EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 January 2019
EMA/132518/2019
Human Medicines Evaluation Division

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/P46/113

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

1. Introduction

On 12 November 2018, the MAH submitted data available from patients less than 18 years of age recruited to the study P15-345 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 stated that study P15-345 An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases (VITALITY) is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Not presented, however, Humira is developed for subcutaneous administration, prefilled syringe and autoinjector.

2.3. Clinical aspects

2.3.1. Introduction

Adalimumab is a recombinant human immunoglobulin monoclonal antibody that is registered for use in multiple immune-mediated inflammatory diseases (IMIDs) in New Zealand across the therapeutic areas of rheumatology, gastroenterology and dermatology (rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis, Crohn's disease (CD) in adults and children, ulcerative colitis, psoriasis (PsO) in adults and children, hidradenitis suppurativa in adults and adolescents, and uveitis in adults and children).

The objective of this study was to assess the effect of adalimumab on health and disability outcomes in adult patients with the IMIDs of RA, CD and PsO, treated in routine clinical practice in New Zealand.

The MAH submitted a final report for:

- Study P15-345: An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases (VITALITY)

2.3.2. Clinical study

Clinical study number and title

Study P15-345: An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases (VITALITY).

Description

Methods

Objective(s)

Assess the effect of adalimumab (Humira) on health and disability outcomes in New Zealand patients with the IMIDs of RA, CD and PsO.

Study design

Study P15-345 was a 6-month prospective, observational, multicentre study designed to investigate the effectiveness of adalimumab on health and disability outcomes in adult patients with RA, CD and PsO, treated in routine clinical practice in New Zealand. The first participant was enrolled in the study in July 2015, with data collection ending in February 2018.

Eligible patients were aged 18 – 75 years, inclusive, that had been diagnosed with CD, RA, or PsO. Before study enrolment, the participant had decided with their physician to commence treatment with adalimumab in accordance with the New Zealand datasheet (prescribing information) and routine medical practice. This decision was clearly separated and independent of the decision to include the participant in the study.

All procedures in the study were conducted in accordance with routine medical practice. Participants were required to attend a minimum of two clinic visits to allow physician-completed assessments to be performed: one at baseline and one within 3 to 6 months of adalimumab initiation, as per standard of care.

Prior to the first dose of adalimumab, participants completed a series of self-assessment questionnaires. Questionnaires were re-administered at 2, 4, and 6 months. The following self-assessment questionnaires were completed by patients:

- World Health Organisation Disability Assessment Schedule (WHODAS) 2.0 12-item version
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) v2.0
- Kessler Psychological Distress Scale (K10)
- Flourishing Scale
- Subjective Vitality Scale

Disease-specific questionnaires. RA patients = Health Assessment Questionnaire–Disability Index (HAQ-DI); CD patients = Short Inflammatory Bowel Disease Questionnaire (SIBDQ); PsO patients = Dermatology Life Quality Index (DLQI).

Study population /Sample size

A total of 164 patients accepted to participate in the study, 70 of these had CD, 37 had PsO and 57 had RA.

Treatments

In accordance with the New Zealand datasheet (prescribing information) and routine medical practice

Outcomes/endpoints

The effect of adalimumab on health and disability outcomes in these patients was assessed by the primary outcome measure:

- Change in WHODAS 2.0 score at 6 months after the initiation of adalimumab, across all indications.

The effect of adalimumab was also assessed by the secondary outcome measures:

- Change in total WHODAS score 2 and 4 months after the initiation of adalimumab across all indications
- Change in total WHODAS score 6 months after the initiation of adalimumab in each indication
- Changes in WPAI:GH V2.0 Scores, K10 scale, Flourishing Scale, Subject Vitality Scale at 6 months after the initiation of adalimumab, across all indications
- Change in disease-specific scores (HAQ-DI, SIBDQ, DLQI) at 6 months after the initiation of adalimumab, in each indication

Subjects were requested to inform the investigators of the occurrence of any adverse events (AEs) either at the study visit or over the phone. All AEs were captured in the source data and recorded in the CRF.

Results

Recruitment/ Number analysed

Of the 168 recruited patients, 4 patients withdrew or were withdrawn prior to baseline measures being completed (i.e., 164 patients had baseline WHODAS data recorded), and a further 50 patients withdrew or were withdrawn prior to the 6-month WHODAS data being recorded (i.e., 114 patients had 6-month WHODAS data recorded).

Efficacy results

Primary outcome measure: Following 6 months' treatment with adalimumab, an improvement in patients' health and disability outcomes was observed. A reduction, considered as significant, was observed in mean total WHODAS 2.0 scores compared with baseline for all indications (RA, CD and PsO).

Secondary outcome measures: Improvements in WHODAS scores, considered as significant, were observed from baseline to 2 months and from baseline to 4 months.

The changes in total WHODAS scores 6 months after the initiation of adalimumab were considered statistically significant for each indication.

Patients (all indications combined) achieved improvements that were judged to be statistically significant across the four measures of the WPAI:GH at 6 months post treatment compared to baseline, indicating that adalimumab decreased the disease impact on their ability to work and perform regular activities.

Reductions in mean K10 scores in patients (all indications combined) indicate according to the MAH that distress levels (anxiety and depressive symptoms) decreased following treatment with adalimumab after 6 months.

An improvement that was considered statistically significant was observed for the Flourishing Scale at 6 months post treatment compared to baseline, demonstrating an improvement in human functioning (positive relationships, feelings of competence, having meaning and purpose in life) across all indications combined.

Improvements from baseline for the Subjective Vitality Scale (state of feeling alive and alert to having energy available to the self) were observed following 6 months of treatment with adalimumab (all indications combined).

Disease-specific questionnaires: There were improvements, considered as significant, following 6 months of treatment with adalimumab in all of the disease-specific questionnaires. Questionnaires included: the HAQ-DI (measures functional status in patients with RA); the SIBDQ (quality of life [QoL] for CD); and the DLQI (QoL for PsO).

Safety results

The AE profile observed in this study was, according to the MAH, consistent with other reports of adalimumab in patients with RA, CD and PsO. A total of 130 AEs were reported by 65 individuals (40% of the study population), and 19 serious adverse events (SAE) were reported by 18 individuals (11% of the study population) during the study period. The majority of AEs were mild in intensity (63 /130 events) with 54/130 events classified as moderate and 13/130 events classified as severe in intensity.

One SAE was considered related to adalimumab. A patient experienced pneumonitis, 48 days from the start of treatment and was withdrawn from the study. The event was considered severe in intensity and required hospitalisation/prolongation of hospitalisation.

One patient died (cause of death unknown) during the study period. The investigator considered this event not related to adalimumab. No other information on this patient is available.

Paediatric Data

Of the 164 patients, one (1) paediatric patient < 18 years of age entered the study in 2015. The patient was aged 16.8 years, with a diagnosis of Crohn's disease. Crohn's Disease Activity Index (CDAI) score was 381. A decision to commence treatment with adalimumab was made by the patient and the physician in accordance with routine medical practice and with the approved adalimumab New Zealand datasheet.

Treatment with adalimumab commenced in 2015 as 160/80 mg induction dose and then 40 mg every other week as a maintenance dose, in line with the recommended dosing regimen in the New Zealand datasheet (prescribing information).

After 6 months of treatment with adalimumab, the CDAI score had reduced to 108.

The patient completed questionnaires at a Baseline and Month 6, but not at Months 2 and 4.

No AEs were reported in this patient.

MAH's discussion

Results from this observational study demonstrate the effectiveness of adalimumab in adult patients with severe inflammatory disease in routine clinical practice in New Zealand. Only one paediatric patient was enrolled, which limits interpretation of the data for a paediatric population. The benefit-risk of adalimumab is unchanged and no update to the Summary of Product Characteristics is proposed as a result of these data.

2.3.3. Discussion on clinical aspects

The MAH has provided results from a post marketing observational study (P15-345), designed as a 6-month single-arm, multi-center, open labelled prospective cohort study. It was conducted in New Zealand, in order to assess the effectiveness of adalimumab on health and disability outcomes in adult patients with RA, CD or PsO, treated in routine clinical practice. For this purpose self-assessment questionnaires were distributed at baseline, and at 2 4 and 6 months.

The primary outcome measure, change in World Health Organisation disability Assessment Schedule (WHODAS) 2.0 core after 6 months, showed improvements, considered as significant, in all 3 indications. Improvements were also seen in WPAI:GH (working productivity and regular activities), K10 scores (addressing anxiety and depressive symptoms) Flourishing Scale (addressing "human functioning") and Subjective vitality scale. Also disease-specific questionnaires HAQ-DI (RA), SIBDQ (quality of life, CD) and DLQI (QoL for PSO) showed improvements.

The AE profile was consistent with the known safety profile of adalimumab in the studied indications.

The above results have not been reviewed in detail, since the scope for this P46 is safety in paediatric subjects.

The one paediatric patient included in the study was a aged 16.8 years, with CD. The patient received 160/80 mg induction dose followed by 40mg eow. The patient's CDAI score decreased from 381 to 108 in 6 months, indicating treatment effect. The subject completed questionnaires at Baseline and Month 6, however results from these were not provided. This is not further pursued, since the focus of this assessment is on safety. No AEs were reported for the paediatric patient.

3. CHMP overall conclusion and recommendation

Overall conclusion

No data that changes the B/R balance of the product or warrants changes to the PI or RMP regarding the use in children has been identified. No further actions are required.

Recommendation

☒ **Fulfilled:**

No regulatory action required.