EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

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

Humira

Adalimumab

Procedure no.: EMEA/H/C/481 P46 091

Note

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

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1. Introduction

On March 3 2016, the MAH submitted the study M13-687 for Humira, including one paediatric subject (17 years old), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study M13-687 was an OL, single arm study to evaluate the efficacy, safety, and pharmacokinetics of adalimumab dose escalation to 80 mg eow in Japanese patients with Crohn's disease who lost response to adalimumab 40 mg eow.

A short critical expert overview has also been provided.

Humira is currently approved for several inflammatory diseases in adults, including rheumatoid arthritis, plaque psoriasis, arthritic psoriasis, ulcerative colitis, Crohn's disease and ankylosing spondylitis. In the paediatric population Humira is indicated for the treatment of juvenile idiopathic arthritis, enthesitis-related arthritis, paediatric plaque psoriasis and Crohn´s disease.

For paediatric Crohn´s disease the current indication is severe active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

However, on 1 April 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation.

The CHMP adopted an extension to the existing indication in paediatric Crohn's disease as follows:

"Humira is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy,and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies."

This new indication is currently pending a decision by the European Commission.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study M13-687 is a stand-alone study.

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

Humira as approved in Japan was used in this study.

2.3. Clinical aspects

2.3.1. Clinical study M13-687

Description

Study M13-687 was an OL, single arm study to evaluate the efficacy, safety, and pharmacokinetics of adalimumab dose escalation to 80 mg eow in Japanese patients with Crohn's disease who lost response

to adalimumab 40 mg eow. A total of 28 subjects received at least 1 dose of adalimumab in Study M13-687. The majority of subjects were male (57.1%) and the mean age was 33.6 years. The mean duration of Crohn's disease for these subjects was 8.61 years. The mean CDAI at Baseline was 308.4 and approximately one-half of the subjects (46.4%) had severe Crohn's disease (baseline CDAI > 300).

Methods

Objective(s)/Endpoints

Primary Endpoint

- **Efficacy:**
  - Proportion of patients who achieved CR-50 (Crohn's disease activity index [CDAI] decrease of >/= 50 from Week 0) at Week 8

Secondary Endpoints

- **Efficacy:**
  - Proportion of patients who achieved remission (CDAI < 150) at each visit
  - Proportion of patients who achieved CR-50 at each visit
  - Proportion of patients who achieved CR-70 (CDAI decrease from Week 0 >/= 70) at each visit
  - Proportion of patients who achieved CR-100 (CDAI decrease from Week 0 >/= 100) at each visit
  - Change in C-reactive protein (CRP) from Week 0 at each visit
- **Safety:**
  - Incidence of adverse events and changes in laboratory tests and vital signs throughout the study

Study design

Study population

Main Inclusion Criteria

- Patient >/= 15 years of age at time of informed consent
- Patient with CD who received induction treatment of commercially available adalimumab (160mg initially and 80mg at 2 weeks after initial dose), achieved CR-70 at 4 weeks after initial dose, and then lost response during maintenance treatment with adalimumab 40mg EOW

  -Definition of loss of response: increased CDAI >/= 50 compared to the time point with the lowest CDAI score after initiation of adalimumab treatment and absolute CDAI >/= 200 at both Screening and Week 0
- Patient with CRP >/= 1mg/dL at Screening
- For females: Negative pregnancy test and using an approved form of birth control throughout the study and for 150 days after the last dose of study drug

- Patient with a negative TB screening assessment or have documented completion of a full course of TB prophylaxis prior to Week 0

Main Exclusion Criteria:

- Patients using oral corticosteroids not on a stable dose for at least 14 days prior to Week 0 or discontinued use within 14 days of Week 0, or received injection of corticosteroids within 28 days of Week 0
- Patients using immunomodulators who initiated treatment within 90 days of Week 0 or not on a stable dose for at least 28 days prior to Week 0 or discontinued use within 28 days of Week 0
- Patients with abscess or suspicion of abscess, or patient with infection(s) requiring treatment with intravenous anti-infectives within 28 days prior to Week 0 or oral anti-infectives within 14 days prior to Week 0

Enrolled patients were followed from week 0 to week 52 of treatment after dose escalation. Information on the effectiveness, safety, and pharmacokinetics was collected at study visits through Week 52 (or early termination visit). The first patient's first visit was on 18 September 2013 and the last patient's last visit (through Week 52) was on 01 October 2015.

Treatments

Patients with Crohn's disease who lost response to adalimumab 40 mg eow were treated with an escalated dose to 80 mg adalimumab eow.

Results

Recruitment/ Number analysed

A total of 28 patients were enrolled in M13-687 across 12 study sites in Japan and all patients received at least 1 dose of adalimumab. Of the 28 patients enrolled in the study, 18 (64.3%) patients completed the study and 10 (35.7%) patients discontinued from the study. The primary reason for discontinuation by these 10 patients was as follows: 3 (10.7%) patients discontinued because of an adverse event, 6 (21.4%) patients discontinued because of a lack of efficacy, and 1 (3.6%) patient discontinued for other reasons (use of concomitant prohibited medicine).

Baseline Demographics:

Of the 28 patients included in the efficacy analysis set, a majority were male (57.1%) and the mean age was 33.6 years (range: 17 to 51 years). There was only one patient (17 years old) under 18 years old. The mean duration of CD at study entry was 8.61 years. The mean CDAI at Week 0 was 308.4 and approximately one-half of patients (46.4%) had severe CD (CDAI > 300). The majority (89.3%) of patients had a Week 0 CRP level of $\geq$ 1.0 mg/dL. The mean duration of exposure to adalimumab at Week 0 was 1.27 years.

Efficacy results

The proportion of patients who achieved CR-50 at Week 8 was 75.0% (95% CI: 55.1%–89.3%) (non-responder imputation [NRI]). The proportion of patients who achieved clinical remission (CDAI < 150) at Week 4 was 14.3% (4 of 28 patients) (NRI). The proportion increased through Week 24 and then was maintained through the end of the study (Week 52: 35.7% [10 of 28 patients]). The proportion of patients who achieved CR-50 at Week 4 was 67.9% (19 of 28 patients) (NRI). The proportion was

maintained through the end of the study (Week 52: 57.1%, 16 of 28 patients). The proportion of patients who achieved CR-70 at Week 4 was 46.4% (13 of 28 patients). The proportion increased over time through Week 24 and was maintained through the end of the study (Week 52: 57.1%, 16 of 28 patients) (NRI). The proportion of patients who achieved CR-100 was 32.1% (9 of 28 patients) at Week 4. The proportion increased over time through Week 24 and was maintained through the end of the study (Week 52: 46.4%, 13 of 28 patients) (NRI). The mean change from Week 0 in CRP was –0.570 mg/dL at Week 4. This mean decrease was maintained through the end of the study (range from –0.426 to -1.008 mg/dL) (last observation carried forward [LOCF]).

CHMP's comment:

The efficacy results are difficult to interpret as this is an open-label study. The effect of dose escalation of adalimumab (Humira®) in patients with Crohn´s disease seems to be clinically relevant for some patients.

Safety results

No deaths were reported in the study. A total of 8 patients (28.6%) experienced 11 treatment emergent serious adverse events (SAE). The most frequently reported SAE was Crohn's disease (4 of 28 patients [14.3%]); all other SAEs were reported by 1 patient each (ileus, intestinal obstruction, small intestinal ulcer haemorrhage, subileus, anal abscess, pneumonia bacterial, and allergic transfusion reaction). All SAEs were moderate in severity and considered to have no reasonable possibility of being related to adalimumab, except for the SAE of pneumonia bacterial experienced by 1 patient that the investigator considered to have a reasonable possibility of being related to adalimumab. Four patients (14.3%) discontinued from adalimumab because of an AE related to their Crohn's disease (Crohn's disease [2 patients], ileus [1 patient] and subileus [1 patient]). The investigator considered these events to be serious and to have no reasonable possibility of being related to adalimumab. All treatment-emergent adverse events (TEAE) leading to discontinuation resolved after discontinuation. One patient under the age of 18 years old experienced a serious TEAE (intestinal obstruction of moderate severity with no reasonable possibility of being related to adalimumab).

Among the categories of AEs of special interest (AESI) that were examined, the following results were observed:

Infections: Nineteen patients (67.9%) reported infectious AEs; nasopharyngitis was the most frequently reported event. The majority of infectious AEs were mild, nonserious, and considered to have no reasonable possibility of being related to adalimumab. All of these events resolved. Two patients (7.1%) reported serious infectious AEs (pneumonia bacterial and anal abscess), both of which resolved.

Immune reactions: Two patients (7.1%) reported events of allergic reaction (urticaria), which the investigator considered to be mild to moderate in severity, and nonserious. One event was considered to have a reasonable possibility of being related to adalimumab and the other event was considered to have no reasonable possibility of being related to adalimumab. Both events resolved.

Gastrointestinal Disorders: One patient (3.6%) reported an event of intestinal stricture, which the investigator considered to be moderate in severity, serious, and to have no reasonable possibility of being related to adalimumab, attributing the event to the patient's Crohn's disease. The event resolved.

Hematologic disorders: Three patients (10.7%) reported hematologic disorders (anemia in 2 patients and leukopenia in 1 patient), which the investigator considered to be moderate in severity, nonserious, and to have no reasonable possibility of being related to adalimumab. All 3 events resolved.

Liver failure and other liver events: One patient (3.6%) reported a liver failure and other liver events (hepatic function abnormal), which the investigator consider to be mild in severity, nonserious, and to have no reasonable possibility of being related to adalimumab. The event resolved.

Injection site reactions: One patient (3.6%) reported an intermittent event of injection site reaction, which the investigator considered to be moderate in severity, nonserious, and to have a reasonable possibility of being related to adalimumab.

In this study, no patients reported events of opportunistic infection.

CHMP's comment:

No new or unexpected safety events were identified. Of note, the paediatric subject (a 17 year old male subject) experienced a TEAE in form of an intestinal obstruction. This event is most likely related to the underlying disease.

3. Discussion on clinical aspects and CHMP's overall conclusion and recommendation

Study M13-687 was an open-label, non-comparative, post marketing study performed in Japan. The study evaluated the efficacy and safety of adalimumab dose escalation to 80 mg eow in patients with Crohn's disease who lost response to adalimumab 40 mg eow. For some patients losing response to 40mg adalimumab (Humira®) eow, a dose escalation to 80 mg eow may be clinically meaningful. No new safety concerns were identified. The effect of adalimumab (Humira®) in patients with Crohn´s disease was generally as expected and no unexpected safety issues occurred. Only one paediatric patients was included in this trial. This patient experienced a TEAE in form of an intestinal obstruction which was likely related tol the underlying disease. The presented data does not change the benefit risk for adalimumab in the paediatric approved indications. No changes are warranted in the SmPC.

Overall conclusion

The study report for Study M13-687 has been provided as requested according to Article 46 of Regulation (EC) No1901/2006, as amended. There were no unexpected findings.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.