



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

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/P46/107

Note

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



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1. Introduction

The MAH stated that the purpose of this submission 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 study P11-973:

Long-term Documentation of the Safety, Effectiveness, and Effects on Quality of Life and Work Productivity in Patients with Rheumatoid Arthritis during HUMIRA® (Adalimumab) Therapy in Routine Clinical Practice (AGIL) and Supplementary Documentation to Record Cardiovascular and Metabolic Risk Factors (AGIL-CV)

Approximately, 7200 patients were enrolled into this study. **A total of 3 paediatric patients were included in the study.** According to the MAH, the data submitted do not influence the benefit-risk balance and therefore do not require taking further regulatory action on the marketing authorisation.

The submission was dated 27 April 2018. The submission included study report/ study results final for P11-973 and a short critical expert overview.

2. Scientific discussion

2.1. Information on the development program

The primary goal of study P11-973 was to document the impact of adalimumab treatment on work-related and therapeutic outcomes during a 5-year non-interventional study of adult German patients with RA.

2.2. Information on the pharmaceutical formulation used in the studies

Adalimumab (HUMIRA®): 40 mg subcutan (s.c.) every other week

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for: P11-973.

2.3.2. Clinical study P11-973:

Description

The study P11-973 was a prospective, multicenter, observational, non-interventional study (Clinicaltrials.gov trial registration NCT01076205, also referred to as GER0805 and AGIL).

Methods

Objectives

The primary objectives of this study were, according to the study report, to determine the impact of adalimumab on employment related outcomes and obtain long-term documentation of the effectiveness and safety of adalimumab treatment as used in daily clinical practice in Germany to treat

adult patients with RA over a time interval of 60 months. An amendment to the study allowed the collection of additional data concerning CV risk factors, including laboratory blood chemistry variables

Study design

Data for the study were collected on a Case Report Form (CRF). The observation period for each individual patient began with the administration of the initial dose of adalimumab (Month 0) and lasted for a maximum of 60 months. Therapy follow-ups were recommended at Month 3, Month 6, Month 12, and then yearly. Patients for the AGIL study were enrolled by clinicians at 326 different clinical sites throughout Germany. The first patient was seen on 12 January 2009 and the last visit occurred on 14 September 2017.

Study population /Sample size

The study population for AGIL was a community non-probability (non-random) sample of patients with RA who resided in Germany and was preparing to initiate adalimumab therapy at the decision of the clinician. German regulations state that all patients are eligible for non-interventional studies as long as they are able to give consent and understand the language of the patient questionnaires; there are no exclusions. Doctors were instructed to enrol patients with moderate to severely active RA who had failed other anti-rheumatic drugs and patients with severe, active and progressive RA regardless of previous treatment; inclusion and exclusion criteria adhered with the European Medical Agencies Summary of Product Characteristics. **Doctors were also instructed to limit enrolment to adult patients (≥ 18 years of age) with RA. However, there was no means of preventing doctors from enrolling patients with other indications or patients younger than 18 years of age.** All patients were required to provide informed consent.

Treatments

Adalimumab (HUMIRA®): 40 mg subcutan (s.c.) every other week

Outcomes/endpoints

Key effectiveness variables included self-reported missed work days, WAI, WPAI, joint counts, laboratory inflammatory markers (CRP and ESR), DAS28, HAQ-DI, and EQ-5D, EQ-VAS. For safety evaluations, patients were asked about AEs at each visit; information on AEs was collected on an AE reporting form. Collected AEs were listed in the study report by system organ class (SOC) and preferred term (PT). Clinicians were also asked to list possible causality with treatment.

Results

Recruitment/ Number analysed and Baseline data

Four patient cohorts were evaluated in this study: employed patients (patients who were employed full- or part-time at baseline) (N = 3285), full analysis set (FAS; patients with sufficient data for effectiveness analyses) (N = 4466), safety set (all enrolled patients who received at least one dose of adalimumab) (N = 7229), and the AGIL-CV substudy cohort (patients enrolled in AGIL-CV) (N = 260). At Month 60, patient cohorts contained fewer than 20% of the baseline population; 1210 patients (16.7%) were ongoing in the safety set and 726 (16.3%) in the FAS. Approximately 40% of patients were lost to follow-up for unknown reasons. The remainder of the patients (approximately 60%) withdrew from the study. Among patients who withdrew, lack of effectiveness was the most frequent reasons for study withdrawal (22.5% of patients in the FAS and 19.7% of patients in the safety set).

Adverse events accounted for fewer than 5% of study discontinuations (4.2% in the FAS and 3.8% in the safety set).

Three patients in the safety set (0.04%) were < 18 years of age. One of the pediatric patients was included in the FAS; the other two were excluded from the FAS due to lack of baseline DAS28 data (n = 1) and DAS28 < 3.2 at baseline (n = 1). There were no pediatric patients in the employed patient cohort or AGIL-CV. The three pediatric patients were included as a deviation from the study protocol. Their demographic information and study disposition data are summarized in the table below.

Table 1: Demographic information and study disposition data for pediatric patients included in P11-973

Demographic and Study Disposition Data for Patients < 18 Years of Age at Treatment Initiation in AGIL				
Patient #	Age at Study Entry	Sex	Last Visit	Reason for Study Discontinuation
1	15	Male	Month 24	Loss of effectiveness
2	16	Male	Month 24	Lost to follow-up
3	16	Female	Month 6	Lost to follow-up

Efficacy results

According to the applicant, the findings of this observational study overall support the conclusion that long-term treatment with adalimumab has a favorable impact on employment-related outcomes in adult patients with RA.

Regarding the three pediatric patients, the applicant states that both of the two patients with baseline DAS28 data (Patients 1 and 3 in the Table above) showed improvements in DAS28 during therapy. All three patients showed improvements (decreases) in pain and patient global assessment (PGA) scores between Baseline and Month 3. For Patient 3, pain and PGA increased from Month 3 to Month 6, but remained below baseline. For Patients 1 and 2, pain and PGA also increased at visits after Month 3 and in some cases exceeded baseline scores.

Safety results

The duration of adalimumab exposure in the safety set (N = 7229) was 2.06 ± 1.77 years. In the safety set, 32.1% of patients experienced an AE during the 60-month study and 12.9% experienced a serious AE (SAE). The most common non-serious AE by SOC was infections and infestations (14.8%). Twenty-three deaths occurred during the study, a review of AEs and deaths did, according to the applicant, not reveal any patterns of concern.

Regarding the three pediatric patients, Patient 3 (see table above) did not report any adverse events. Patient 1 was diagnosed with iritis approximately 18 months after initiation of adalimumab, and this disorder lasted 23 days. Causality with respect to adalimumab was not given; infection was listed under "other causality." Patient 2 underwent arthroscopy of the right knee approximately 8 months after initiation of adalimumab. Assessment of adalimumab causality was not provided. Neither AE was considered serious.

2.3.3. Discussion on clinical aspects

The applicant concludes that the small number of pediatric patients enrolled in study P11-973 limits interpretation, but that adalimumab showed some signs of effectiveness in adolescents with RA and did not result in any new safety signals.

The Rapporteur considers that the data that can be extracted from the three paediatric subjects (adolescents aged 15-16 years) that were accidentally included in study P11-973 are highly limited but it is agreed with the applicant that no data that changes the B/R balance of the product or warrants changes to the PI or RMP has been retrieved.

3. Rapporteur's overall conclusion and recommendation

The data that can be extracted from the three paediatric subjects (adolescents aged 15-16 years) that were erroneously included in the observational, non-interventional study P11-973 are very limited. However, it is agreed with the applicant that no data that changes the B/R balance of the product or warrants changes to the PI or RMP has been retrieved. No further actions are required.

Requirements are considered

Fulfilled:

No regulatory action required.

4. Additional clarification requested

None