31 January 2019
EMA/145491/2019
Human Medicines Evaluation Division

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/P46/112

**Note**

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

On 16 October 2018, the MAH submitted data available from a patient less than 18 years of age, recruited in study P13-684, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study P13-684 Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation of Humira was 40 mg for subcutaneous administration. 290 of 300 patients in the safety analysis administered 40 mg every other week.

2.3. Clinical aspects

2.3.1. Introduction

In Japan, Humira at 40 mg and 80 mg was approved on April 16, 2008 and launched in the market on June 18, 2008. The results of a recent retrospective data analysis of the all-patient prescribed Humira study of Japanese patients with RA suggested that the effectiveness of adalimumab in bio-naïve patients with RA was more efficacious when they receive adalimumab in combination with MTX at a dose of ≥10 mg/week. A prospective non-interventional study of ADA + MTX ≥12 mg/week in patients with early (≤2 years) RA without previous biological treatment was performed, in order to assess the effectiveness and safety in daily routine practice. Data available from patients less than 18 years of age was submitted.

The MAH submitted a final report for:

- Study P13-684 Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice
2.3.2. Clinical study

Clinical study number and title

Study P13-684 Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice.

Description

Methods

Objective(s)

The primary objective was to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week) by assessing the percentage of patients with the DAS28 score of <2.6 at week 52.

The secondary objective was to assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week) by assessing the proportion of patients with a change in the following variables from baseline to week 104:

- Clinical Disease Activity Index (CDAI)
- Simplified Disease Activity Index (SDAI)
- The severity of functional impairment (HAQ)
- The health-related quality of life (EQ-5D)
- The inhibition of structural progression will be assessed by measuring the modified van der Heijde Total Sharp Score (mTSS).

Study design

This was a single-arm, multi-center, open labelled and prospective cohort study (post marketing observational study).

In daily clinical setting, patients with RA who receive adalimumab (Humira) and high-dose MTX (≥12 mg/week) was observed prospectively and the effectiveness was assessed by DAS28, HAQ and mTSS, in addition the safety the safety profile was assessed by measuring all serious adverse events (SAEs) and adverse events (AEs).

The observation period was 104 weeks.

Study population /Sample size

350 subjects; Adult subjects (≥16 years) with early (≤2 years) RA without previous biological treatment, who received adalimumab in combination with MTX ≥12 mg/week.

Inclusion criteria

The subjects of this study are patients with a diagnosis of RA and to whom adalimumab is prescribed as part of their normal treatment of RA. All subjects were to fulfil the following:
1) Disease duration of RA ≤ 2 years
2) MTX administration ≥ 3 months prior to starting adalimumab
3) Dose of MTX ≥ 12mg/week
4) DAS28-CRP > 3.2

Exclusion criterion
Patients who have been previously treated with biologics (including other TNF inhibitors)

Treatments
Humira sc in accordance to the Japanese label, 96.7% received 40mg eow.

Statistical Methods
This was an observational study; therefore, the analyses were primarily involved the generation of descriptive summary statistics.

Results

Recruitment/ Number analysed and baseline data

There were 346 subjects enrolled at 128 sites. The number of subjects in the safety analysis set was 300, and the number of subjects in the efficacy analysis set was 292. Age (Mean ± SD) of subjects in the safety analysis set was 54.1 ± 13.9 years, and 73.7% (221/300) were females.

Efficacy results

The remission rate was 71.2% (208/292) in the last observation. The remission rate at week 52 was 77.1% (162/210) in the subjects with available data set to calculate DAS28 score. Out of 292 subjects in the efficacy analysis set 210 subjects had an available data set that permitted calculation of DAS28 score at this time point. The remission rate at week 104 was 92.3% DAS28-4 (120/130) in the 130 subjects with available data set permitting assessment of the DAS28 score.

Differences were also observed throughout the entire assessment period from 4 weeks to 104 weeks after start of treatment regarding change in DAS28-4CRP, DAS28-ESR scores, CDAI, SDAI and HAQ and EQ-5D-3L. The change of mTSS at week 52 was ≤ 0.5 in 86% (135/157) of the subjects remaining in the study at this time point. At week 104, a change in mTSS of ≤ 0.5 was reported for 74.3% (52/70) of the remaining subjects.

Safety results

No deaths were reported in this study. 226 adverse events were observed in 124 patients out of 300 patients in the safety analysis set, and the incidence rate of adverse events was thus 41.33%(124/300). 35 serious adverse events were observed in 29 patients, and the incidence rate of serious adverse events was thus 9.67% (29/300).

Paediatric Data

One paediatric subject participated in this study. The subject was a 16 year-old female who received Humira for 393 days and did not report any adverse event.
2.3.3. Discussion on clinical aspects

MAH’s discussion

Adalimumab in combination with high dose MTX improved the signs and symptoms of Japanese subjects with rheumatoid arthritis during 104 weeks of treatment as measured by DAS28, CDAI, SDAI, HAQ, EQ-5D-3L and suppressed the bone destruction during 104 weeks of treatment measured by mTSS. The safety findings were consistent with the known and described safety profile of adalimumab.

3. CHMP overall conclusion and recommendation

Overall conclusion

The MAH has provided results from a post marketing observational study (P13-684), designed as a single-arm, multi-center, open labelled prospective cohort study. It was conducted in Japan, in order to investigate the effectiveness and safety in patients with early (≤2 years) RA without previous biological treatment, who received adalimumab in combination with MTX ≥12 mg/week.

At baseline, disease activity was high in 71 subjects (24.3%) and moderate in 221 subjects (75.7%). At week 52, DAS28-4CRP remission was achieved in 162/210 subjects (77.1%), and at week 104, in 120/130 subjects (92.3%).

Improvement was also shown for all secondary efficacy variables, which were DAS28-4CRP, DAS28-ESR scores as well as change of CDAI, SDAI, HAQ, EQ-5D-3L and the change of mTSS after 104 weeks. The safety results did not raise any new concerns. A full assessment of the results from the adult study has not been made since it is out scope for this submission.

Among the included subjects was a 16 year old female, who received Humira for 393 days, without reporting any adverse events. No efficacy data has been provided for this subject, however the scope for P46 submissions is mainly safety, and no additional information is therefore currently requested.

No data that changes the B/R balance of the product or warrants changes to the PI or RMP regarding the use in children has been identified. No further actions are required.

Recommendation

- Fulfilled

No regulatory action required.