

## 1.0 Abstract

### Title

Post-Marketing Surveillance of Humira<sup>®</sup> Injection in Korean Pediatric CD Patients under the "New-Drug Re-examination"

### Keywords

Humira<sup>®</sup>, Pediatric CD, Crohn's Disease (CD), Post-Marketing Surveillance (PMS)

### Rationale and Background

This non-interventional, observational study was conducted in compliance with the New Drug Re-examination Guideline in Korea.

### Research Question and Objectives

To evaluate the safety profile of Humira<sup>®</sup> for Pediatric 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**

### Post-Marketing Surveillance

Setting

### Selection of Study Population

Pediatric CD patients who have been prescribed Humira<sup>®</sup> by the treating physician as per Korean label were enrolled.

### Inclusion Criteria

1. Pediatric patients with Crohn's Disease who are prescribed Humira<sup>®</sup> in accordance with the Korean label for Humira<sup>®</sup> 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.

Physician referred to the product market authorization (label) for inclusion criteria.

### Exclusion Criteria

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

1. Any contraindications to Humira<sup>®</sup> as listed on the approved product market authorization (labeling)
2. Patients who is participating on other clinical trials.

Physician referred to the product market authorization (label) for exclusion criteria.

## **Subjects and Study Size, Including Dropouts**

This Post-Marketing Surveillance (PMS) was planned to recruit 600 subjects for 4 years to meet the local requirements for regulatory PMS. However, the number of subjects to be enrolled was adjusted to 141 subjects mainly because of the significantly low incidence and prevalence of Pediatric CD, and the criteria for using biologics for Pediatric CD. The study actually 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 didn't have any parameter value from effectiveness evaluation, 38 subjects didn't meet the visit window, and 1 subject both didn't have any parameter value and didn't 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 didn't have any parameter value from effectiveness evaluation, and 28 subjects didn't meet the visit window.

## **Variables and Data Sources**

### Variables

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

### **Data Sources**

Paper Case Report Form

## Results

### Subject 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 ( $\pm$  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 pediatric CD symptoms was 24.60 ( $\pm$  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<sup>®</sup>, 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 were categorized into 'before enrollment' and 'after enrollment.' 'Before enrollment' group is for the subjects who had been administered Humira<sup>®</sup> before enrollment into this study. 'After enrollment' group is for the subjects who had been administered Humira<sup>®</sup> 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 enrollment' were 30.77% (44/143 subjects), and 'after enrollment' were 69.23% (99/143 subjects). The mean of total dose of administration was 1,160.00 ( $\pm$  943.77) mg and the mean length of treatment was 52.81 ( $\pm$  45.58) weeks.

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

### Safety

The safety analysis data set includes all subjects who have received at least one administration of Humira<sup>®</sup> following the initiation of surveillance and have completed follow up for the safety information. All adverse events that occurred during the study period were reported regardless of the causal relationship with Humira<sup>®</sup>.

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. The most frequent adverse event was leukopenia which occurred in 2.80% (4/143 subjects) with 4 cases. Rash, alanine aminotransferase increased, and aspartate aminotransferase increased were found in 2.10% (3/143 subjects) with 3 cases each. 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.

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. The most frequently reported unexpected adverse drug reaction was aspartate aminotransferase increased which occurred in 1.40% (2/143 subjects) with 2 cases, ileus paralytic and appendicitis were reported in 0.70% (1/143 subjects) with 1 case each.

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira<sup>®</sup>) and the adverse events following Humira<sup>®</sup> were explored. Univariate analysis and logistic regression analysis were conducted on demographic, medical, and treatment with Humira<sup>®</sup>, 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. And there was no statistically significant difference in the incidence rate of adverse events/adverse drug reactions in other factors.

Overall, the safety of Humira<sup>®</sup> 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.

### Effectiveness

The effectiveness analyses were performed using effectiveness population including the subjects who administered Humira<sup>®</sup> for induction/maintenance therapy with the record of PCDAI (Pediatric Crohn's Disease Activity Index, PCDAI) among the safety

population. CDAI (Crohn's Disease Activity Index, CDAI) score were collected as well, if possible. 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<sup>®</sup> induction therapy and maintenance therapy was presented by the number and percentage of the subjects with clinical response.

1. *Effectiveness of Humira<sup>®</sup> Induction Therapy (at 4 Weeks)*

The mean PCDAI decrease at baseline visit and following visit was 30.09 ( $\pm$  10.79) and it showed statistically significant result (p-value < 0.0001). And the mean CDAI decrease at baseline visit and following visit was 24.38 ( $\pm$  15.46) and it was not statistically significant (n = 4). The results of the main analysis on the clinical response rate of induction therapy show 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). 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). 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<sup>®</sup>) and effectiveness results following Humira<sup>®</sup> were explored. The result of univariate analysis on demographic, medical, and treatment with Humira<sup>®</sup>, all factors were not statistically significant. Logistic regression analysis was conducted to determine the clinical response rate based on the duration of Pediatric CD symptoms and the treatment with Humira<sup>®</sup> of the subjects. As the total dose of Humira<sup>®</sup> increased by 1 mg, the odds for the clinical response rate in the subject was 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 pediatric CD, length of treatment).

## 2. *Effectiveness of Humira<sup>®</sup> Maintenance Therapy (at 6 Months)*

The mean PCDAI decrease at baseline visit and following visit was 32.81 ( $\pm$  13.55) and it showed statistically significant result (p-value < 0.0001). And the mean CDAI decrease at baseline visit and following visit was 62.98 ( $\pm$  76.78) and it was not statistically significant (n = 5). The 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). 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 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). 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<sup>®</sup>) and effectiveness results following Humira<sup>®</sup> were explored. The result of univariate analysis on demographic, medical, and treatment with Humira<sup>®</sup>, it showed statistically significant result according to start date of treatment with Humira<sup>®</sup> (p-value = 0.0238). Subjects who categorized to 'Before enrollment 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 enrollment participation,' the subjects who showed response were 95.56% (43/45 subjects) and 4.44% (2/45 subjects) showed non-response. And 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 Pediatric CD symptoms and the treatment with Humira<sup>®</sup> of the subjects. As the duration of pediatric 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). As the total dose of Humira<sup>®</sup> 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).

### **Discussion**

Based on the safety evaluations of 143 patients who received Humira<sup>®</sup> during the study period, the safety of Humira<sup>®</sup> was not remarkably different from the previously documented safety profile of the product, as described in the label and periodic safety update reports. In terms of effectiveness, the results demonstrate Humira<sup>®</sup> to be effective for pediatric CD. The safety of Humira<sup>®</sup> will continue to be monitored after the submission of this report through spontaneous reporting of adverse events and collection of safety information.

### **Marketing Authorisation Holder(s)**

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