13 October 2016
EMA/621044/2016
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/P46/095

Note

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

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1. Introduction

Humira (adalimumab) 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.

On 25 July 2016, the MAH submitted a completed study (P10-559) for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The submission pertains to data available from patients less than 18 years of age recruited to a non-interventional, open-label, post-marketing observational study (PMOS) in which Humira was prescribed for rheumatoid arthritis (RA) in routine medical practice in Japanese patients, titled:

"Humira 40mg/0.8ml for Subcutaneous Injection-Drug Use Investigation (All Patient Investigation) for Rheumatoid Arthritis"

In total, 13 subjects below 18 years of age were enrolled in this PMOS.

The study was submitted in synoptic format since the full study report is only available in the Japanese language.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study P10-559 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Humira as approved in Japan was used in this study.

2.3. Clinical aspects

2.3.1. Study P10-559

Humira 40mg/0.8ml for Subcutaneous Injection-Drug Use Investigation (All Patient Investigation) for Rheumatoid Arthritis

Description

Post-marketing observational study

Methods

Objective(s)

To clarify the following:

1) Unknown adverse reactions (especially clinically significant adverse reactions)

2) Incidence and conditions of occurrence of adverse reactions in the clinical setting

3) Factors that may affect the safety and effectiveness of Humira in Japanese patients for whom Humira was prescribed for Rheumatoid Arthritis (RA) in routine medical practice.

Study design

This was a non-interventional, open-label, all-case, central registration method, post marketing observational study in which Humira was prescribed for rheumatoid arthritis in the routine medical practice.

Study population /Sample size

As a result of discussion with Pharmaceuticals and Medical Devices Agency (PMDA), the MAH committed to report with a minimum of 3000 patients having completed the study at which time the results were submitted for PMDA review. A total of 7740 patients have been recruited.

Treatments

Marketed product of Humira, 40mg/0.8ml for subcutaneous injection; the duration of treatment (for data collection) was 24 weeks.

Outcomes/endpoints

Primary Outcome Measures:

- Total number of patients with adverse events (Time Frame: at Week 24)
- Improvement rating on the basis of Disease Activity Score 28 (Time Frame: at Weeks 4, 12, 24)

Secondary Outcome Measures:

- Effectiveness evaluation by the investigator (Time Frame: at Week 24)

Clinical effectiveness as primary outcome measure (improvement rating based on Disease Activity Score 28 [DAS28]) was assessed using EULAR (European League Against Rheumatism) response criteria. Patients were classified as having good, moderate or non-response based on both the present DAS28 and DAS28 improvement (defined as the change of DAS from baseline DAS). For instance, when present DAS28 is <3.2 and the DAS28 improvement is >1.2, it is considered as Good response. Scores of good and moderate response were considered to have therapeutic response (Effective rate).

DAS28 improvement / present DAS28	> 1.2	0.6 - 1.2	< 0.6
<3.2	Good response	Moderate response	No response
3.2−5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Overall improvement rating (the effectiveness evaluation done by each physician) was defined as secondary outcome measure. The level of overall improvement rating was categorized into “Markedly improved”, “Improved”, “Not changed” or "Not assessable", comparing clinical conditions at Week 24 or at discontinuation with baseline conditions. Investigators could describe the reasons for the rating.

Statistical Methods

Data were analysed using descriptive methods.

DAS missing data were processed using the last observation carried forward method, except for baseline values.

Results

Recruitment / Number analysed

In total, 7740 patients were treated with Humira.

The total number of discontinuing patients was 2250 (2250/7740, 29.1%).

Lack of efficacy (849/7740, 11.0%) and AEs (767/7740, 9.9%) were the most common reasons for discontinuation (see Table 1 below).

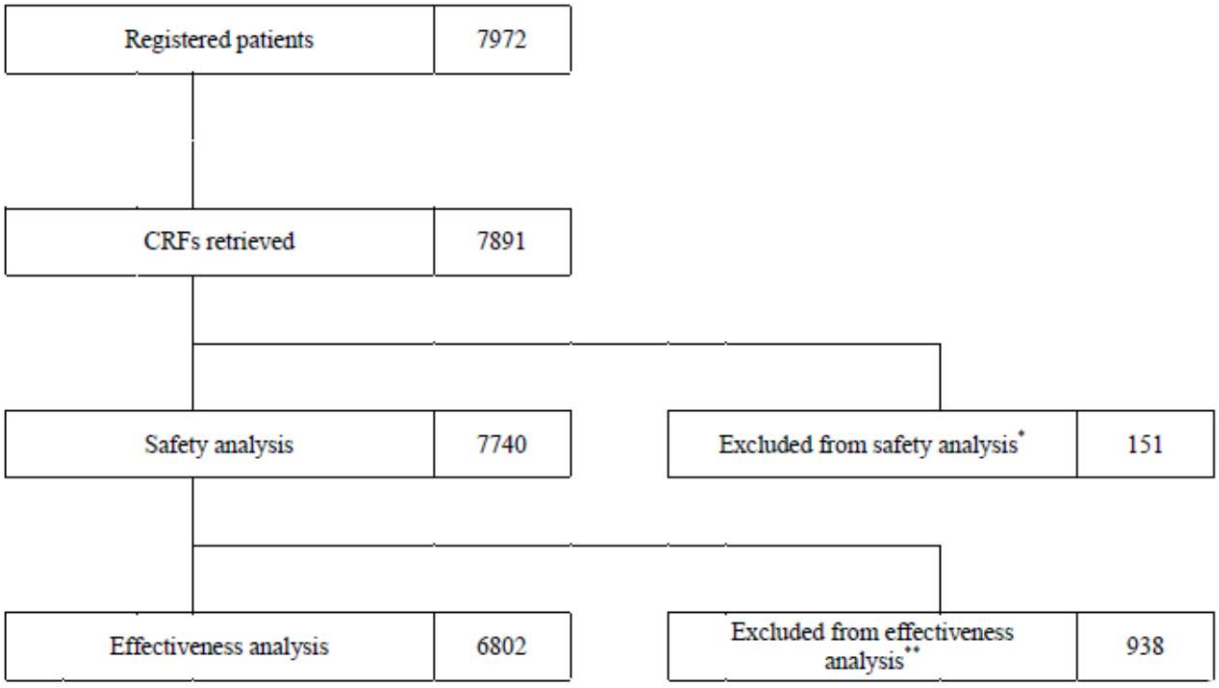
Table 1: Reasons for discontinuation

Reason	Patients (%)
N	7740
Total number of discontinuation patients	2250 (29.1)
Adverse event	767 (9.9)
Lack of efficacy	849 (11.0)
Patient's refusal to receive Humira	274 (3.5)
Lost to follow up	241 (3.1)
Others	76 (1.0)
Unknown	43 (0.6)

The PMDA had required a minimum of 3000 patients to complete the study.

The flow of participants is shown in Figure 1 below.

Figure 1: Participant Flow



* Breakdown of the 151 excluded patients was 1 case in another survey, 150 duplicated cases due to production of double Case Record Form in changing hospitals.

** Breakdown of the 938 excluded patients was 16 cases that were non-eligible (off-label use), 812 cases that were non-assessable (data at baseline and at least 1 time-point during treatment are missing for DAS components (Morning stiffness, Tender joint counts, Swollen joint counts, patient Visual Analog Scale, Erythrocyte Sedimentation Rate, C-Reactive Protein) of effectiveness evaluation), and 254 cases with a treatment period less than 2 weeks (multiple counting).

Baseline data

In total, 7740 patients were treated with Humira. The majority of patients were women (82.5%, n=6388). Patient age was 60.1 ± 13.0 years (mean ± SD). Disease duration was 10.5 ± 9.6 years (mean ± SD). Patients with prior treatment with biologics or DMARDs were 42.1% (n=3260) and 94.2% (n=7289), respectively. Concomitant use of methotrexate was 71.1% (n=5503) and that of glucocorticoids was 67.4% (n=5215).

Assessor's comment:

There were 13 patients under the age of 18 years who participated in this study.

Efficacy results

Effectiveness of Humira treatment was assessed for 6802 of 7740 patients. A total of 938 patients were excluded due to diagnoses other than RA (n=16), lack of assessable data (n=812) and too short treatment period (less than 2 weeks, n=254).

The EULAR response was evaluated as a Primary Outcome Measure at Weeks 4, 12 or 24 (see Table 2 below).

Table 2: EULAR response

	Treatment time point of assessment (week)		
	4	12	24
EULAR response	**Patients (%)**		
N*	3341	3927	4410
Good response	681 (20.4)	1036 (26.4)	1356 (30.7)
Moderate response	1528 (45.7)	1671 (42.6)	1735 (39.3)
No response	1132 (33.9)	1220 (31.1)	1319 (29.9)
Effective rate**	2209 (66.1)	2707 (68.9)	3091 (70.1)

The number of patients having the available data to calculate the EULAR response was 3341 at week 4, 3927 at week 12 and 4410 at week 24, respectively and each number was used for the denominator at each week. DAS missing data were processed using the last observation carried forward method, except for baseline values.
We describe the data like (0, -, 12), if patient have (baseline DAS exist, no DAS data at week 4, and at 12 week DAS data exist)
At week 4. 3341 pts are consist of (0, 4)
At week 12, 3927 pts are consist of (0, 4, 12) (0 ,4, -) (0, -, 12)
At week 24, 4410 pts are consist of (0, 4, 12, 24) (0, -, 12, 24) (0, -, -, 24) (0, 4, 12, -) (0, 4, -, 24) (0, 4, -, -) (0, -, 12, -)

** Effective rate = Good response + Moderate response

Physician's overall response rating was assessed as Secondary Outcome Measure for all 6802 patients (see Table 3 below).

Table 3: Physician's overall response rating

Effectiveness evaluation	Patients (%)
N	6802
Markedly improved	1979 (29.1)
Improved	3077 (45.2)
Not changed	1333 (19.6)
Not assessable	413 (6.1)

Assessor's comment:

No efficacy results were provided specific for the few paediatric patients in this study. Given the absence of data, no conclusions can be drawn for this population.

Safety results

The safety analysis was performed in 7740 patients.

A total of 2155 patients (27.8%) experienced AEs. The incidence of SAEs and nonserious AEs was 6.1% (n = 469) and 23.2% (n = 1796), respectively. The most frequent SAE was pneumonia (0.5%, n = 41) followed by interstitial lung disease (0.5%, n = 40). Among the 40 patients with interstitial lung disease, 13 patients had documented pre-existing interstitial lung disease. Rash was the most

frequently observed nonserious AE (3.3%, n = 255), followed by injection site erythema (2.1%, n = 160). No overall safety profile change of Humira was seen and unknown clinically significant adverse events were not detected.

Four of the 13 paediatric subjects experienced a total of 5 AEs (all nonserious) as follows:

One 15-year-old patient experienced erythema

One 15-year-old patient experienced a fungal infection and pruritus

One 15-year-old patient experienced nasopharyngitis

One 17-year-old patient experienced paronychia

2.3.2. Discussion on clinical aspects

Given the few paediatric patients enrolled into this study (13/7740) and the very limited data that were provided for these patients, no conclusions on the impact for a European paediatric population can be drawn. Thus, these data are considered to have no influence on the benefit/risk for Humira. No changes to the SmPC are warranted.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

A study report for Study P10-559 (synoptic format) has been provided as requested according to Article 46 of Regulation (EC) No1901/2006, as amended. No changes to the SmPC are warranted.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.