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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/P46/104

Note

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

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Introduction

On 22 November 2017, the MAH submitted the final study report for P15-619 (Post- Marketing Surveillance of Humira in Korean Paediatric CD Patients under the "New-Drug Re-examination") for Humira, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This is a Post Authorisation Measure (PAM).

A short critical expert overview has also been provided.

The applicant states that the data submitted do not influence the benefit-risk balance and therefore do not require taking further regulatory action on the marketing authorisation.

1. Scientific discussion

1.1. Information on the development program

In Korea, the paediatric CD indication for adalimumab (Humira®) was approved in September 2013. Study P15-619 was set up as a Post-Marketing Surveillance (PMS) study as per the New Drug Re-examination Guideline in Korea. The requirements in Korea are that a PMS study is conducted for each new compound or each new indication of an approved compound. The aim of the study was to evaluate the safety and effectiveness of adalimumab in Korea paediatric patients with moderate to severe Crohn's disease (CD).

1.2. Information on the pharmaceutical formulation used in the studies

Paediatric patients who were prescribed Humira as per physician's medical judgment in accordance with the approved SmPC were enrolled in the study.

The MAH states that as this is a post marketing surveillance, the MAH was NOT involved in the product supply since the drug was being used according to the approved marketing label and was to be prescribed by the physician under usual and customary practice of physician prescription.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted the final study report for P15-619 (Post- Marketing Surveillance of Humira in Korean Paediatric CD Patients under the "New-Drug Re-examination").

1.3.2. Clinical study P15-619; description of the study methods and results as presented by the applicant

Methods

Objectives

To evaluate the safety profile of Humira for Paediatric CD patients in normal medical practice:

1. Serious adverse event adverse drug reaction

2. Unexpected adverse event adverse drug reaction

3. Already known adverse drug reaction

4. Non-serious adverse drug reaction

5. Adverse events resulting from drug misuse, drug abuse or drug interaction

6. Other information related to the product's safety and effectiveness (including the influence to the laboratory value)

Study design

This study was a non-interventional, observational study of Humira in the treatment of paediatric CD as per the New Drug Re-examination Guideline in Korea. Paediatric patients who were prescribed Humira as per physician's medical judgment in accordance with the approved SmPC were enrolled in the study.

Patients were observed for 6 months following first dose of Humira.

Study population /Sample size

Study population

All patients who were prescribed Humira for paediatric CD treatment during the surveillance period and who met the inclusion/exclusion criteria were enrolled in the study until the assigned number of subjects were registered at the site:

Inclusion Criteria

1. Paediatric patients with Crohn's Disease who are prescribed Humira in accordance with the Korean label for Humira authorization (labeling).

2. Patients who have given written authorization or patients whose legal representatives have given it to use their personal health data for the purposes of this study.

Exclusion Criteria

Patient with any of the following was not registered in this surveillance:

1. Any contraindications to Humira as listed on the approved product market authorization (labeling)

2. Patients who is participating on other clinical trials.

Study Size and Study Duration

This Post-Marketing Surveillance (PMS) was planned to recruit 600 subjects for 4 years to meet the local requirements for regulatory PMS. However, according to the MAH, the number of subjects to be enrolled was adjusted to 141 subjects because of: 1) Low incidence and prevalence of Paediatric CD, and 2) Criteria for using biologics for Paediatric CD (as Humira is indicated only for a subgroup of CD patients, only a very limited number of patients with the disease receives the drug) and 3) Difficulties in getting patients' consents.

The study actually enrolled 152 subjects from 13 study sites during the PMS study period (4 years, 13 September 2013 through 12 September 2017), see further below.

The study duration designated by MFDS (Ministry of Food and Drug Safety) was from 13 September 2013 to 12 September 2017. The study was started after the launch of the product as a new drug for paediatric CD and the final report was to be submitted to MFDS by 11 December 2017. Interim study

reports were submitted to MFDS every 6 months for the first 2 years, then annually thereafter during PMS period.

Treatments

Patients were administered Humira as per the package label. Unit dose, frequency and length of treatment (start date, end date) were recorded on the appropriate case report form.

Concomitant medications, including TB prophylaxis regimen, corticosteroids, immunosuppressants, were recorded and included: generic name (brand name in case of combination drug), total daily dose, length of administration (start date and end date), indications.

Outcomes/endpoints

Variables were Demographics, Medical History, PPD Skin Test, Chest X-ray, Interferon Gamma Release Assay, Concomitant Medication, Safety, PCDAI score (CDAI score if it was evaluated).

Regardless of results of causality assessment, presence of adverse event(s), type of adverse event(s), onset, end date, severity, causality assessment by physician on the adverse event(s), action taken, outcome were captured, during the study, from the first administration to the surveillance period (Safety data was collected from informed consent to up to 70 days following the last administration of Humira).

Statistical Methods

Justification for the Planned Sample Size

The sample size of 600 had been selected in order to give at least 95% probability of detecting at least one uncommon SAE that occurs in the Korean patient population at a rate of at least 0.5%. This estimate was based on the assumption that the occurrence of AEs has a Poisson distribution and that if the population rate of occurrence of an AE is 0.5% then the expected number of AEs in the proposed sample size of 600 would be 3. The probability of observing 1 or more events with a Poisson parameter of 3 is 0.95 or 95%.

Analysis Population

The safety analysis data set includes all subjects who have received at least one administration of Humira following the initiation of surveillance and have completed follow up for the safety information.

For induction effectiveness of Humira, the effectiveness analysis data set includes all subjects who have been administered Humira and prescribed Humira for 4 weeks including induction period (± 1 week) and for whom effectiveness evaluation parameters have been recorded. And for maintenance effectiveness of Humira, effectiveness analysis data set includes all subjects who have been administered Humira and prescribed Humira for 6 months (± 4 weeks) and for whom effectiveness evaluation parameters have been recorded.

Safety Analysis

The number and percentage of subjects reporting any serious adverse events/adverse drug reactions were tabulated.

If the incidence of adverse events in the subjects who began the administration before/after the registration date was statistically significant, it was presented as a separate item. In addition, if there are patients who have already been administered Humira when participating in the surveillance, their

adverse events from the first administration of Humira to the inclusion were presented in a separate table.

Effectiveness Analysis

The effectiveness assessment of Humira induction therapy and maintenance therapy was presented by the number and percentage of the subjects with clinical response. To investigate the factors affecting the effectiveness, the number and percentage of subjects with clinical response were also be classified by background factors (e.g., demographic factors, treatment factors such as medical history, dosing and administration, concomitant medications, beginning of administration before/after the registration date, etc.) and tabulated. If the effectiveness evaluation of above factors was statistically significant, it was presented as a separate item.

Main Statistical Methods

In final report, safety and effectiveness outcome by background factor was summarized and analyzed. The analysis for categorical variables was performed using Chi-square test or Fisher's exact test and continuous variables was performed using Wilcoxon rank sum test or t-test. Also, incidence rate of adverse event collected in overall PMS period was analyzed and 95% CI was presented.

No statistical imputations were planned for missing values.

Results

Recruitment/ Number analysed

The study enrolled 152 subjects from 13 study sites during the PMS study period (4 years, 13 September 2013 through 12 September 2017). Among these 152 subjects, 143 subjects were included in the safety analysis population excluding 9 subjects who did not use the drug according to the approved indication or dosage. The effectiveness analysis of induction therapy was conducted on 92 subjects excluding 51 subjects from 143 safety evaluation subjects – 12 subjects did not have any parameter value from effectiveness evaluation, 38 subjects did not meet the visit window, and 1 subject both did not have any parameter value and did not meet the visit window. The effectiveness analysis of maintenance therapy was conducted on 74 subjects except 69 subjects from 143 safety evaluation subjects – 41 subjects did not have any parameter value from effectiveness evaluation, and 28 subjects did not meet the visit window.

Baseline data; patient characteristics

Of 143 subjects in the safety population, 60.84% (87/143 subjects) were male and 39.16% (56/143 subjects) were female. None of the subjects were pregnant. The mean age was 14.14 (± 2.43) years old ranged from 6.00 to 17.00 years old. 89.51% (128/143 subjects) were between the age of 12 and 18 years old, and 10.49% (15/143 subjects) were between 24 months and 11 years old. None of the subjects were infants less than 24 months and adults over 19 years old.

The mean duration of paediatric CD symptoms was 24.60 (± 27.60) months. In involved intestinal area, colon had been the most commonly reported as 86.01% (123/143 subjects), followed by 84.62% (121/143 subjects) with ileum, 41.96% (60/143 subjects) with anal/perianal, 36.36% (52/143 subjects) with rectum, 24.48% (35/143 subjects) with gastroduodenum, 20.28% (29/143 subjects) with jejunum, and 2.10% (3/143 subjects) with other. Those without presence of draining fistula were 62.94% (90/143 subjects), and those with previous CD related therapy were 98.60% (141/143 subjects). Before treated with Humira, 78.01% (110/143 subjects) had been treated with immunosuppressants, 75.89% (107/143 subjects) with 5-ASA, 72.34% (102/143 subjects) with

antibiotics, 68.09% (96/143 subjects) with steroids, 46.81% (66/143 subjects) with nutritional therapy, 30.50% (43/143 subjects) with biologics, and 2.84% (4/143 subjects) with other.

The subjects with concomitant medications were 95.80% (137/143 subjects) and 458 cases of concomitant medications were reported. 51.75% (74/143 subjects, 93 cases) had been treated with 'Intestinal antiinflammatory agents' which was the most common, 45.45% (65/143 subjects, 73 cases) with immunosuppressants, 23.78% (34/143 subjects, 36 cases) with antidiarrheal microorganisms, 20.28% (29/143 subjects, 38 cases) with other antibacterials, and 18.88% (27/143 subjects, 28 cases) with antimetabolites.

The subjects were categorized into 'before enrolment' and 'after enrolment.' 'Before enrolment' group is for the subjects who had been administered Humira before enrolment into this study. 'After enrolment' group is for the subjects who had been administered Humira on the same date or after they signed the informed consent form for this study. Of 143 subjects in the safety population, the subjects included in before enrolment' were 30.77% (44/143 subjects), and 'after enrolment' were 69.23% (99/143 subjects). The mean of total dose of administration was 1,160.00 (± 943.77) mg and the mean length of treatment was 52.81 (± 45.58) weeks.

Humira® treatment at the last administration was ongoing for 96.50% (138/143 subjects), discontinuation for 3.50% (5/143 subjects). The reasons for discontinue of Humira administration were 'Adverse event' for 60.00% (3/5 subjects), 20.00% (1/5 subjects) 'Lack of drug effect' and 'Others' each.

Safety results

A total of 47 adverse events in 18.18% (26/143 subjects) were reported from 143 safety evaluation subjects. Of these adverse events, 26 adverse events which occurred in 14.69% (21/143 subjects) were considered as adverse drug reactions, see table below.

Table 1: Number (%) of Subjects Reporting Adverse Events/Adverse Drug Reactions

Adverse events		Adverse Events		Adverse Drug Reactions	
		Subject No. (%)		Subject No. (%)	
	Yes	26 (18.18)		21 (14.69)	
	No	117 (81.82)		122 (85.31)	
	Total	143 (100.00)		143 (100.00)	
		Adverse Events		Adverse Rrug Reactions	
Type of AE/ADR[†]		Subject No. (%)	Case No.	Subject No. (%)	Case No.
Gastrointestinal disorders		**7 (4.90)**	**15**	**5 (3.50)**	**5**
	Abdominal pain	2 (1.40)	2	-	-
	Diarrhoea	2 (1.40)	2	2 (1.40)	2
	Haematochezia	2 (1.40)	2	1 (0.70)	1
	Intestinal stenosis	2 (1.40)	2	-	-
	Colonic haematoma	1 (0.70)	1	-	-
	Gastrointestinal inflammation	1 (0.70)	1	-	-
	Gastrointestinal necrosis	1 (0.70)	1	-	-
	Ileus paralytic	1 (0.70)	1	1 (0.70)	1
	Intestinal obstruction	1 (0.70)	1	-	-
	Intestinal perforation	1 (0.70)	1	1 (0.70)	1
	Small intestinal obstruction	1 (0.70)	1	-	-
Skin and subcutaneous tissue disorders		**5 (3.50)**	**6**	**5 (3.50)**	**6**
	Rash	3 (2.10)	3	3 (2.10)	3
	Pruritus	1 (0.70)	1	1 (0.70)	1
	Skin reaction	1 (0.70)	1	1 (0.70)	1
	Urticaria	1 (0.70)	1	1 (0.70)	1
Investigations		**4 (2.80)**	**7**	**3 (2.10)**	**5**
	Alanine aminotransferase increased	3 (2.10)	3	2 (1.40)	2
	Aspartate aminotransferase increased	3 (2.10)	3	2 (1.40)	2
	Liver function test abnormal	1 (0.70)	1	1 (0.70)	1
Blood and lymphatic system disorders		**4 (2.80)**	**4**	**4 (2.80)**	**4**
	Leukopenia	4 (2.80)	4	4 (2.80)	4
Infections and infestations		**3 (2.10)**	**3**	**1 (0.70)**	**1**
	Appendicitis	1 (0.70)	1	1 (0.70)	1
	Helicobacter gastritis	1 (0.70)	1	-	-
	Peritonitis	1 (0.70)	1	-	-

	Adverse Events		Adverse Drug Reactions	
Adverse events	Subject No. (%)		Subject No. (%)	
General disorders and administration site conditions	**2 (1.40)**	**4**	**1 (0.70)**	**1**
Pyrexia	1 (0.70)	2	-	-
Malaise	1 (0.70)	1	1 (0.70)	1
Pain	1 (0.70)	1	-	-
Investigations	**1 (0.70)**	**2**	-	-
C-reactive protein increased	1 (0.70)	1	-	-
Red blood cell sedimentation rate increased	1 (0.70)	1	-	-
General disorders and administration site conditions	**1 (0.70)**	**1**	**1 (0.70)**	**1**
Injection site erythema	1 (0.70)	1	1 (0.70)	1
Infections and infestations	**1 (0.70)**	**1**	**1 (0.70)**	**1**
Candida infection	1 (0.70)	1	1 (0.70)	1
Infections and infestations	**1 (0.70)**	**1**	**1 (0.70)**	**1**
Pyelonephritis acute	1 (0.70)	1	1 (0.70)	1
Infections and infestations	**1 (0.70)**	**1**	**1 (0.70)**	**1**
Folliculitis	1 (0.70)	1	1 (0.70)	1
Injury, poisoning and procedural complications	**1 (0.70)**	**1**	-	-
Anastomotic complication	1 (0.70)	1	-	-
Nervous system disorders	**1 (0.70)**	**1**	-	-
Dizziness	1 (0.70)	1	-	-
Total	**26 (18.18)**	**47**	**21 (14.69)**	**26**

† Overlapping count; MedDRA 18.0.

The most frequent adverse event was leukopenia which occurred in 2.80% (4/143 subjects) with 4 cases. The most frequently reported adverse drug reaction was leukopenia which occurred in 2.80% (4/143 subjects) with 4 cases. Rash was found in 2.10% (3/143 subjects) with 3 cases.

A total of 13 serious adverse events in 5.59% (8/143 subjects) were reported from 143 safety evaluation subjects. Of these adverse events, 5 serious adverse events which occurred in 3.50% (5/143 subjects) were considered as serious adverse drug reactions. The most frequent adverse event was abdominal pain which occurred in 1.40% (2/143 subjects) with 2 cases. Gastrointestinal necrosis, haematochezia, ileus paralytic, intestinal obstruction, intestinal perforation, small intestinal obstruction, appendicitis, peritonitis, pyrexia, candida infection, and pyelonephritis acute were reported in 0.70% (1/143 subjects) with 1 case each. The 5 serious adverse drug reactions were ileus paralytic, intestinal perforation, appendicitis, candida infection, and pyelonephritis acute which occurred in 3.50% (5/143 subjects) with 1 case each.

Of the 47 adverse events, 25 were assessed as mild, 18 as moderate and 4 as severe. The four severe events were all gastrointestinal disorders; Haematochezia, Intestinal perforation, Intestinal obstruction and Ileus paralytic.

The distribution of adverse events by action taken were investigated. In 53.19% (25/47 cases) no action was taken, in 36.17% (17/47 cases) Humira was transiently discontinued, in 6.38% (3/47 cases) the action was reported as "other", and in 4.26% (2/47 cases) Humira was permanently discontinued. The two adverse events that led to permanent discontinuation of the drug were reported as Intestinal perforation and Skin reaction.

The distribution of adverse events by outcome were investigated, and 91.49% were resolved, 4.26% were resolved with sequelae, and 2.13% were not resolved and other, respectively. There were no

outcome of fatal/death. Adverse events which resolved with sequelae were intestinal perforation and acute pyelonephritis. Intestinal perforation has judged as resolved with sequelae, because it left a scar. Acute pyelonephritis has judged as resolved with sequelae which lead to kidney damage. The event that was reported as not resolved was an event of leukopenia.

A total of 17 unexpected adverse events (not on the list of local label) in 6.29% (9/143 subjects) were reported from 143 safety evaluation subjects. Of these adverse events, 4 unexpected adverse events which occurred in 2.80% (4/143 subjects) were considered as unexpected adverse drug reactions. The most frequent adverse event was aspartate aminotransferase increased which occurred in 2.10% (3/143 subjects) with 3 cases. Intestinal stenosis was found in 1.40% (2/143 subjects) with 2 cases. Colonic haematoma, gastrointestinal inflammation, gastrointestinal necrosis, ileus paralytic, intestinal obstruction, small intestinal obstruction, appendicitis, helicobacter gastritis, C-reactive protein increased, red blood cell sedimentation rate increased, pain, and anastomotic complication were reported in 0.70% (1/143 subjects) with 1 case each.

Of the unexpected events, 16 adverse events were reported as the subjects recovered except 1 adverse event for appendicitis. And 13 adverse events were reported the causality with Humira as not related. All of 17 adverse events were already reported through the Periodic Safety Update Report (PSUR) for Adalimumab. Therefore, although these unexpected adverse events are, according to the applicant, not listed per se in the product label, it has been reported and the MAH considers them as AEs that could be expected to occur among Humira users.

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira) and the adverse events following Humira were explored. Univariate analysis and logistic regression analysis were conducted on demographic, medical, and treatment with Humira and according to the application, it showed statistically significant result according to sex (p-value = 0.0014 (AEs), 0.0115 [ADRs]), with a higher incidence rate in males than in females. It was stated that there was no statistically significant difference in the incidence rate of adverse events/adverse drug reactions in other factors. The applicant states that due to the relatively small sample size in this study, these results should be interpreted with caution.

Overall, the MAH concluded that safety of Humira observed during the course of this PMS study was not remarkably different than the previously documented safety profile of the product, as described in the label and periodic safety update reports. The MAH further stated that the safety of Humira will continue to be monitored after the submission of this report through spontaneous reporting of adverse events and collection of safety information.

Efficacy results

The effectiveness analyses were performed using effectiveness population including the subjects who administered Humira for induction/maintenance therapy with the record of PCDAI (Paediatric Crohn's Disease Activity Index, PCDAI) among the safety population. CDAI (Crohn's Disease Activity Index, CDAI) score were collected as well, if possible.

According to the study protocol, the effectiveness of induction and maintenance therapies were evaluated according to main and sub analysis. Main analysis was conducted based on the data excluded out of window study visit cases. Sub analysis was conducted based on the data included out of window study visit cases. The effectiveness assessment of Humira induction therapy and maintenance therapy was presented by the number and percentage of the subjects with clinical response. In the Clinical Expert Overview it was explained that when evaluating the clinical response rate, the subjects who violated the defined period was included for effectiveness population, as a sensitivity analysis.

1. Effectiveness of Humira Induction Therapy (at 4 Weeks)

The mean PCDAI decrease at baseline visit and following visit was 30.09 (± 10.79) and it showed, according to the applicant, statistically significant result (p-value < 0.0001). The mean CDAI decrease at baseline visit and following visit was 24.38 (± 15.46) and it was, according to the applicant, not statistically significant (n = 4).

The results of the main analysis on the clinical response rate of induction therapy show, according to the study report, that the subjects who had clinical response were 88.04% (81/92 subjects) and the subjects without clinical response were 11.96% (11/92 subjects). The proportion of clinical response was statistically significant higher than 50% (p-value < 0.0001). It is further stated in the study report that the results of the sub analysis on the clinical response rate of induction therapy show that the subjects who had clinical response were 87.69% (114/130 subjects) and the subjects without clinical response were 12.31% (16/130 subjects). It is explained in the Clinical Expert Overview that in this analysis 38 subjects with observations outside of the defined period were included in the analysis set. The proportion of clinical response was statistically significant higher than 50% (p-value < 0.0001).

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira) and effectiveness results following Humira were explored. The result of univariate analysis on demographic, medical, and treatment with Humira, all factors were, according to the applicant, not statistically significant. Logistic regression analysis was conducted to determine the clinical response rate based on the duration of Paediatric CD symptoms and the treatment with Humira of the subjects. As the total dose of Humira increased by 1 mg, the odds for the clinical response rate in the subject was, according to the applicant, statistically significant at 0.999 (Odds ratio CI: 0.998, 1.000) (p-value = 0.0444). There was no statistically significant difference in the clinical response rate in other factors (duration of paediatric CD, length of treatment.

2. Effectiveness of Humira Maintenance Therapy (at 6 Months)

The mean PCDAI decrease at baseline visit and following visit was 32.81 (± 13.55) and it showed, according to the applicant, statistically significant result (p-value < 0.0001). The mean CDAI decrease at baseline visit and following visit was 62.98 (± 76.78) and it was, according to the applicant, not statistically significant (n = 5).

It is stated in the study report, that results of the main analysis on clinical response rate of maintenance therapy show that the subjects who had clinical response were 87.84% (65/74 subjects) and the subjects without clinical response were 12.16% (9/74 subjects). It is further stated that the proportion of clinical response was statistically significant higher than 50% (p-value < 0.0001). The results of the sub analysis on clinical response rate of maintenance therapy show, according to the study report, that the subjects who had clinical response were 85.29% (87/102 subjects) and the subjects without clinical response were 14.71% (15/102 subjects). It is explained in the Clinical Expert Overview that this analysis 28 subjects with observations outside of the defined period, were included in the analysis set. The study report states that proportion of clinical response was statistically significant higher than 50% (p-value < 0.0001).

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira) and effectiveness results following Humira were explored. The result of univariate analysis on demographic, medical, and treatment with Humira, showed, according to the applicant, statistically significant result according to start date of treatment with Humira (p-value = 0.0238). Subjects who categorized to 'Before enrolment participation,' the subjects who showed response were 75.86% (22/29 subjects) and 24.14% (7/29 subjects) showed non-response. Subjects who categorized to 'After enrolment participation,' the subjects who showed response were 95.56%

(43/45 subjects) and 4.44% (2/45 subjects) showed non-response. According to the applicant, there was no statistically significant difference in the clinical response rate in other factors.

Logistic regression analysis was conducted to determine the clinical response rate based on the duration of Paediatric CD symptoms and the treatment with Humira of the subjects. The applicant states that as the duration of paediatric CD increased by 1 month, the odds for the clinical response rate in the subject was statistically significant lower at 0.976 (Odds ratio CI: 0.958, 0.995) (p-value = 0.0143). The applicant further states that as the total dose of Humira increased by 1 mg, the odds for the clinical response rate in the subject was statistically significant at 0.999 (Odds ratio CI: 0.999, 1.000) (p-value = 0.0087). As the length of treatment increased by 1 week, the odds for the clinical response rate in the subject was statistically significant at 0.988 (Odds ratio CI: 0.978, 0.997) (p-value = 0.0120).

The MAH concluded that in terms of effectiveness, the results demonstrate Humira to be effective for paediatric CD. Only data for clinical response are given, no data on clinical remission are provided.

1.3.3. Discussion on clinical data from study P15-619

Study P15-619 was a non-interventional, observational study of Humira in the treatment of paediatric CD that included Korean patients who were prescribed Humira in accordance with the approved SmPC. The aim of the study was to evaluate the safety and effectiveness of adalimumab in Korean paediatric patients with moderate to severe CD. The study aimed to recruit 600 subjects for 4 years. However, the number of subjects to be enrolled was adjusted due to low incidence and prevalence of Paediatric CD, the fact that only a very limited number of patients with the disease receive the drug and difficulties in getting patients' consents. It was stated that patients were observed for 6 months following first dose of Humira.

In summary, a total of 47 adverse events in 18.18% (26/143 subjects) and 13 serious adverse events in 5.59% (8/143 subjects) were reported. From the tabulated data there appeared to be 6 cases of infections: appendicitis, helicobacter gastritis, peritonitis, candida infection, pyelonephritis and folliculitis. Injection site erythema was reported in 1 patient. Serious adverse events included abdominal pain, gastrointestinal necrosis, haematochezia, ileus paralytic, intestinal obstruction, intestinal perforation, small intestinal obstruction, appendicitis, peritonitis, pyrexia, candida infection, and pyelonephritis acute. Regarding actions taken in relation to the adverse events, in 53.19% (25/47 cases) no action was taken, in 36.17% (17/47 cases) Humira was transiently discontinued, in 6.38% (3/47 cases) the action was reported as "other", and in 4.26% (2/47 cases) Humira was permanently discontinued. The two adverse events that led to permanent discontinuation of the drug were reported as Intestinal perforation and Skin reaction. Regarding outcome of the adverse event, 91.49% was reported as resolved.

A total of 17 unexpected adverse events (not on the list of local label) in 6.29% (9/143 subjects) were reported from 143 safety evaluation subjects. These events included: aspartate aminotransferase increased which occurred in 2.10% (3/143 subjects) with 3 cases and Intestinal stenosis which was found in 1.40% (2/143 subjects) with 2 cases. Colonic haematoma, gastrointestinal inflammation, gastrointestinal necrosis, ileus paralytic, intestinal obstruction, small intestinal obstruction, appendicitis, helicobacter gastritis, C-reactive protein increased, red blood cell sedimentation rate increased, pain, and anastomotic complication were reported in 0.70% (1/143 subjects) with 1 case each. All of 17 adverse events were already reported through the Periodic Safety Update Report (PSUR) for Adalimumab. Therefore, although these unexpected adverse events are not listed per se in the local product label, it has been reported and the MAH considers them as AEs that could be expected to occur among Humira users.

The majority of the studied subjects were reported to have a clinical response both at 4 weeks and at 6 months. Due to the study design, the efficacy data from this study is of limited interest. Further, no data on clinical remission, which is the preferred primary endpoint in EU, was given.

Overall, due to the study design, the Rapporteur considers that the data on efficacy generated by the study is of limited interest, although there does not seem to be anything in this data that remarkably deviates from previous knowledge on the efficacy of Humira for the paediatric CD indication. Also the data generated by the attempts to investigate the relationship between various patient characteristics and study outcome are of limited interest due to the small study size. Regarding the overall safety data, the AEs observed in the study appear to be either events that are expected to occur in a paediatric CD population (and which are to a large extent caused by the underlying disease) or events that are expected to occur in children treated with Humira (with infections being the most obvious example). It should be noted that elevated liver enzymes is listed as a very common adverse reaction in section 4.8 of the EU SmPC. Thus, it is preliminary agreed with the applicant that no new safety issues that would warrant changes to the PI or RMP were observed, although the probability of detecting uncommon SAEs are clearly impacted by the drop in study size compared to what was originally planned. Moreover, the interpretation of safety data is hampered by the fact that sufficient data on administered dose and drug exposure was not submitted by the applicant. Finally, it is not clear whether the Korean label for Humira authorization is consistent with the EU SmPC regarding the indication (section 4.1 of the SmPC). For a final assessment of the data, the applicant is therefore requested to:

- Present the dose of Humira that the children in the study received and clarify whether this dose is consistent with the posology in the approved EU SmPC. It should also be clarified whether the Korean label is consistent with the EU SmPC regarding the indication
- Clearly summarize and present the amount of drug exposure generated by the study
- Present the P15-619 study incidence rate of adverse events, serious adverse events, infections, serious infections and injection site reaction as AEs/100 patient years. Moreover, the applicant should compare these incidence rates to the incidence rates in the development programme for paediatric CD and discuss any important differences observed.

2. Applicant's response to Rapporteur's List of Questions and the Rapporteur's assessment of the responses

Summary of the MAH response

- All 143 analyzable pediatric subjects in Study P15-619 were dosed per clinical practice following the approved Korean label. The indication and dose provided in the approved Korean label for pediatric subjects with CD is consistent with the approved EU SmPC. Three (2.10%) subjects switched from every other week to weekly dosing, and another 3 (2.10%) subjects received weekly dosing directly after induction therapy.
- Across the pediatric population in Study P15-619 (N = 143), a total of 47 adverse events (AEs) and 13 serious adverse events (SAEs) were observed, which corresponded to an overall observed rate of 32.5 events (E)/100 patient-treatment years (PTYs) and 9.0 E/100 PTYs, respectively. In addition, an overall observed rate of 2.8 E/100 PTYs, 2.1 E/100 PTYs, and 0.7 E/100 PTYs was observed for the total number of infections, serious infections, and injection site reactions, respectively.

The exposure-adjusted AE rate in Study P15-619 is lower than the rate observed in the global adalimumab pediatric CD clinical program, please refer to table below. However, it is similar to the rate observed in Study P11-292, which is a multinational long-term non-interventional registry to assess the safety and effectiveness of adalimumab in pediatric subjects with moderately to severely active CD. The exposure adjusted SAE, infection, and serious infection rates are lower in Study P15-619 than the rates observed in the global adalimumab pediatric CD clinical program and also lower than in Study P11-292. The exposure-adjusted injection site reaction rate is lower compared to the rate observed in the global adalimumab pediatric CD clinical program.

Table 2: Overall Rate per 100 PTYs in Study P15-619, Study P11-292, and the Global Adalimumab Pediatric CD Program

	Study P15-619 N = 143 Total PTYs[a] = 144.7		Study P11-292[b] N = 518 Total PTYs = 378.8		Global Adalimumab Pediatric CD Program N = 192 Total PTYs = 522.1	
	Reported Events	E/100 PTYs	Reported Events	E/100 PTYs	Reported Events	E/100 PTYs
AE	47	32.5	129	34.1	2917	558.7
SAE	13	9.0	82	21.6	165	31.6
Infection	4	2.8	30	7.9	679	130.1
Serious infection	3	2.1	17	4.5	34	6.5
Injection site reaction	1	0.7	-[c]	-[c]	104	19.9

AE = adverse event; CD = Crohn's disease; E = events; PTYs = patient-treatment years; SAE = serious adverse event.

a [Sum of (End date of treatment - Start date of treatment +1)]/365.25; not analyzed: the start date of treatment was unknown (n = 1 subject).

b Registry treatment-emergent AE was defined as any AE with an onset date on or after the first dose date in the registry and up to 70 days from the last dose date for subjects in the adalimumab arm or up to the cut-off date for the interim analysis, whichever came first. Events are shown through 31 May 2017.

c Injections site reactions are not collected during this study. Only SAEs and AEs of special interest related to infections and malignancies are reported.

The differences in the rates between the global clinical program and the post-marketing registry/post-marketing observational study (PMOS) are explained by the methodological differences of AE collection between the studies. In the global adalimumab pediatric CD clinical program (Studies M06-806 and M06-807), all AEs and SAEs were solicited or spontaneously reported and collected from the time of first study drug administration until 70 days following discontinuation of study drug. In addition, SAEs were collected from the time the subject or parent/legal guardian had signed the informed consent. In the PMOS (Study P15-619), non-serious AEs and SAEs were collected from the time the subjects or subjects' legal representatives had signed the informed consent to up to 70 days following the last administration of study drug. In the post-marketing authorization safety study (PASS registry P11-292), all SAEs and AEs of special interest are collected at each doctor's visit during the first 5 years. Starting at Year 6, SAEs and AEs of special interest related to infections and malignancies are collected through Year 10. Other than at regular doctor's visits, SAEs and AEs

of special interest, as appropriate, are collected from spontaneous reports throughout the registry.

Rapporteurs' assessment of the response and conclusion

The applicant clarified that subjects in Study P15-619 were dosed per clinical practice following the approved Korean label and that the indication and dose provided in the approved Korean label for pediatric subjects with CD is consistent with the approved EU SmPC.

The applicant presented the overall exposure from Study P15-619 as well as the incidence rate of adverse events, serious adverse events, infections, serious infections and injection site reaction as AEs/100 patient years. Moreover, the applicant compared these incidence rates to the incidence rates in the development programme for paediatric CD. It was found that the exposure-adjusted AE, SAE, infection, serious infection and injection reaction rate in Study P15-619 is lower than the rate observed in the global adalimumab pediatric CD clinical program. The applicant put forward that differences in the rates between the global clinical program and the post-marketing registry/post-marketing observational study (PMOS) are explained by the methodological differences of AE collection between the studies.

In summary, the applicant has responded satisfactory to the Rapporteur's question and no further action is required.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

Due to the study design, the Rapporteur considers that the data on efficacy generated by the study is of limited interest. Regarding the overall safety data, the AEs observed in the study appear to be either events that are expected to occur in a paediatric CD population (and which are to a large extent caused by the underlying disease) or events that are expected to occur in children treated with Humira (with infections being the most obvious example). The exposure-adjusted AE, SAE, infection, serious infection and injection reaction rate in Study P15-619 was lower than the rate observed in the global adalimumab pediatric CD clinical program. It thus is agreed with the applicant that no new safety issues that would warrant changes to the PI or RMP were observed, although the probability of detecting uncommon SAEs is clearly impacted by the drop in study size compared to what was originally planned.

Recommendation

The Rapporteur considers the requirements as:

☒ Fulfilled

No further regulatory action required.