31 May 2018
EMA/CHMP/428944/2018
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/P46/103

Note

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

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Introduction

On 31 Oct 2017, 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.

1. Scientific discussion

1.1. Information on the development program

Humira, a human monoclonal antibody against tumour necrosis factor, is approved for the treatment of Behçet's disease in Japan but not in the EU.

This study was requested by the Pharmaceuticals and Medical Devices Agency in Japan and it was only conducted in Japan. It was submitted to comply with Article 46 of Regulation (EC) No1901/2006, as amended, by submitting data available from patients less than 18 years.

The MAH stated that Humira 40mg Syringe 0.8mL subcutaneous injection Special investigation in patients with intestinal Behcet's disease P14-152 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

40 mg Syringe 0.8 mL for Subcutaneous Injection was used.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

Study P14-152 Humira 40mg Syringe 0.8mL subcutaneous injection Special investigation in patients with intestinal Behçet's disease.

1.3.2. Clinical study

Methods

Objective(s)

The objective was to verify the safety and efficacy of Humira in patients with intestinal Behçet's disease.

Study design

Study P14-152 was a post marketing observational study in which Humira was prescribed for intestinal Behçet's disease in routine medical practice as per the Japanese label. It was a single-arm, multi-center, post marketing cohort study. Patients were observed for 156 weeks at the longest.

Assessor's comment: *The Japanese label was not provided, but it is stated in the Result Report that*

"Humira 160 mg is administered at the first dosing by subcutaneous injection and 80 mg is administered at 2 weeks after the first dosing. At 4 weeks after the first dosing and thereafter, 40 mg/dose is administered once weekly by subcutaneous injection."

It is assumed that this is the dosing used in this study which was post marketing and observational. However, the posology for use in children with Behçet's disease in the Japanese label is unknown, and the MAH is asked to provide this information.

Study population

Japanese patients with intestinal Behçet's disease.

Inclusion Criteria:

Patients receiving Humira for the treatment of Behçet's disease after the approval of the indication.

Exclusion Criteria

Patients included in "Contraindication" in the package insert:

1. Patients with serious infection (sepsis etc.) [Symptomatic worsening may occur.]

2. Patients with active tuberculosis [Symptomatic worsening may occur.]

3. Patients with a history of hypersensitivity to any of the ingredients of HUMIRA

Patients with a current or past history of demyelinating disorder (multiple sclerosis, etc.) [Symptomatic relapse or worsening may occur.]

Assessor's comment: *These are all, except demyelinating disorder, contraindications also in the EU label. In addition, moderate to severe heart failure is a contraindication for Humira treatment in the EU, but apparently not in Japan.*

Treatments

Study subjects were treated with Humira per the Japanese label.

Assessor's comment: *See comment above under study design.*

Outcomes/endpoints

A specified use-results survey of HUMIRA 40 mg Syringe 0.8 mL for Subcutaneous Injection was performed for the purpose of obtaining the following information in Japanese patients with intestinal Bechet's disease.

Primary Endpoints

Safety

- List of ADRs and infections
- Stratified analyses of safety (Factors likely to affect the safety)
- Incidence of ADRs stratified by patient background (sex, age, morbidity period, smoking history, presence or absence of concomitant symptom, presence or absence of past medical

history, presence or absence of past history of allergic disease, presence or absence of foregoing medication, presence or absence of concomitant medication)

- Incidence of ADRs stratified by non-intestinal symptom of Behcet's disease
- Incidence of ADRs stratified by the changes in the corticosteroid dose in the patients treated with corticosteroids
- Adverse events which were developed during or after administration
- List of serious AEs
- Onset of self-injection malpractice
- Relation with the safety when anti-adalimumab antibody is measured

Secondary Endpoints

Effectiveness

- Overall evaluation of gastrointestinal symptoms, evaluation of gastrointestinal symptoms of Behçet's disease , evaluation of main symptoms of Behçet's disease , evaluation of secondary symptoms of Behcet's disease, degree of improvement of endoscopic findings, and CRP
- Stratified analyses of efficacy(Factors considered to have efficacy influence)
- Factors stratified by patient background (sex, age, morbidity period, smoking history, presence or absence of concomitant symptom, presence or absence of past medical history, presence or absence of past history of allergic disease, presence or absence of foregoing medication, presence or absence of concomitant medication)
- Factors stratified by the diagnosis type of intestinal Behçet's disease
- Factors stratified by the changes in the corticosteroid dose in the patients treated with corticosteroids
- Relation with the efficacy when anti-adalimumab antibody is measured

Statistical Methods

Regarding both the safety and efficacy analyses in this survey, subgroup analysis was performed to investigate incidence rates of ADRs and efficacy rates by patient background factors. Subgroup analysis was performed employing the Fisher's exact test for variables on nominal scales and the Mann-Whitney u test for variables on ordinal scales (however, the Fisher's exact test was employed for two categorical variables (2 × 2) on ordinal scales). All tests were performed with the two-sided significance level of 5%.

Results

Recruitment/ Number analysed

The number of registered patients was 473. Among these registered patients, there were 470 patients whose data in the survey forms were fixed, excluding 3 patients whose survey forms could not be recovered because cooperation of the doctors could not be obtained.

Among the 470 patients whose data in the survey forms were fixed, there were 6 patients under 15 years old, 22 patients under 18 years old.

Assessor's comment: *It is noted in Table 1 that 4 of the 22 patients actually were 18 years old at enrolment. Provided this is correct, 18 subjects were younger than 18 years old.*

Baseline data

Assessor's comment: *No information on baseline data for the paediatric subjects was provided.*

Efficacy results

Five of the 383 patients included in the efficacy analysis were <15 years of age. The efficacy rate was 100%, as compared to 84.4% (318/377) among the non-paediatric subjects.

Assessor's comment: *Only efficacy results for the paediatric subjects < 15 years were provided. Efficacy of the drug was measured through a final global improvement rating of effect. In all 5 subjects the drug was evaluated as "markedly effective" or "effective".*

Safety results

Seven of the 22 paediatric patients (31.8%) experienced AEs. 4 paediatric patient (18.18%) experienced SAEs.

Table 1: List of Patients Under the Age of 18

Case No.	Gender	Age	Discontinuation		Adverse event			
			Presence/ absence	Reason	Disease name (MedDRA PT term)	Seriousness	Causality	Outcome
1	Females	15	Absence					
2	Females	18	Absence					
3	Females	13	Absence					
4	Males	17	Absence					
5	Males	16	Absence					
6	Males	17	Absence					
7	Females	18	Absence					
8	Females	10	Presence	No return visits	Influenza	Non-serious	Not related	Resolved
9	Males	17	Presence	No return visits	Behcet's syndrome	Serious	Possibly related	Resolving
					Transaminases increased	Non-serious	Possibly related	Resolved
10	Males	15	Presence	Inadequate response	Pyrexia	Serious	Not related	Resolved
					C-reactive protein increased	Serious	Not related	Resolved
11	Females	12	Absence					
12	Females	18	Absence					
13	Males	17	Presence	Inadequate response				
14	Males	17	Absence					
15	Males	16	Absence					

Case No.	Gender	Age	Discontinuation		Adverse event			
			Presence/ absence	Reason	Disease name (MedDRA PT term)	Seriousness	Causality	Outcome
16	Males	5	Presence	Onset of adverse events	Herpes zoster	Non-serious	Possibly related	Resolved
					Nasopharyngitis	Non-serious	Possibly related	Resolving
					Nasopharyngitis	Non-serious	Possibly related	Resolving
					Oral candidiasis	Non-serious	Possibly related	Not resolved
					Oral candidiasis	Non-serious	Possibly related	Resolved
					Otitis media	Non-serious	Possibly related	Resolved
					Pneumonia bacterial	Non-serious	Possibly related	Resolved
					Myelodysplastic syndrome	Serious	Not related	Fatal
					Febrile neutropenia	Non-serious	Possibly related	Resolving
					Febrile neutropenia	Non-serious	Possibly related	Resolving
					Hypogammaglobulinaemia	Non-serious	Possibly related	Not resolved
					Urticaria	Non-serious	Not related	Not resolved
					Antithrombin III decreased	Non-serious	Possibly related	Unknown
17	Females	18	Presence	No return visits	Oral herpes	Non-serious	Possibly related	Resolved with sequelae
					Oral herpes	Non-serious	Possibly related	Resolved
					Oral herpes	Non-serious	Possibly related	Resolved
					Injection site reaction	Non-serious	Related	Unknown
18	Males	7	Absence					
19	Females	17	Absence					
20	Females	16	Absence					
21	Males	17	Absence		White blood cell count decreased	Non-serious	Possibly related	Resolved
22	Females	14	Absence		Pyrexia	Serious	Possibly related	Resolved

There was a report of fatal mycosis (aspergillosis) that occurred about 6 months after last dose of Humira. The patient was 7 years old at time of death. His medical history, beyond intestinal Behçet's disease, included a rare autoimmune leukoproliferative disorder as well as other medical problems.

On Day 385 of treatment with Humira, the patient developed 'pancytopenia' and based on a bone marrow examination a diagnosis of a malignant bone marrow disorder was made. Bone marrow transplant was performed on Day 554 of treatment and administration of Humira was discontinued on the same day. The reporting physician considered the event of the malignant bone marrow disorder attributable to the autoimmune leukoproliferative disorder with no causal relationship to Humira.

About 6 months after bone marrow transplantation, a CT scan showed multiple nodular shadows consistent with Aspergilloma lesions in the lung and he died after 3 days.

MAH´s conclusion: The findings of this non-interventional study support the conclusion that adalimumab is effective and safe intestinal Behçet's disease in Japanese patients. The small number of paediatric patients enrolled limits interpretation of the data from this patient population. There were no new safety signals observed and the data are consistent with the known safety profile of adalimumab.

1.3.3. Rapporteur's discussion on clinical aspects

The MAH has provided a report on an observational study on patients with Behçet's disease, conducted in Japan, where Humira holds a marketing authorisation for this indication. The reason for submitting the study report to the CHMP is that 22 of the 470 subjects were 18 years old or younger, whereof 6 younger than 15 years. The report was thus provided in accordance with Article 46.

No information on the doses administered to the children was provided, which is a shortcoming. This information is asked for.

The subjects were treated for a maximum of 152 weeks. However, the exposure times (individual as well as mean and median) for the included children have not been provided and is asked for.

Seven of the paediatric subjects (31.8%) experienced AEs. It is noted that a fatal case of aspergillosis occurred in a 7 year old male with a rare autoimmune leukoproliferative disorder and other medical problems, who died six months after the discontinuation of Humira. It is agreed that the medical history of this patient is a strong confounder.

In addition to this case, Influenza, pyrexia (2), increased transaminases, increased CRP and oral herpes, injection site reaction and Behçet's disease were reported. These AEs are in line with the known safety profile of Humira.

Four paediatric patients (18.18%) experienced SAEs; these were pyrexia, pyrexia + CRP increased, MDS and Behçet's disease. The incidence rate is not possible to interpret without information on how long the included children (< 18 years old) participated in the study. Information on this, as well as the AE and SAE rates in children per 100 patient years is asked for.

Efficacy in children younger than 15 years seems to have been in line with that in older subjects.

Additional clarifications requested

Based on the data submitted, the MAH should provide

- Information on the dose of Humira administered to children in this study.
- exposure times (individual as well as mean and median) for the included children
- AE and SAE rate per 100 PTY in the paediatric population.

as part of this procedure..

The timetable is a 30 day response timetable without clock stop.

2. Assessment of responses from the MAH

Summary of the MAH´s response

The following information is provided in response to the Committee for Medicinal Products for Human Use (CHMP) Rapporteur's Assessment Report/Request for Supplementary Information (European Medicines Agency [EMA]/91643/2018) on AbbVie's submission of a completed study in subjects with intestinal Behcet's disease (Study P14-152) for Humira (adalimumab) on 15 November 2017 (EMEA/H/C/481 P46 103).

CHMP comment 1

The Japanese label was not provided, but it is stated in the Result Report that "Humira 160 mg is administered at the first dosing by subcutaneous injection and 80 mg is administered at 2 weeks after the first dosing. At 4 weeks after the first dosing and thereafter, 40 mg/dose is administered once weekly by subcutaneous injection."

It is assumed that this is the dosing used in this study which was post marketing and observational. However, the posology for use in children with Behçet's disease in the Japanese label is unknown, and the MAH is asked to provide this information.

AbbVie Response:

Upon review of the Rapporteur's comment, it was determined that the dosing described in the Study P14-152 Result Report was incorrect due to a translation error. Subjects in Study P14-152 were actually dosed per clinical practice following the approved Japanese label, which included an initial dose of adalimumab 160 mg by subcutaneous injection and 80 mg administered two weeks after the first dose. This was followed by 40 mg administered every other week four weeks after the initial dose (and not 40 mg administered once weekly as incorrectly described in the Result Report). Of note, the Japanese label does not specify a paediatric dose for Behcet´s disease.

Additional details regarding the dosing and exposure for the paediatric population is provided below.

Additional clarifications requested

Based on the data submitted, the MAH should provide

- **Information on the dose of Humira administered to children in this study.**
- **Exposure times (individual as well as mean and median) for the included children.**
- **AE and SAE rate per 100 PTY in the paediatric population as part of this procedure.**

AbbVie Response:

All pediatric subjects were dosed according to the approved Japanese label, with the exception of the two youngest subjects who did not receive the loading dose (one of these subjects received adalimumab 40 mg every other week, which was later reduced to 20 mg every other week and one subject received 40 mg every other week).

The overall duration of adalimumab exposure in the paediatric population ranged from 127 days to 1093 days, with a mean duration of 526.36 days (median: 365 days). The dose and exposure duration of adalimumab for each individual paediatric subject in the study population is provided in Table 2.

Table 2 Dose and Exposure Duration of Adalimumab in the Pediatric Population in Study P14-152

No.	Sex	Age	Dose (mg)	Duration (Days)
1	Female	15	160→80→40[a]	729
2	Female	18	160→80→40[a]	729
3	Female	13	160→80→40[a]	1093
4	Male	17	160→80→40[a]	1093
5	Male	16	160→80→40[a]	1093
6	Male	17	160→80→40[a]	729
7	Female	18	160→80→40[a]	729
8	Female	10	160→80→40[a]	222
9	Male	17	160→80→40[a]	331
10	Male	15	160→80→40[a]	197
11	Female	12	160→80→40[a]	365
12	Female	18	160→80→40[a]	365
13	Male	17	160→80→40[a]	127
14	Male	17	160→80→40[a]	729
15	Male	16	160→80→40[a]	365
16	Male	5	40[b]	552
17	Female	18	160→80→40[a]	307
18	Male	7	40→20[c]	365
19	Female	17	160→80→40[a]	365
20	Female	16	160→80→40[a]	365
21	Male	17	160→80→40[a]	365
22	Female	14	160→80→40[a]	365
			Mean	**526.36**
			SD	**294.75**
			Median	**365**

SD = standard deviation.

a. Represents 160 mg at Week 0, 80 mg at Week 2, followed by 40 mg given every other week from Week 4.

b. Represents 40 mg given every other week.

c. Represents 40 mg given at Week 0, followed by 20 mg every other week from Week 2.

Across the pediatric population (N = 22), a total of 24 adverse events (AEs) and 5 serious adverse events (SAEs) were observed, which corresponded to an overall observed rate of 75.44 events (E)/100 patient-treatment years (PTYs) and 15.72 E/100 PTYs, respectively. Of note, the exposure-adjusted AE rate is lower than the rates observed in the global adalimumab paediatric clinical programs, which ranged from 239.4 E/100 PTYs in paediatric ulcerative colitis to 558.7 E/100 PTYs in paediatric Crohn's disease. The exposure-adjusted SAE rate is within the range observed in the global adalimumab pediatric clinical programs (7.4 E/100 PTYs in paediatric psoriasis to 31.6 E/100 PTYs in paediatric Crohn's disease).

Table 3: AE and SAE Rate per 100 PTYs by Preferred Term in the Paediatric Population (Study P14-152); N = 22 Subjects, Total PTYs = 31.81

Preferred Term	AE	AE/100 PTYs	SAE	SAE/100 PTYs
C-reactive protein increased	1	3.14	1	3.14
Antithrombin III decreased	1	3.14		
Influenza	1	3.14		
Transaminases increased	1	3.14		
Behcet's syndrome	1	3.14	1	3.14
Oral candidiasis	2	6.29		
Oral herpes	3	9.43		
Myelodysplastic syndrome	1	3.14	1	3.14
Pneumonia bacterial	1	3.14		
Herpes zoster	1	3.14		
Otitis media	1	3.14		
Injection site reaction	1	3.14		
Hypogammaglobulinemia	1	3.14		
White blood cell count decreased	1	3.14		
Pyrexia	2	6.29	2	6.29
Febrile neutropenia	2	6.29		
Nasopharyngitis	2	6.29		
Urticaria	1	3.14		

AE = adverse event; PTY = patient treatment year; SAE = serious adverse event.

Definition of the total administration period: number of days until the last administration day = last dose date - first dose date + 1.

If multiple cases of the same event (same preferred term) occurred in the same patient, they were each counted as the number of occurrences.

Rapporteur´s discussion on MAH´s response

The MAH has provided the requested information on dosing and exposure of the children included in this study. All children except 2 were treated with the same dose as adults, meaning a substantial exposure. The exposure-adjusted AE and SAE rates have also been presented. These are not substantially higher than earlier observed in clinical studies, although it is noted that the comparison with paediatric ulcerous colitis made by the MAH is not fully relevant, since this is not yet an approved indication.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

In an observational study of Humira in 470 Japanese subjects with Behçet's disease, 22 subjects were 18 years old or younger. No new safety signals emerged in this very small population. The safety profile seems to be consistent with earlier findings.

Recommendation

☒ Fulfilled:

No regulatory action required.