Amsterdam, 26 March 2020
EMA/160077/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Humira

International non-proprietary name: adalimumab

Procedure no.: EMEA/H/C/000481/P46 100

Note

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

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1. Introduction

On 9th December 2019, the MAH submitted a Final Study Report for P10-446 as submission type PAM 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 P10-446 Long term Documentation of the Safety and Efficacy as well as the Effects on Work Productivity in Patients with Moderate to Severe Plaque Psoriasis treated with HUMIRA® (Adalimumab) in Routine Clinical Practice (LOTOS) is a stand alone study(ies).

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

HUMIRA® was used according to the approved label for psoriasis vulgaris. HUMIRA®-injection solution as available in ready-to-use syringes and as pre-filled pen (injector, pre-filled/FertigPEN) included 40 mg adalimumab

2.2.1. Introduction

The MAH submitted a final report for:

- Study P10-446 Long term Documentation of the Safety and Efficacy as well as the Effects on Work Productivity in Patients with Moderate to Severe Plaque Psoriasis treated with HUMIRA® (Adalimumab) in Routine Clinical Practice (LOTOS).

2.2.2. Clinical study

The submitted study P10-446 is a non-interventional study (NIS). It was a single-arm, multicenter, prospective cohort study. The goal of this NIS was designed to document long-term data on the efficacy and tolerability of HUMIRA® in the treatment of ***adult*** patients with moderate to severe chronic plaque Ps under conditions of routine care, including data of patient groups that are usually excluded from clinical trials (e.g., due to comorbidities, varied concomitant medication).

Clinical study number and title -please refer to section 2.2.1

Description

Methods

Objective(s)

In this NIS, a long-term documentation of treatment with HUMIRA® over 60 months with 12 data collection points (visits) or as per amendment over 24 months with 6 visits was performed as planned. The documentation was performed by the physician as well as by patients' self-assessment. The primary objectives of the NIS were:

● to explore changes in health-related care utilization data by the evaluation of

- the number of missed working days

- the number of visits to doctor's office

- the number and duration of hospitalizations

- the self-assessed work ability

● to explore efficacy for different subgroups by the analysis of

- changes in the Psoriasis Area and Severity Index (PASI)

- the number of patients achieving a PASI 75 response

● to evaluate safety by

- the documentation and analysis of serious adverse events and adverse events

Secondary objectives included:

● the exploration of changes in quality of life measurements (Dermatology Life Quality Index [DLQI], EuroQol-5D [EQ-5D])

● the exploration of the influence of the BMI and body weight on efficacy measurements (PASI)

● the evaluation of physician's assessment of the antipsoriatic treatment with HUMIRA®

● the evaluation of patients' assessments of the antipsoriatic treatment with HUMIRA®

● the evaluation of the safety and tolerability of the HUMIRA® treatment for subgroups of patients with common concomitant diseases, especially diabetes type I and II, cardiovascular, liver and renal insufficiencies, and related concomitant medications.

The following secondary objectives were additionally included through the amendment of the study protocol:

● Itch Visual Analogue Scale (Itch VAS)

● Palmoplantar Psoriasis Area Severity Index (pPASI)

● Reasons for and duration of dose escalation

● Median drug survival rates of different dosing regimes

● PASI (mean, min, max) at start of the dose escalation

● Assessment of Psoriasis Scalp Severity Index (PSSI)

● Target Nail Psoriasis Severity Index (target-NAPSI)

In addition, a substudy was conducted: "Long-term Documentation of Risk Factors of Metabolic Syndrome and Cardiovascular Disease in Patients with Moderate to Severe Plaque Psoriasis Treated with HUMIRA® in Routine Clinical Practice (LOTOS Metabolism)": The research question explored in this substudy was whether treatment with HUMIRA® altered lipid and glucose metabolism or cardiovascular risk factors in patients with psoriasis. The primary objectives were:

● To explore the effects of HUMIRA® therapy on the parameters of metabolic and cardiovascular risk

● To explore whether there exists a correlation between therapeutic effectiveness on skin disease and changes in the parameters of metabolic and cardiovascular risk

Study design

This was a non-interventional single-armed, multicenter, prospective cohort study The observational study documentation started with the first application of HUMIRA® and was repeated at Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60.The patients had to be at least 18 years old at the start of the investigation and provided written informed consent. Per the original protocol, the study was ended after the overall target size of 850 patients was reached. Dose escalations that were documented for the LOTOS Amendment patients turned out to be less common than anticipated in daily routine care. For the LOTOS patients, the first patient was included into the study on 12 November 2007 and the last contact/last visit of the last patient was on 28 June 2019; for the LOTOS Amendment patients, these were 16 January 2017 and 30 June 2019, respectively.

Results

Recruitment/ Number analysed

Overall, 5,205 patients (LOTOS patients: n = 4,793; LOTOS Amendment patients n = 412) were analyzed in the safety analysis set (SAF) and 3,684 patients (LOTOS patients: n = 3,390; LOTOS Amendment patients: n = 294) in the full analysis set (FAS). *All patients were adults >18 years of age except one LOTOS Amendment patient who was < 18 years of age*. This single paediatric patient was included in the SAF; however, as the start date of treatment with HUMIRA® was prior to baseline date, the patient was excluded from the FAS and included as a deviation from the study protocol.

Baseline data

In the SAF, the LOTOS patient population was composed of slightly more male patients (62%); the LOTOS Amendment patient population was more or less equally distributed (male 52%, female 48%). The mean ± standard deviation (SD) age of the LOTOS and LOTOS Amendment patient population was 47.5 ± 13.11 and 47.1 ± 14.70 years, respectively. The characteristics of Ps were chronic-stationary for most of the patients (LOTOS patients: 86.8%; LOTOS Amendment patients: 81.3%). The duration of disease was > 10 to ≤ 20 years for 31.4% of the LOTOS patients and ≤ 10 years or > 10 to ≤ 20 years for 31.8% and 31.3% of the LOTOS Amendment patients, respectively.

Paediatric patient

Only baseline visit data were documented for this single patient (refer to Table 1 below).

Table 1. Summary of Demographic and Baseline Data of Patient 4052-05 (< 18 Years of Age)

Baseline Visit and ICF Date	12 April 2018
Age [Years]	16
Gender	Male
Height [cm]	179
Weight [kg]	86
Baseline BMI	26.8
Onset Date of Ps	2017
Duration of Disease	≤ 10 years
PASI	22.5
HUMIRA Start Date	27 November 2017

BMI = body mass index; ICF = Informed Consent Form; PASI = Psoriasis Area and Severity Index; Ps = psoriasis

Effectiveness results

Long-term treatment with HUMIRA® during routine clinical care had a favorable impact on health-related care utilization and employment-related and clinical outcomes *in adult patients* with Ps. HUMIRA® was shown to be highly effective by both the physician as well as patient measures of disease activity in Ps patients remaining on therapy.

Safety results

No new safety signals or unexpected trends of treated *adults* were detected during the 60 (LOTOS patients) and 24 (LOTOS Amendment patients) months.

2.2.3. Discussion on clinical aspects

Only one of the included patients of the LOTOS study and LOTOS Amendment study patients was < 18 years of age. As only baseline visit data were documented for this patient and the patient excluded from the FAS and included as a deviation from the study protocol, no further conclusion can be drawn relating to paediatric effectiveness and safety from this study(ies).

3. Rapporteur's overall conclusion and recommendation

No meaningful conclusions of the paediatric population can be made based on these data of the final study report for P10-446 as only baseline visit data were documented for one single paediatric patient.

☒ **Fulfilled**:

No regulatory action required.