Amsterdam, 28 May 2020
EMA/280488/2020
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, as amended

Humira

adalimumab

EMEA/H/C/000481/P46/117

Note

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

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1. Introduction

The purpose of this submission submitted on 28 January 2020 is to comply with Article 46 of Regulation (EC) No1901/2006, as amended, by submitting data available from patients less than 18 years of age recruited to the following study: P16-052_P18-839 Post-marketing surveillance study of adalimumab (Humira®) for hidradenitis suppurativa and pediatric chronic severe plaque psoriasis patients according to the standard for "Re-examination of New Drugs"

A short critical expert overview has also been provided.

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent, follicular skin disease which causes significant pain and distress. HS is typically diagnosed in young adults with ongoing disease throughout adult life.

Psoriasis is an autoimmune disease affecting multiple organs including the skin, joints and heart, characterized by skin thickening resulting from the rapid accumulation of epidermal cells. Psoriasis affects approximately 2% of the population and is common in pediatrics. 30 – 32% of psoriasis patients develop psoriasis before 15 years of age, 20% from 15– 19 years of age, among these 10% before 10 years old, and 2% before 2 years old.

Adalimumab (Humira®) was approved in Korea to treat active moderate to severe HS in adults with an inadequate response to conventional systemic HS therapy and severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy. The submitted post-marketing surveillance study was conducted to fulfill the post-approval regulatory requirement.

Originally two separate 40-week studies were planned, (study P16-052 (adult HS) and study P18-839 (ped PsO)), these are now presented as one combined study (P16-052_P18-839). In accordance with the Korean Standard for Re-examination of New Drugs requirement, at least 600 subjects should have been recruited. However, the MAH explains that, according to the data reported to Health Insurance Review & Assessment Service (HIRA), the number of HS and ped PsO patients is expected to be small in Korea and among them, only a limited number of patients can be prescribed adalimumab (Humira) considering national health insurance benefits criteria. Due to above reasons, minimum number of patients to be enrolled was adjusted after Ministry of Food and Drug Safety (MFDS) approval.

The study P16-052 (adult HS) and the study P18-839 (ped PsO) is presented as one combined study (P16-052_P18-839). This AR focuses on evaluation of the pediatric subjects included in the study.

Milestone	Planned Date	Actual Date	Comments
Start of Data Collection:	HS: 2016 3Q ped PsO: 2018 1Q	HS: 10 March 2017 ped PsO: 25 June 2019	First subject's consent date
End of Data Collection:	2019 4Q	06 August 2019	Last Subject Last Visit
Registration in the EU PAS:	-	-	Not applicable
Study Progress Report	-	-	Not applicable
Interim Report:	-	-	Not applicable
Final Report of Study Results:	2020 1Q	TBD	Both studies were presented as one CSR upon request of MFDS.

2. Scientific discussion

2.1. Information on the development program

P16-052_P18-839 *Post-marketing surveillance study of adalimumab (Humira) for hidradenitis suppurativa and pediatric chronic severe plaque psoriasis patients according to the standard for "Re-examination of New Drugs"* is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

The MAH states that patients were administered adalimumab (Humira) injection as per the package label.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has submitted a final report for the study P16-052_P18-839 *Post-marketing surveillance study of adalimumab (Humira) for hidradenitis suppurativa and pediatric chronic severe plaque psoriasis patients according to the standard for "Re-examination of New Drugs".*

As determined by the Korean Ministry of Food and Drug Safety (MFDS) the study should be conducted within 4 years from the drug approval (Dec 2015).

The study P16-052 (adult HS) and the study P18-839 (ped PsO) are presented as one combined study (P16-052_P18-839).

2.3.2. Clinical study

Study P16-052_P18-839 *Post-marketing surveillance study of adalimumab (Humira) for hidradenitis suppurativa and pediatric chronic severe plaque psoriasis patients according to the standard for "Re-examination of New Drugs"*

Description

This study was designed as a non-interventional, prospective, post-marketing surveillance in accordance with Korean Standard of Re-examination of New Drugs. The goals of the study were designed to evaluate the real-world safety and effectiveness of adalimumab in Korean HS and pediatric chronic severe plaque psoriasis (ped PsO) patients under routine treatment practice.

Methods

The data for the study were collected from medical institutions (clinics and hospitals) in Korea. The observational study documentation started with the first application of adalimumab (Baseline) and was repeated at Weeks 12 and 24 for HS patients and Weeks 16 and 40 for ped PsO patients.

Participating sites throughout Korea registered patients who were prescribed with adalimumab (Humira) for the treatment of hidradenitis suppurativa and pediatric chronic severe plaque psoriasis. The prescription of adalimumab (Humira) was done by each patient's physician under a normal medical treatment condition in accordance with the approved use of the drug and the decision to prescribe adalimumab (Humira) is independent from the enrollment into the study. The investigators obtained consent of participation from a patient (and their legally authorized representative) who was subject to the registration for the study. The ped PsO subjects were administered with adalimumab (Humira) for

40 weeks from his/her first administration (baseline) and HS subjects were followed up for 24 weeks from baseline. The visitation for a follow-up was done according to the actual clinical process, and the safety evaluation was conducted during the observation period.

The data sources in this study were from institute's medical chart and the data were collected prospectively.

Objective(s)

The primary objectives were:

- To evaluate the following safety measures
  - Serious adverse event/drug reaction
  - Unexpected adverse event/drug reaction
  - Known (labelled) adverse drug reaction
  - Nonserious adverse event/drug reaction
- To explore effectiveness in the adult population by the analysis of:

For HS:

- Hidradenitis Suppurativa Clinical Response(HiSCR)
- Change in Dermatology Life Quality Index (DLQI)

For ped PsO:

- Psoriasis Area and Severity Index (PASI) 75, 90, and 100
- Change in involved body surface area

Study design

This was a prospective, non-interventional (observational), single country (Korea), post-marketing surveillance study.

Study population /Sample size

In accordance with the Korean Standard for Re-examination of New Drugs requirement, at least 600 subjects should have been recruited. However, due to reasons stated in the Introduction Section, the minimum number of patients to be enrolled was adjusted after Ministry of Food and Drug Safety (MFDS) approval and 19 subjects (17 HS subjects and 2 ped PsO subjects) were enrolled.

The study population consisted of patients with HS and pediatric patients with chronic and severe plaque PsO.

HS patients had to be at least 18 years old at the start of the investigation, eligible to be treated with adalimumab for HS in accordance with the approved Korean label and provided written informed consent. For the HS patients, the first patient was included into the study on 10 March 2017 and the last contact/last visit of the last patient was on 06 August 2019.

Ped PsO patients had to be children/adolescents, from 4 to 17 years old at the start of the investigation, prescribed adalimumab treatment prior to participating in the study, and provided written informed consent. For the ped PsO patients, the first patient was included into the study on 25 June 2019 and the last contact/last visit of the last patient was on 06 August 2019.

Treatments

Patients were administered adalimumab (Humira) injection as per the package label. Unit dose, frequency and duration of treatment (start/end date) were recorded on the case report form. If the study drug was suspended or terminated during the treatment period, the reason was recorded. The treatment compliance was collected.

Outcomes/endpoints

Presence of adverse event(s), type of adverse event(s), onset date, end date, severity, causality assessment by investigator on the adverse event(s), action taken, and outcome were captured from all subjects over the study period. Safety information was captured for 24 weeks + 70 days (for HS subjects) or 40 weeks + 70 days (for ped PsO subjects). And for early termination subjects, the 1st administration ~ the last administration + 70 days.

Effectiveness assessment

HS: HiSCR and DLQI were assessed at baseline, Week 12, and Week 24.

Ped PsO: PASI score and BSA were to be assessed at baseline, Week 16, and Week 40

Statistical Methods

The study population was classified by safety group and effectiveness group.

Safety group: Subjects who have received at least one administration of adalimumab and have completed a follow up for obtaining safety information.

Effectiveness group: Subjects who have been assessed for safety and for whom effectiveness evaluation parameters has been recorded at baseline and Week 12 (for HS subjects) or Week 16 (for ped PsO subjects).

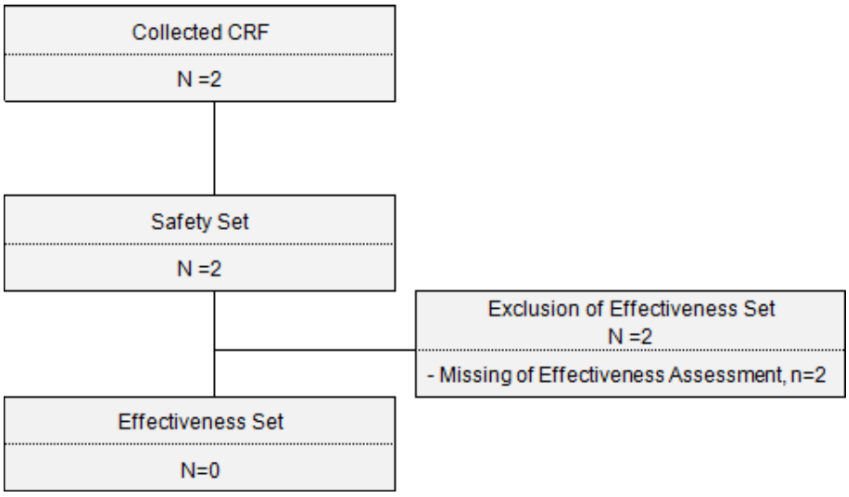
The collected and analyzed patient number were presented using the following items: planned number in a contract with sites, collected number of CRFs, cases for safety evaluation, cases for effectiveness evaluation, drop-out cases, and drop-out reasons.

Results

From the approval of both HS and ped PsO in adalimumab (Humira) on 14 Dec 2015 to Dec 2019, the post-marketing surveillance period, eight investigators participated in eight institutions. The two pediatric patients were recruited from the Ajou University Hospital. A total of 19 patients (17 HS subjects and 2 ped PsO subjects) were enrolled and completed the study to evaluate safety and effectiveness. The study was concluded early due to low recruitment.

Recruitment/ Number analysed

Subject Disposition Flow Chart – Pediatric Chronic Severe Plaque Psoriasis



Baseline data

For the two ped PsO subjects, there were one female and one male. The mean age was 7.00± 1.41 years. Height and weight were 118.50± 2.12 cm and 22.50± 2.12 kg, respectively. One subject was allergic, and one had a family history. None had hepatic disease (current disease) or renal disease (current disease). The disease duration of ped PsO was 4.51± 2.79 years.

Previous Treatment – Pediatric Chronic Severe Plaque Psoriasis

The 2 pediatric subjects had previously received ciclosporine and topical group III steroids. No information on concomitant medication with Humira was provided.

Previous medical histories or current disease

No previous medical histories or current disease were reported in subjects with ped PsO.

Effectiveness results

The effectiveness of adalimumab treatment was evaluated in 17 subjects. Overall, 94.12% (16/17) of subjects showed HiSCR response at Week 12 and 100% (13/13) of subjects showed response at Week 24. The changes in DLQI scores at Weeks 12 and24 from baseline were –8.41± 8.02 and –7.85± 10.15, respectively. The changes in DLQI scores over time were statistically significant.

For ped PsO subjects, the mean (± SD) duration of treatment was 0.11± 0.07 years and the total dosage was 40.00± 28.28 mg. No subjects with ped PsO were included in the effectiveness group. PASI and BSA at Baseline was recorded in both ped PsO patients, but there were no records at Week 16 (the datacut-off date was before Week 16). All subjects (2 subjects) with ped PsO discontinued the study due to other reasons. Last follow up date for both subjects were 2019-08-06.

Safety results

Neither of the two subjects with ped PsO reported adverse events.

Adverse events were developed in 8 of 19 subjects (42.11%, 12 cases) included in the safety set, all in the adult HS population. Among those, adverse drug reactions were reported in 6 subjects (31.58%, 10 cases). Unexpected adverse events occurred in 4 subjects (21.05%, 6 cases), all of which were adverse drug reactions. No serious adverse events were reported. Adverse events in the "Skin and

subcutaneous tissue disorders" system organ class (SOC) were the most frequently reported events (26.32% of subjects [5/19 subjects, 7 cases]). Also, events in the "Infections and infestations" and "General disorders and administration site conditions" SOCs were reported in 10.53% of subjects (2/19 subjects, 2 cases) each. At the preferred term (PT) level, "Hidradenitis" was reported in 15.79% of subjects (3/19 subjects, 4 cases) and "Acne" in 5.26% (1/19 subjects, 2 cases). Among adverse drug reactions, the "Skin and subcutaneous tissue disorders" SOC was reported in 26.32% of subjects (5/19 subjects, 7 cases), "Infections and infestations" in 10.53% (2/19 subjects, 2 cases) and "General disorders and administration site conditions" in 5.26% (1/19 subjects, 1 case).

2.3.3. Discussion on clinical aspects

Study report P16-052_P18-839 presents the results from two non-interventional, prospective, post-marketing surveillance studies combined into one report. The goals of the studies were to evaluate the real-world safety and effectiveness of adalimumab in Korean adult patients with hidradenitis suppurativa (HS) and pediatric chronic severe plaque psoriasis (ped PsO) patients under routine treatment practice. Although the initial goal was to include in total 600 patients, the actual number of study participants had to be reduced in agreement with the authorities, due to low prevalence of the two diseases in Korea and limited prescription of adalimumab in these patient groups. The final combined study report includes 17 adult patients with HS and 2 children with ped PsO.

The two patients with ped PsO are not individually presented, information is provided in statistic terms which is not very meaningful, and hampers evaluation. The posology is not clear, the report states that the pediatric subjects were treated in accordance with the Korean label in which the posology is not known to the assessor; however, it is assumed that this is consistent with the EU-approved label.

The report clearly states that none of the two children experienced an adverse event, and the presented mean duration of treatment was short (approximately 40 days) and the total dosage low (40.00± 28.28 mg). The reason for the early discontinuation of the children is not clearly presented (“other”), but it may be concluded that it was due to the early termination of the study. The date of the first child´s first visit was 25 June 2019 and last child´s last visit was 06 August 2019 which is identical with the indicated date for end of data collection. The MAH states that no subjects with ped PsO were included in the effectiveness group as the study was ended before any of them had reached week 16. It is not clear for how long the children were followed for safety, but it is assumed that no more data was collected after 06 August 2019.

Due to the incompleteness of the provided information, no firm evaluation of the results is possible. However, given what is indeed known, two children, followed at the longest for 43 days and during this time not showing any AEs, it is not considered meaningful to pursue this issue further.

Safety profile is consistent with the known safety profile of Humira for the treated patient population.

3. Overall conclusion and recommendation

Only two pediatric patients were enrolled in this study, which limits interpretation of the data for a pediatric population. No new safety signals have emerged. The benefit-risk of adalimumab is unchanged.

☒ Fulfilled:

No regulatory action required.