- Outcomes/endpoints

Primary variable: ACR Pedi 30 response rate at Week 16

Secondary variables:

1. ACR Pedi 50, ACR Pedi 70 and ACR Pedi 90 response rates at Week 16, and ACR Pedi 30, ACR Pedi 50, ACR Pedi 70 and ACR Pedi 90 response rates at Week 2, 4, 8, 24 and every 12 weeks after Week 24.
2. Tender Joint Count (TJC)
3. Swollen Joint Count (SJC)
4. Pain on Passive Motion Joint Count (POM)
5. Limitation of Passive Motion Joint Count (LOM)
6. Active Joint Count (AJC)
7. CRP
8. CHAQ

ACR Pedi 30 response rate at Week 16 in study M10-240 was to be compared to that in open-label lead-in phase of study DE038 (detailed results were reported in 24-week CSR [R&D/10/099]).

The primary efficacy variable was to be evaluated at Week 16, and the study data for 24 weeks was to be summarized to apply the approval from MHLW.

- Pharmacokinetic sampling

Blood samples for serum adalimumab and AAA analysis were to be collected at Baseline, Week 2, 4, 8, 12, 16, 20, 24, 36, 48 and 60.

- Analytical methods

Adalimumab serum samples were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) method.
Samples for anti-adalimumab antibodies (AAA) were analyzed using a validated ELISA method.

- **Results**

  - Recruitment/ Number analysed

25 subjects in total (MTX: 20 subjects, non-MTX: 5 subjects) were enrolled to the study and received treatment with the study drug. Twenty-four subjects (MTX: 19 subjects, non-MTX: 5 subjects) completed Week 24.

  - Baseline data

The majority of subjects were female (80%). The mean age in total was 13 years (range: 7 - 17 years), and 3 (12%) subjects were 4 to 8 years, 9 (36%) subjects were 9 to 12 years, and 13 (52%) subjects were 13 to 17 years. The mean duration of JRA was 4.7 years, and the majority of subjects (96%, 24/25 subjects) had polyarticular JRA.

CHMP's comment: It is unclear what disease the 25th subject had. However, this does not change the assessment of the report.

  - Efficacy results

Efficacy analyses were performed in the Full-Analysis-Set (FAS) population (MTX: 20 subjects, non-MTX: 5 subjects, Total: 25 subjects). Because no major protocol deviation was observed and the Per-Protocol Set (PPS) was same as the FAS, the PPS population was not used for any analyses. Safety analyses (25 subjects) were performed in the Safety Analysis Set which was the same as the FAS.

The primary efficacy variable; ACR Pedi 30 response rate at Week 16 was 90% (18/20) in the MTX stratum, 100% (5/5) in the non-MTX stratum, and 92% (23/25) in the total population.

In the MTX stratum, the improvements in ACR Pedi 30, ACR Pedi 50, and ACR Pedi 70 response rates seen at Week 24 were maintained until study completion. In addition, further improvement in ACR Pedi 90 response rate was observed after Week 24 and maintained throughout. In the non-MTX stratum, the improvements in ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, and ACR Pedi 90 response rates seen at Week 24 were maintained until study completion.

  - Safety results

Six subjects (24%) reported 11 SAEs (all subjects were in the MTX stratum). The SAEs were pyrexia (2 events), hepatitis B, pharyngitis, pneumonia, dehydration, arthralgia, juvenile arthritis, and pharyngolaryngeal pain (1 event, respectively), and herpes zoster and amnesia were reported after Week 60. Four subjects reported 4 serious infectious AEs. Seven SAEs were moderate and 4 SAEs were mild in severity. Seven SAEs were assessed as at least "possibly related" to the study drug, and 6 of them were moderate in severity. All SAEs were resolved as of the final visit with the exception of 2 events (one hepatitis B, one amnesia). One subject (4%) reported 1 AE leading to discontinuation of the study drug. Twenty-four subjects (96%) reported 136 infectious AEs, 3 subjects (12%) reported 3 hepatic related AEs, and 6 subjects (24%) reported 8 injection site reaction related AEs. No hepatic related AEs and injection site reaction related AEs were reported after Week 60. No deaths, malignant AEs, opportunistic infection

related AEs excluding TB, congestive heart failure related AEs, demyelinating disease related AEs, allergic reaction related AEs, Lupus-like syndrome AEs, and hematologic related AEs were reported.

No clinically significant changes were observed in laboratory parameters and vital signs through Week 60. There were 20/25 subjects (80%) who switched to self-injection. There were no safety concerns in administering the study drug by self-injection.

- Pharmacokinetic results

Adalimumab serum concentrations
Out of 25 subjects (age 7 to 17 years) enrolled in Study M10-240, 8 subjects were in the 20 mg eow treatment with body weight < 30 kg at Baseline. Two subjects had body weight increased to ≥ 30 kg at Week 16. Therefore, their dose was increased to 40 mg eow starting at Week 16. After Week 24, two additional subjects had dose increase from 20 mg eow to 40 mg eow due to body weight increase.

Summary statistics for serum adalimumab concentrations from Japanese JRA subjects stratified by concomitant use of methotrexate (MTX) and adalimumab doses in Study M10-240 are presented in the table below:

MTX Use	Dose	N	Mean ± SD (Range), N_{nmiss}		
			Week		
			36	48	60
No	20 mg	2^	1.53 (0.892, 2.16), 2	2.75 (1.61, 3.89), 2	3.04 (0.00, 6.08), 2
No	40 mg	3	10.3 ± 6.77 (3.14 – 16.6), 3	7.24 ± 6.45 (0.00 – 12.4), 3	8.50 ± 7.45 (0.00 – 13.9), 3
Yes	20 mg	6*,$	9.62 ± 7.78 (1.36 – 24.5), 6	9.71 ± 6.90 (1.10 – 19.6), 6	14.3 ± 9.75 (0.00 – 24.6), 6
Yes	40 mg	14	13.2 ± 6.54 (0.00 – 24.9), 11	14.5 ± 9.03 (0.00 – 33.8), 12	14.4 ± 6.3 (0.00 – 21.6), 11

^ Since there were only 2 subjects, summary calculations presented as Mean (individual results), Nnmiss.
* Two subjects had body weight increase form < 30 kg to ≥ 30 kg at Week 16. Their dose was increased from 20 mg eow to 40 mg eow.
$ Two subject had dose increase from 20 mg eow to 40 mg eow at Week 48 and Week 36 due to body weight increase, respectively.

One of the objectives of this study was to compare adalimumab serum concentrations observed at Week 36 and 48 to those reported in the Western juvenile idiopathic arthritis (JIA) study (DE038). No data were available at Week 60 in Study DE038. In the Western study body size-adjusted doses were used (24 mg/m2) with a maximum of 40 mg. The doses administered in the Western study range from 10 to 40 mg. The age range in this study was 4 to 17 years of age.

A comparison of mean serum adalimumab concentrations (µg/ml) observed in the two studies is shown in the table below. Only data for subjects with concomitant MTX are shown as the number of subjects without MTX was very small in the Japanese study and a comparison is therefore difficult to make.

Week 36	Japanese 20 mg (n=6)	Japanese 40 mg (n=11)	Western 10-40 mg (n=15)
	9.62 ± 7.78	13.2 ± 6.54	10.23 ± 6.07
Week 48	Japanese 20 mg (n=6)	Japanese 40 mg (n=12)	Western 10-40 mg (n=10)
	9.71 ± 6.9	14.5 ± 9.03	9.94 ± 3.20

CHMP's comment: The comparison of PK in Japanese and Western paediatric subjects should be made with some caution as different doses were used and as it is a between-study comparison. In addition, the data from the Japanese study is very limited. Nevertheless, the data do not indicate substantial differences.
It is agreed that the new pharmacokinetic data do not warrant further regulatory action.

Anti-adalimumab antibodies
At Week 60 AAA positive rates were generally lower for subjects on adalimumab with concomitant MTX than for subjects on adalimumab mono-therapy. The number of AAA positive subjects in this study was too small to make definitive conclusion on the impact of immunogenicity on efficacy or safety.

3. Summary of MAH´s Discussion on clinical aspects

The results of study M10-240 demonstrated that adalimumab was effective in reducing disease activity in Japanese subjects with JRA. Adalimumab treatment with 20 mg or 40 mg eow was generally safe and well tolerated in Japanese patients with JIA. The adverse event profile and frequency of AEs reported in this study were consistent with previous clinical studies of adalimumab (patients with RA, plaque psoriasis, Crohn's disease and ankylosing spondylitis) conducted in Japan. No new safety signals were observed.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH submitted a clinical study report on a study performed in Japanese paediatric subjects between the ages of 4 and 17 (inclusive) years with active polyarticular Juvenile Rheumatoid Arthritis, and the pharmacokinetic report of the same study. The open label study was designed to evaluate the efficacy and safety of subcutaneous adalimumab and to confirm the similarity between the data obtained from this study and those from study DE038 conducted in Western subjects with juvenile idiopathic arthritis (JIA).

The MAH concluded that the results of the study demonstrate that adalimumab treatment was generally safe and well tolerated in Japanese patients with JIA, and that they do not influence the benefit risk for Humira.

The conclusion of the MAH is endorsed, although it is not possible to assess efficacy by this study design. No consequential regulatory action is needed.

- **Recommendation**

☒ **Fulfilled –** No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable