23 February 2017
EMA/174639/2017
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/P46/099

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# 1. Introduction

In December 2016, the MAH submitted final study report for a 60-month prospective, multicenter, observational study of adalimumab in adult patients with Crohns disease (CD) who resided in Germany, 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 observational Study P10-278 is a stand-alone study.

## *2.2. Information on the pharmaceutical formulation used in the study<ies>*

Humira was to be administered in accordance with the approved SmPC.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for: Study P10-278.

This was a 5 year prospective, multicenter, observational study of adalimumab in patients with CD who resided in Germany. Patients were seen during regular visits for routine clinical care. Visits were scheduled every 3 months for the first year and every 6 months thereafter. Patients continued in the study for a maximum of 60 months or until discontinuation from adalimumab therapy.

### 2.3.2. Clinical study P10-278

### Methods

#### *Objective(s)*

Primary study objectives were to evaluate:

- Effectiveness in reducing disease activity as assessed by the Crohn's Disease Activity Index (CDAI)
- Effectiveness in improving HRQOL as assessed by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
- Safety as assessed by reports of adverse events (AEs)

Secondary objectives included changes in the Harvey-Bradshaw Index (HBI), inflammatory markers, and socioeconomic outcomes. Exploratory regression analyses were conducted to determine predictors of response to therapy at Month 12.

***Study design***

This was a prospective, multicenter, observational study. The study population was a community sample of patients with CD who resided in Germany. Visits were scheduled every 3 months for the first year and every 6 months thereafter. Patients continued in the study for a maximum of 5 years or until discontinuation from adalimumab therapy. The first patient was seen on 27 May 2007 and the last patient visit occurred on 21 December 2015.

***Study population /Sample size***

Doctors were instructed that adult patients (≥ 18 years of age) with a diagnosis of CD who were preparing to initiate adalimumab therapy were eligible for study enrolment. In accordance with the indication for adalimumab and guidance for initiating anti-TNF therapy in CD patients at the time of enrolment, patients were generally those with severe, active CD with insufficient response to a complete and adequate therapy of glucocorticoid and/or immunosuppressive drugs, or those with hypersensitivity against or contradictions to these therapies. However, there was no means of preventing doctors from enrolling patients younger than 18 years of age or those who did not meet the criteria for CD diagnosis or anti-TNF use. The safety set consisted of 4107 patients who received at least one dose of adalimumab. Of these patients, 32 (0.8%) were < 18 years of age whereas the full analysis set (FAS) consisted of 1621 patients (12 patients [0.7%] < 18 years of age) with adequate data to evaluate adalimumab effectiveness.

Patients with inadequate data or who met other specified criteria were not included in the FAS (Table 6; more than one reason was possible). The major reasons for being excluded from the FAS involved patients with inactive CD at baseline (HBI ≤ 4) and those with previous adalimumab therapy, as the impact of adalimumab treatment on disease activity is difficult to evaluate in these subpopulations. At 60 months, 263 patients (6.4%) remained in the safety set and 79 (4.9%) in the FAS. Approximately 65% of patients were lost to follow-up for unknown reasons. The remainder of the patients withdrew from the study. Loss of effectiveness (10.6% of patients in the safety set and 13.0% in the FAS) was the most frequent reason for study withdrawal.

In the paediatric population the baseline disease activity levels were similar. None of the paediatric patients withdrew due to adverse drug reactions. Three patients withdrew for lack of effectiveness, 4 withdrew for "other reasons," and 21 were lost to follow-up, leaving 4 ongoing patients at the end of the 60-month study.

**Table 6. Reasons for Exclusion from Analyses of Effectiveness[a]**

| Criterion | n | % |
|---|---|---|
| **Total number of excluded patients (one or more of the following criteria were met)** | **2486** | **60.5** |
| Patients with inactive Crohn's disease at baseline (HBI ≤ 4) | 1259 | 30.7 |
| Patients with previous adalimumab therapy | 1089 | 26.5 |
| Patients with baseline information only (no post-baseline for CDAI, HBI, C-reactive protein (CRP), SIBDQ or withdrawal) | 395 | 9.6 |
| No date and/or documentation for start of therapy | 296 | 7.2 |
| HBI not available at baseline | 295 | 7.2 |
| Therapy initiated more than 14 days before documentation | 237 | 5.8 |

a. More than one answer was possible.

Reference: Appendix 1 Table 1.1

***CHMP comment:***

As the study was primarily designed to include adults, the number of paediatric subjects is low. The number of patients withdrawn from the data sets was large and thus very few children remained in the study.

### *Outcomes/endpoints*

The key outcome measures were:

- Crohn's Disease Activity Index
- Harvey-Bradshaw Index
- Short Inflammatory Bowel Disease Questionnaire
- Adverse events

## Results

### *Efficacy results*

Adalimumab treatment was associated with marked reductions in disease activity and improvements in HRQOL in the FAS. During 60 months of adalimumab therapy, mean CDAI decreased (improved) from 256 at baseline to 117 at Month 60 in patients remaining on therapy. Most of the reduction was observed in the first 6 months of therapy. Patients who remained on therapy showed sustained reductions in disease activity through 60 months. The proportion of FAS patients in remission, as defined by CDAI < 150, increased from 12.2% at baseline to 69.8% at 12 months, 70.7% at 24 months, 75.4% at 36 months, 72.7% at 48 months, and 68.4% at 60 months in patients who stayed on therapy. Improvements were also observed in SIBDQ, HBI, inflammatory markers, and socioeconomic outcomes. Higher disease activity at baseline was a positive predictor of therapeutic

response at Month 12, while negative predictors included smoking, age, immunosuppressive use at baseline, and number of CD-related operations.

The 12 paediatric patients in the FAS showed clinical responses that were similar to those observed in the population as a whole.

***CHMP comment:***

Due to the low number of subjects it is difficult to draw conclusions from the study. However, no unexpected findings were recorded.

***Safety results***

The duration of adalimumab exposure in the safety set (N = 4107) was 1.78 ± 1.53 years. In the safety set, 16.7% of patients experienced an AE and 13.34% experienced a serious AE (SAE). The most common nonserious AE by SOC was infections and infestations (7.23%) and the most common nonserious AE by PT was nasopharyngitis (3.21%). The most common SAE by SOC was gastrointestinal disorders (6.04%), mostly related to CD complications including CD (1.4%, intestinal stenosis (0.8%), ileal stenosis (0.6%), and anal fistula (0.5%). Two deaths were reported during the study, one due to liver and kidney failure associated with hepatic cirrhosis and the other due to Hodgkin's disease in a patient who refused oncology therapy. AE reports were consistent with the known adalimumab safety profile and no new safety signals were observed.

The mean duration of adalimumab exposure among the 32 pediatric patients in the safety set was 2.35 ± 1.84 years (Appendix 5, Table 1.7). One paediatric patient (3.1%) experienced 2 non-serious AEs (SOCs of infections and infestations and nervous system disorders) (Appendix 5, Table 9.3). Three paediatric patients (9.4%) experienced 4 SAEs (1 gastrointestinal disorder, 2 surgical and medical procedures, and 1 neoplasm).

***CHMP comment:***

The safety findings are considered as consistent with the known safety profile. One unspecified neoplasm was reported. This is considered a chance finding.

### 2.3.3. Discussion on clinical aspects

The MAH has in this application submitted a final report for Study P10-278. This was a 5 year prospective, multicenter, observational study of adalimumab in patients with CD who resided in Germany. This was a postmarketing study in adult patients (safety set n=4107) However as the study included 32 paediatric the study report has been provided as requested according to Article 46 of Regulation (EC). No new or unexpected safety findings occurred.

## 3. Overall conclusion and recommendation

### Overall conclusion and Recommendation

The benefit risk remains unchanged and no updates of the SmPC are warranted.

☒ Fulfilled:

No regulatory action required.