22 May 2025
EMADOC-1700519818-1965497
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Humira

Adalimumab

Procedure no: EMA/PAM/0000257452/P46/01207/1

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2025. Reproduction is authorised provided the source is acknowledged.

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2025	25 April 2025
☐	CHMP comments	12 May 2025	n/a
☐	Updated CHMP Rapporteur AR	15 May 2025	n/a
☒	CHMP outcome	22 May 2025	22 May 2025

Table of contents

1. Introduction

On 5 March 2025, the MAH submitted a completed paediatric study for Humira, 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 submitted a final study report for: Study P20-379 An open-label, multi-center, post-marketing, observational study to assess the effectiveness and safety of adalimumab (Humira) in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA) in China.

2.2. Information on the pharmaceutical formulation used in the study

Adalimumab (Humira) was administered according to the Chinese product label, which was not provided.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for a multicenter, single-arm, prospective, observational study Study P20-379 to assess the effectiveness and safety of adalimumab in pJIA patients in China, under Article 46.

According to the MAH, Adalimumab, a fully human monoclonal antibody against tumor necrosis factor, has demonstrated efficacy and safety to treat pJIA patients in Japan, United States, and Europe. Moreover, a multi-national, long-term, real-world registry study (STRIVE registry study) conducted across 16 countries also supports the safety of adalimumab in children with pJIA. Adalimumab was submitted for pJIA indication with local trial waiver and launched in China at the end of 2019. However, there is limited evidence on the effectiveness and safety of this treatment in Chinese patients with pJIA, through either clinical trials or real-world studies.

The results from the current study of adalimumab in Chinese pJIA patients was required by the Center for Drug Evaluation (the Regulatory Authority of China) to collect data in the local population and evaluate effectiveness and safety of adalimumab in real-world clinical practice as a post-authorization commitment.

2.3.2. Clinical study

Study P20-379 – An open-label, multi-center, post-marketing, observational study to assess the effectiveness and safety of adalimumab (Humira) in pediatric patients with polyarticular juvenile idiopathic arthritis (pJIA) in China

Study Design

Study P20-379 was a multicenter, single-arm, prospective, observational study to assess the effectiveness and safety of adalimumab in pJIA patients in China. Eligible pJIA patients were recruited from the clinical settings of pediatric rheumatologists or specialists participating in the study. These

patients were administered adalimumab according to the approved local prescribing information of adalimumab at the judgment of investigators.

The patients/investigators followed routine clinical practice at each site. The study visits were defined as baseline (Visit [V]) 1), Week 4 (V2), Week 8 (V3), Week 16 (V4), Week 24 (V5), Week 36 (V6), and Week 52 (V7). All enrolled patients were scheduled to receive adalimumab at each of the aforementioned visits.

At any time, patients and physicians could choose to interrupt adalimumab therapy for any reason. If treatment was interrupted, patients continued to be monitored during and after this interruption for safety (serious adverse events [SAEs], pregnancy) and effectiveness. Patients who missed 2 consecutive adalimumab injections or a total of ≥ 3 non-consecutive adalimumab injections within the first 16 weeks of treatment, and patients who missed 3 consecutive or a total of ≥ 6 non-consecutive adalimumab injections in the last 36 weeks of treatment were discontinued from the study, with the reason of discontinuation documented in the appropriate electronic case report form. If the reason for treatment discontinuation was due to an adverse event (AE) or SAE, it was reported to AbbVie within 24 hours of physician's awareness.

All patients had a follow up of approximately 70 days (5 half-lives) after the last administration of study drug to obtain information on any new or ongoing AEs. For adolescent girls of childbearing potential, pregnancy follow up was also done through 150 days following the last dose of adalimumab taken during the study.

The following variables were collected for assessment of effectiveness of adalimumab:

- Pediatric American College of Rheumatology (Ped ACR), the core set of variables
    a) Physician's global assessment of patient's disease activity (PhGA) by visual analog scale (VAS) (100 mm VAS, 0 = very good and 100 = very bad)
    b) Parent's or child's global assessment of patient's disease activity (Pa/ChGA) by VAS (100 mm VAS, 0 = very well and 100 = very bad)
    c) Number of active joints (joints with swelling not due to deformity or joints with limitation of passive motion [LOM] and with pain and/or tenderness)
    d) Number of joints with LOM
    e) Disability Index of Childhood Health Assessment Questionnaire (CHAQ- DI)
    f) C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) if collected and available only when part of the physician's site routine care.
- Juvenile Arthritis Disease Activity Score (JADAS/clinical JADAS (cJADAS), the core set of variables
    a) Physician's global assessment of patient's disease activity measured by 100 mm VAS
    b) Parent's or child's global assessment of patient's disease activity measured by 100 mm VAS
    c) Number of active joints (joints with swelling not due to deformity or joints with LOM and with pain on passive motion (POM), tenderness or both)
    d) Normalized ESR or CRP if collected and available only when part of the physician's site routine care.

- Change from baseline in dosage of methotrexate/NSAIDs/corticosteroid
- AEs and special safety situations were collected during the observational period. Safety measures included counts, percentages, patient-year of AEs, SAEs, deaths, and AEs leading to discontinuation from the study; and counts and percentages of pre-specified AEs of special interest (including malignant conditions, opportunistic infections, cases of tuberculosis, demyelinating diseases, or lupus like reactions.
- Physical examination data (including height and body weight) and vital signs Thes start of data collection was on 10 November 2022 and ended on 8 September 2024.

Study Population

Study P20-379 enrolled eligible male or female patients 2 to 17 years of age with a body weight of ≥ 10 kg who met the study inclusion and exclusion criteria and were diagnosed with pJIA by the treating physician. Patients who received any biological DMARDs (bDMARDs) within 6 months prior to screening or who were on concomitant use of any bDMARD were not enrolled.

Baseline Demographics

In Study P20-379, all 20 screened patients were eligible and enrolled into the study from 2 sites. Most patients (80%) completed the Week 52 visit, and all were included in the Full Analysis Set and the Safety Analysis Set.

The mean (standard deviation [SD]) age of the patients was 9.2 (4.42) years. There were more females (n = 13, 65.0%) than males (n = 7, 35.0%). All patients (n = 20, 100.0%) belonged to the Han ethnic group and the mean (SD) body mass index was 16.589 (2.6452) kg/m^2.

pJIA Diagnosis and Treatment History

Overall, none of the patients with available data (1 patient did not provide medical history) had a history of inflammatory bowel disease (n = 19), enthesitis (n = 19), uveitis (n = 19), or tuberculosis (exposure/risk factors) (n = 20).

All 20 patients received medications for pJIA prior or during the study. The most frequently received medications (≥ 70.0%) were folic acid (n = 19, 95.0%), methotrexate (n = 19, 95.0%), and naproxen (n = 14, 70.0%).

Overall, 11 patients (55.0%) received other prior medications.

Comorbidities

The majority of patients (n = 17, 85.0%) had a past or current medical history (except pJIA). The most frequent comorbidity system organ class (SOC) was infections and infestations (n = 8, 40.0%). In this SOC, the most common preferred terms (PTs) were Epstein-Barr virus infection, upper respiratory tract infection, mycoplasma infection, and streptococcal infection (n = 2, 10.0% each).

Other frequent comorbidities (≥ 20.0%) by SOC (PT) included metabolism and nutrition disorders in 7 patients (35.0%) (vitamin D deficiency: n = 6, 30.0%), and general disorders and administration site conditions in 4 patients (20.0%) (pyrexia: n = 4, 20.0%).

Over the study period, all 20 patients received at least 1 dose of adalimumab, with 10 patients (50.0%) receiving adalimumab as a 40 mg/0.4 mL pre-filled syringe and 10 patients (50.0%) receiving it as a 20 mg/0.2 mL pre-filled syringe; 1 patient (5.0%) received adalimumab as a 40 mg/0.4 mL pre-filled pen-injector. Adalimumab dose adjustment occurred for 1 patient (5.0%) due to weight > 30 kg. Median (Q1 to Q3, range) duration of exposure to adalimumab was 353.0 days (350.5 to 365.0, 16

to 377), with average interval between doses as median (Q1 to Q3, range) 16.020 (15.060 to 17.380, 14.96 to 19.58) days.

Efficacy Results

Among the 20 eligible patients, 80% completed the Week 52 visit. At Week 16, most of the patients (80% [95% confidence interval (CI): 62.5% to 97.5%]) (n = 16/20) achieved Ped ACR 30. At Week 52, 50% (95% CI: 28.1% to 71.9%) of the patients achieved Ped ACR 50. There were reductions from baseline in the average scores of PhGA, Pa/ChGA, CHAQ-DI, and JADAS/cJADAS, that decreased by 71.9%, 72.4%, 86.5%, 64.7%, and 68.7% at Week 52, respectively. The mean numbers of active joints and joints with LOM and POM decreased during the study (-4.5, -3.4, and -5.3 at Week 52). The CRP level and ESR decreased, with limited numbers of patients with available test results. Patient weight and height increased during the study period.

Safety Results

All 20 patients experienced treatment-emergent AEs (TEAEs) (exposure-adjusted incidence rate [EAIR]: 10.4 [95% CI: 6.4, 16.1]) with 75.0% of patients experiencing infections and infestations and none leading to study termination or death.

Causality of TEAEs

Overall, 7 patients (35.0%) experienced TEAEs that were deemed to be causally related to adalimumab by the investigator. Three patients (15.0%) experienced TEAEs in the SOC respiratory, thoracic, and mediastinal disorders, whose PT included oropharyngeal pain, pneumonia mycoplasmal, and pneumonitis (n = 1, 5.0% [each]). Two patients (10.0%) experienced TEAEs in the SOC investigations, whose PT included blood bilirubin increased, transaminases increased, and blood cholesterol abnormal (n = 1, 5.0% [each]). Two patients (10.0%) experienced TEAEs in the SOC skin and subcutaneous tissue disorders, whose PT included rash and dermatitis allergic (n = 1, 5.0% [each]).

One patient (5.0%) experienced a TEAE in the SOC metabolism and nutrition disorders, whose PT was dyslipidemia, and 1 patient (5.0%) experienced a TEAE in the SOC hepatobiliary disorders, whose PT was hepatic function abnormal.

Treatment-emergent SAEs (TESAEs) and Severity of TESAEs

A total of 4 patients experienced TESAEs (20.0%; 95% CI: 2.5%, 37.5%; EAIR: 0.2 [95% CI for EAIR: 0.1, 0.6]), with 1 patient (5.0%) experiencing 1 event (mycoplasmal pneumonia) related to adalimumab and 3 patients (15%) experiencing TESAEs of severe intensity.

Three patients experienced TESAEs in the SOC infections and infestations (15.0%; 95% CI: 0%, 30.6%; EAIR: 0.2 [95% CI for EAIR: 0.0, 0.5]), whose PTs included pneumonia, mycoplasmal pneumonia, and gastroenteritis (n = 1, 5.0% [each]).

Patient-level Summary of TESAEs:

- Patient 1: Experienced gastroenteritis (not drug-related, severe intensity) and mycoplasmal pneumonia (drug-related, severe intensity), treated with drug therapy and recovered.
- Patient 2: Documented with intracranial mass (not drug-related, severe intensity) and 2 astrocytoma events (not drug-related, severe intensity), treated with surgical therapy and resulting in persisting or significant disability.
- Patient 3: Experienced mycoplasmal pneumonia (not drug-related, moderate intensity). Admitted to the local hospital, received drug therapy for the event, and recovered.

- Patient 4: Experienced pneumonia (not drug-related, severe intensity), treated with drug therapy and recovered.

AEs of Special Interest

There was 1 patient who experienced an AE of special interest (5.0%, Epstein-Barr virus infection) which was non-serious, unrelated to adalimumab, and moderate in intensity. A total of 3 (15.0%) patients experienced TEAEs leading to adalimumab discontinuation.

Concomitant Medications

All 20 patients used other concomitant medications during the study period. The most frequent (≥ 20.0%) medications were azithromycin (n = 8, 40.0%), cetirizine hydrochloride (n = 4, 20.0%), xylometazoline hydrochloride (n = 4, 20.0%), and tuberculin purified protein derivative PPD (n = 4, 20.0%).

Conclusions

The current prospective study described the clinical outcomes of 20 eligible pJIA patients from 2 sites in China treated with adalimumab through up to 1 year of treatment. The effectiveness and safety of adalimumab from the current study were in line with previous studies and literature. No new safety trends or concerns were identified.

2.3.3. Discussion on clinical aspects

CHMP comments:

The performed single-arm, prospective, observational multicenter study in patients with pJIA was required by the Center for Drug Evaluation (the Regulatory Authority of China) to collect data in the local population in China.

Humira was dosed according to the Chinese label in paediatric patients with pJIA. All 20 patients received medications for pJIA prior or during the study. The most frequently received medications were folic acid (n = 19), methotrexate (n = 19), and naproxen (n = 14).

Primary effectiveness outcome was the percent of patients with Ped ACR 30 response at week 16. Descriptive statistics for effectiveness variables were presented. All patients had a follow up of approximately 70 days (5 half-lives) after the last administration of study drug to obtain information on any new or ongoing AEs.

Results

A total of 20 patients were enrolled in this study from 2 sites. The mean (SD) age of the patients was 9.2 (4.42) years. All patients belonged to the Han ethnic group. All patients were included in the Full Analysis Set and the Safety Analysis Set. The sample size of the study was small and no hypothesis testing was conducted.

Among the 20 eligible patients, 18 (90.0%) completed the Week 16 visit and 80% completed the Week 52 visit. Of the 4 patients who did not complete week 52 treatment, 3 patients discontinued adalimumab, while for 1 patient, the family requested to withdraw from the study due to doubt about the diagnosis of JIA. No patient terminated treatment due to AEs.

At Week 16, 16 of the patients (80% [95% CI: 62.5% to 97.5%]) achieved Ped ACR 30. At Week 52, 50% (95% CI: 28.1% to 71.9%) of the patients achieved Ped ACR 50.

All 20 patients experienced TEAEs, of which 7 patients (35.0%) experienced TEAEs that were deemed to be causally related to adalimumab by the investigator (3 patients in the SOC respiratory, thoracic, and mediastinal disorders, 2 patients in the SOC investigations, and 2 patients in the SOC skin and subcutaneous tissue disorders).

The study had 75.0% of patients experiencing infections and infestations, or Exposure-adjusted Incidence Rate 8.46 Person-years of exposure. This seems to be a rather high number, as, according to the EU SmPC, in the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the Humira treated patients. However, the small sample size hampers the conclusions that can be drawn from this data.

The results of this small observational study were overall consistent with the currently documented profile of the product, as described in the label. The benefit-risk of adalimumab is unchanged and no update to the Summary of Product Characteristics has been proposed because of these data. This is supported by the CHMP.

3. CHMP overall conclusion and recommendation

No new findings of clinical efficacy and safety were observed in the performed post-marketing observational study of 20 subjects <18 years old with pJIA in China. Descriptive data on efficacy at 16 weeks and adverse events for 52 weeks treatment in this population has been presented. The submission of this data under Article 46 is acknowledged and appreciated. No update to the Product Information is required based on the reported study. The benefit-risk balance for Humira remains unchanged and positive.

☒ **Fulfilled:**

No regulatory action required.