STATISTICAL ANALYSIS PLAN

EUREKA Study

A Prospective Multi-Center study to observe the Effectiveness on Ulcerative Colitis and predictive factors of clinical response in Korean Patients treated with Adalimumab

Product Name : Adalimumab

Protocol No. : P15-346

Version : V2.0

Effective Date : 02-NOV-2018

Revisions

DATE OF REVISION	INDICATION REVISION	REASON FOR CHANGE	AUTHOR'S NAME
02-NOV-2018	ALL	Addition of 1st and 3rd quartiles to the descriptive statistics	[redacted]
	2.5.2 PP Set	Detailed modification of the PP set selection criteria	
	4.1.2 Secondary Effectiveness Evaluation	Addition of secondary effectiveness endpoints	
	6. Statistical Analysis Method	Addition of the contents of the normality test	
		Addition of p-value reporting criteria	
	6.2 Demographic Characteristics	Integration of the interim analysis items	
	6.3.2 Secondary Effectiveness Endpoints	Modification of the clinical remission criteria	
		Precise description of analysis criterion	
		Changes in analysis details	
		Addition of secondary effectiveness endpoints	
		Addition of nonparametric analysis method	
	6.4.1 Adverse Events	Changes in the manner of description and precise description of analysis items (classified into AEs causing discontinuation of the drug and SAEs that occurred during the entire study period)	
		Addition of "probably not" to the adverse drug reaction (ADR) evaluation criteria	
		Addition of incidence rate analysis (incidence rate per 100 PTYs)	
	6.4.2 Missing Data Handling and Analysis Method	Movement to item 6.7 (Missing Data Handling and Analysis Method) and addition of LOCF and mean imputation as a missing data handling method	
	6.5 Exploratory Analysis	Detailed modification of the analysis method	
		Addition of analysis items	

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1. Rationale and Background

1.1 Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by a relapsing and remitting course. In Korea, the incidence and prevalence of CD and UC are low compared to that in Europe and the USA, but are increasing rapidly. According to a recent epidemiological survey of IBD in Korea that extrapolated the national incidence from the actual measured incidence in a sample from an urban district in Seoul, the mean annual incidence of UC in Korea increased from 0.34 per 100,000 inhabitants in 1986-1990 to 3.08 per 100,000 inhabitants in 2001-2005(1). The adjusted prevalence rate of UC per 100,000 inhabitants was 30.87 (95% CI, 27.47-34.27). Genotypic features and clinical characteristics of Korean IBD are somewhat different from those seen in Western countries. For example the HLA-DRB1*1502 allele was shown to be positively associated with UC in Korea, whereas in Western populations this association is absent(2). The clinical features of UC at diagnosis are reported to be similar in Koreans and Westerners(3), however, the clinical course of UC in Korean patients seems milder than that in Western countries, as indicated by the lower rates of colectomy and better responses to pharmacological management(4). In terms of drug toxicity, Korean patients with IBD who are treated with AZA/6-MP experience myelotoxicity more frequently than similarly treated Europeans. Among 133 IBD patients treated with azathioprine in Korea, leucopenia occurred in 75 cases (56.4%), which more frequent than the rates reported in Western studies(5). In a retrospective study of infliximab in 134 Korean UC patients, the rates of clinical response and remission were 87% and 45% at week 8(6). Long-term clinical response and remission rates were 71% and 52%, respectively, and mucosal healing was the only factor influencing long-term response. Recently (2013), adalimumab was already used in the treatment of CD, was approved treating moderately to severely active UC in adults with an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. To our best knowledge, there is no published data about the effectiveness and safety of adalimumab for the treatment of UC in Korean patients. In addition, gut bacteria play an important role in the onset and perpetuation of intestinal inflammation in IBD. Some dysbiosis have been found in UC as well as Crohn's disease, and also their relationship to the clinical course of IBD has been suggested. Composition of Fecal microbiota (16S rRNA gene sequencing) will be regarded as predictive factors of clinical response in this study(7-9).

1.2 Rationale

This will be the first prospective study to evaluate the effectiveness of adalimumab in Korean patients with UC in the real-life clinical setting and to explore clinical predictive factors of response.

2. Research Methods

2.1 Study Design

This is a prospective, single-country, multi-center study in UC patients treated with adalimumab. The prescription of adalimumab is at the discretion of the physician in accordance with clinical practice and label, is made independently from this study and precedes the decision to offer the patient the opportunity to participate in this study.

Up to 147 subjects will be enrolled at approximately 20 sites. The baseline assessment should be performed prior to the first dose of adalimumab (Visit1). Patients will be given adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week on label. Study visits will be conducted at weeks 8, 16, 24, 32, 40, 48 and 56 after baseline in accordance with clinical practice (window period for each follow up visit will be ±1 week). All subjects will have one Follow-up for safety approximately 70 days after the last dose of adalimumab.

Clinical response will be assessed at week 8, and patients with clinical response at week 8 will be allowed to continue on adalimumab treatment as per Korean reimbursement guidelines and will be followed up in the study.

2.2 Study Objectives

To evaluate the real world effectiveness of adalimumab in Korean UC patients through a prospective study and explore potential predictive factors of clinical response to adalimumab treatment.

2.3 Setting

2.3.1 Study Population

Subject will be adults with UC who meet the eligibility criteria.

2.3.2 Inclusion Criteria

(1) Subject must be an adult ≥ 19 years
(2) Subject with active moderate-to-severe ulcerative colitis patients with Mayo score of ≥ 6 points and endoscopic sub-score of ≥ 2 points despite treatment with corticosteroids and/or immunosuppressants.
(3) Subject who must have tuberculosis (TB) Screening Assessment in accordance with Korean reimbursement guideline
(4) Subjects who are started on adalimumab treatment in normal clinical practice setting by their physician.
(5) Subject must provide written authorization form to use personal and/or health data prior to the entry into the study

2.3.3 Exclusion Criteria

(1) Female subjects who are pregnant or breast feeding

(2) Subjects with any contraindication to adalimumab

(3) Subjects that is participating in other clinical trials

2.4 Study Size

The primary endpoint of this study is to investigate the effectiveness of adalimumab in Korean patients with Ulcerative Colitis (UC) in real life settings. With reference to adalimumab real life data in UC, clinical response rate to adalimumab at week 12 was about 75% (10). Assuming 95% confidence interval, 15% confidence interval width and an estimated drop-out rate of 5%, we aim to recruit up to 147 subjects in this study.

2.5 Data Analysis Set

The study population will be classified by ITT (Intend-To-Treat) set and PP (Per-Protocol) set.

2.5.1 ITT Set

The ITT set will include all subjects intended to treat with adalimumab.

At week 8, all subjects who have received adalimumab treatment at least once will be included and, at week 56, all subjects who have clinical response at week 8 will be included.

2.5.2 PP Set

The PP set will include all subjects who meet the eligibility criteria for this study and complete the evaluation without any major protocol deviation among the ITT set.

At week 8, all subjects who meet the eligibility criteria and complete the evaluation at week 8 will be included and at week 56, all subjects who complete the evaluation and the study follow-up without any major protocol deviation.

2.5.3 Principles of Analysis

Demographics and safety will be analyzed by ITT set and effectiveness will be analyzed in the ITT and PP set.

3. Drop-out Subjects

Subjects who meet the below categories will be dropped out from the study.

(1) If the subjects choose to withdraw from the study

(2) Where ethical or practical conflicts hinder the procedure of the study, and such cases will be determined

based on the investigator's judgment

(3) In case of Adalimumab discontinuation at any point during study period

4. Variables

4.1 Effectiveness

If necessary, the analysis for week 24 will be performed for interim results.

4.1.1 Primary Endpoint

Clinical response at week 8, 24, and 56

4.1.2 Secondary Endpoints

(1) Clinical remission at week 8 and 56

(2) Steroid-free remission at week 8 and 56

(3) Steroid-free response at week 8 and 56

(4) Mucosal healing at week 8 and 56

(5) The change of partial Mayo score from baseline to week 56

(6) The change of full Mayo score from baseline to week 56

(7) The change of fecal calprotectin, hemoglobin, albumin, CRP, and ESR level from baseline to week 56

(8) The change of the composition of Fecal micro biota from baseline to week 56

4.2 Safety

Adverse events

5. Assessment Methods

5.1 Effectiveness Assessment

The subjects participating in this study will be followed up at weeks 8, 16, 24, 32, 40, 48, and 56 according to the clinical procedure after enrollment. (The window period of each follow-up is ±1 week.) At baseline, demographic, disease, and drug-related data will be collected. Additionally, the Mayo score will be measured along with the routine laboratory tests.

For the enrolled subjects, 160 mg will be administered at the time of enrollment, 80 mg 2 weeks after the first dose, and 40 mg biweekly thereafter, according to the Korean authorization details. At week 8, the clinical

response will be assessed. At this time, the subjects with a clinical response will be able to continue adalimumab treatment according to the Korean insurance coverage standards, and will be followed up through this study.

The clinical response is defined as 3 points or more reduction and 30% or more reduction in the full Mayo score (endoscopic findings, stool frequency, rectal bleeding, physician's global assessment) at week 8 from the baseline plus 1 point or more reduction in the rectal bleeding subscore or an absolute rectal bleeding subscore of 1 point or less.

At every follow-up visit, the partial Mayo score (stool frequency, rectal bleeding, physician's global assessment) will be measured to observe the effect of adalimumab, and routine laboratory tests will be conducted according to the routine treatment procedures.

At baseline, week 8, week 56, and when there is an inadequate response, the full Mayo score will be measured with endoscopy, which will also be conducted according to the routine treatment procedures.

5.2 Safety Assessment

An adverse event (AE) is defined as an unusual medical event that occurred in a subject, and is not necessarily causally related to the drug. Therefore, AEs are undesirable and unintended signs (including abnormal clinical test values), symptoms, or temporary illnesses, regardless of the causality with the use of the drug.

Such AEs may not only be due to unintentional or intentional overdose, drug abuse, and discontinuation of the drug but may also be caused by the use of a drug in accordance with the authorization details within the product instruction. Deterioration of the existing disease and conditions is also considered an AE.

6. Statistical Analysis Methods

All statistical analyses will be performed with the SAS software version 9.4 or higher. For all the statistical tests, two-sided tests will be conducted at the 0.05 significance level. Where applicable, an analytical method will be employed depending on whether or not to satisfy the normality assumptions.

For the continuous variables, the number of subjects, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum values will be presented. For the categorical variables, the frequency and percentage will be presented. The figures with decimal places, such as the mean, standard deviation, and percentage, will be rounded off to the second decimal place, and the p-value will be rounded off to the fourth decimal place.

When day is converted to month, it will be based on 30 days per month.

6.1 Distribution of Study Subjects

The frequencies and percentages of the number of subjects enrolled, the ITT set and the reason for exclusion therefrom, and the PP set and the reason for exclusion therefrom will be presented.

6.2 Demographic Characteristics

Descriptive statistics will be obtained for the demographic data and health status in the ITT set. For the continuous data, the mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum values will be obtained, while for the categorical data, the frequencies and percentages will be calculated.

The variables representing demographic data are as follows:

(1) Continuous Data

<Basic and Disease Information>

- Age (years)
- Onset age (years)[a]
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Disease duration (months)[b]
- Full Mayo score (endoscopic findings, stool frequency, rectal bleeding, physician's global assessment) at baseline
- Initial fecal calprotectin level
- Laboratory tests (hemoglobin (g/dl), albumin (g/dl), ESR (mm/hr), CRP (mg/dl))
- Adalimumab trough level (μg/mL)[c]
- Antibody adalimumab (μg/mL)[d]

<Medication Administration Information>

- Total administration period (days)[e]
- Total administration frequency (times)
- Total administration dose (mg)
- Period to dose escalation (days)[f]

(2) Categorical Data

<Basic and Disease Information>

- Gender (male/female)
- Age (19-29 years / 30-39 years / 40-49 years / 50-59 years / ≥60 years)
- Family history of UC (yes / no / unknown)
- UC extent (proctitis / left-sided colitis / extensive colitis / others)
- Co-morbidities (yes/no/unknown) and details[g]
- Study completion (yes/no) and reason for study discontinuation (loss of follow-up/inadequate response/ withdrawal of patient consent/others)

<Medication Administration Information>

- Previous medication for UC (yes/no/unknown) and details
  (Systemic steroids/antibiotics/non-biologics (5-ASA/methotrexate/azathioprine/6-mercaptopurine/cyclosporine/tacrolimus) / biologics[h] (1 medication / 2 medication and above) / others)
- Concomitant medication for UC (yes/no) and details[g]
  (5-ASA / methotrexate / azathioprine / 6-mercaptopurine / cyclosporine / tacrolimus / steroid (20 mg and above (daily dose) / less than 20 mg (daily dose))
- Administration status
  (First dose (80/160 mg), second dose (40mg/80mg), dose escalation (yes/no), administration frequency (2 times and below / more than 2 times), reason for discontinuation (inadequate response / adverse event / others))
- TNF antagonist naivety (yes/no)

※ The categories can be modified according to the structure and characteristics of the collected data.

[a] Onset age: The period from the date of birth to the date of diagnosis

[b] Disease duration: The period from the date of diagnosis to the date of consent of the subject

[c] Adalimumab trough level: The below the quantification limit (BQL) value of the adalimumab trough level is <0.040 μg/mL. If collected like this, it is analyzed by replacing it with 0.040 μg/mL, and the total number of replacements will be specified.

[d] Antibody adalimumab: The below the quantification limit (BQL) value of antibody adalimumab will be confirmed at the central lab after the final data collection is completed. The data at the BQL will be analyzed by replacing them with the lowest measurable value, and the total number of replacements will be specified.

[e] Total administration period: It is calculated as the period from the administration start date to the administration end date, and if administration is ongoing, the administration end date is replaced with the last visit date.

[f] Period to dose escalation: The period from the administration start date to the first dose escalation (every 1 week)

[g] The classification of the co-morbidities and concomitant medications for UC is presented with the terms classified based on the dictionary specified in the latest version of DMP. Here, the co-morbidities and concomitant medications are summarized with the system organ class (SOC) and preferred term (PT) based on the MedDRA classification. The concomitant medications for UC are summarized with anatomical therapeutic chemical 1 (ATC1) and anatomical therapeutic chemical 2 (ATC2) based on the WHODDE classification.

[h] Biologics: Single-dose infliximab or a single dose of another medication is classified as 1 medication, and if infliximab and another medication are both administered, it is classified as 2 medications and above.

6.3 Effectiveness Endpoint Analysis Method

6.3.1 Primary Effectiveness Endpoint

(1) The frequency and percentage of the subjects who showed a clinical response[a] at visit 2 (week 8) will be presented, and the 95% confidence interval will be calculated.

(2) The frequency and percentage of the subjects who showed a persistent clinical response[a] at visit 2 (week 8), visit 4 (week 24), and visit 8 (week 56) will be presented, and the 95% confidence interval will be calculated.

Here, if any item in either the full or partial Mayo score was not collected, the subject will be excluded from this analysis.

[a] Clinical response: It is defined as the case with 3 points or more reduction and 30% or more reduction in the full Mayo score at visit 2 (week 8) from visit 1 (baseline) plus 1 point or more reduction in the rectal bleeding subscore or an absolute rectal bleeding subscore of 1 point or less.

[b] Persistent clinical response: Defined as the case of 3 points or more reduction and 30% or more reduction in the full Mayo score both at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline) plus 1 point or more reduction in the rectal bleeding subscore or absolute rectal bleeding subscore of 1 point or less. At visit 4 (week 24), however, it is defined as the case of 2 points or more reduction and 30% or more reduction in the partial Mayo score plus 1 point or more reduction in the rectal bleeding subscore or an absolute rectal bleeding subscore of 1 point or less.

6.3.2 Secondary Effectiveness Endpoint

If any item in either the full or partial Mayo score was not collected, the subject will be excluded from the relevant secondary effectiveness endpoint analysis.

(1) Percentage (%) of subjects who showed clinical remission[c] at visit 2 (week 8) and who showed clinical remission[c] at visit 4 (week 24) and visit 8 (week 56) among those who showed a clinical response at visit 2 (week 8)

The frequency and percentage of subjects who showed clinical remission[c] at visit 2 (week 8) will be presented. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed clinical remission[c] at visit 4 (week 24) and visit 8 (week 56) will also be presented.

[c] Clinical remission: Defined as the case of full Mayo score ≤2 points and each subscore ≤1 point. For visit 4 (week 24), however, it is defined as the case of partial Mayo score ≤2 points and each subscore ≤1 point.

(2) Percentage (%) of subjects who showed a clinical response at visit 2 (week 8) without steroid administration[d], and who showed a clinical response at visit 4 (week 24) and visit 8 (week 56) without steroid administration[d] among those who showed a clinical response at visit 2 (week 8)

The frequency and percentage of subjects who showed a clinical response at visit 2 (week 8) without steroid administration[d] will be presented. Among these subjects, the frequency and percentage of those who showed a clinical response at visit 4 (week 24) and visit 8 (week 56) without steroid administration[d] will also be presented.

[d] Clinical response without steroid administration: Defined as the case where the subject showed a clinical response without using systemic steroids within 12 weeks before he/she was evaluated. For visit 2 (week 8), however, it is defined as the case where the subject showed a clinical response without using systemic steroids within 8 weeks before he/she was evaluated.

(3) Percentage (%) of subjects who showed clinical remission without steroid administration[d] at visit 2 (week 8), and among the subjects who showed a clinical response at visit 2 (week 8), those who showed clinical remission without steroid administration[d] at visit 4 (week 24) and visit 8 (week 56)

The frequency and percentage of subjects who showed clinical remission without steroid administration[d] at visit 2 (week 8) will be presented. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed clinical remission without steroid administration[d] at visit 4 (week 24) and visit 8 (week 56) will also be presented.

[d] Clinical remission without steroid administration: Defined as the case where the subject showed clinical remission without using systemic steroids within 12 weeks before he/she was evaluated. For visit 2 (week 8), however, it is defined as the case where the subject showed clinical remission without using systemic steroids within 8 weeks before he/she was evaluated.

(4) Percentage (%) of subjects who showed mucosal healing[e] at visit 2 (week 8), and among the subjects who showed a clinical response at visit 2 (week 8), those who showed mucosal healing[e] at visit 8 (week 56)

The frequency and percentage of subjects who showed mucosal healing[e] at visit 2 (week 8) will be presented. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed mucosal healing[e] at visit 8 (week 56) will also be presented.

[e] Mucosal healing: Defined as the case of an endoscopy subscore of 0 or 1 in the full Mayo score

(5) Changes in the partial Mayo score over time from visit 1 (baseline)

For the partial Mayo score, descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit by dividing the subjects into two groups according to the clinical response at visit 8 (week 56). T-test or Wilcoxon rank sum test will be performed to determine if there is a difference in the mean partial Mayo score depending on the clinical response.

In addition, for the difference in the change of the partial Mayo score at each visit from visit 1 (baseline), the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented for each group. Paired t-test or Wilcoxon signed rank test will be performed to determine if there is a difference in the change within the group at each visit compared to visit 1 (baseline).

(6) Changes in the full Mayo score at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the full Mayo score, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at visit 1 (baseline), visit 2 (week 8), and visit 8 (week 56) by dividing the subjects into two groups according to the clinical response at visit 8 (week 56). T-test or Wilcoxon rank sum test will be performed to determine if there is a difference in the mean full Mayo score depending on the clinical response.

In addition, for the difference in the change of the full Mayo score at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline), the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented for each group. Paired t-test or

Wilcoxon signed rank test will be performed to determine if there is a difference in the change within the group at each visit compared to visit 1 (baseline).

(7) Changes in the rectal bleeding subscore at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the rectal bleeding subscore, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at visit 1 (baseline), visit 2 (week 8), and visit 8 (week 56) by dividing the subjects into two groups according to the clinical response at visit 2 (week 8) and visit 8 (week 56). T-test or Wilcoxon rank sum test will be performed to determine if there is a difference in the mean rectal bleeding subscore depending on the clinical response.

In addition, for the difference in the change of the rectal bleeding subscore at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline), the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented for each group. Paired t-test or Wilcoxon signed rank test will be performed to determine if there is a difference in the change within the group at each visit compared to visit 1 (baseline).

(8) Mean change in the fecal calprotectin level[a] at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the fecal calprotectin level[a], the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit for the following subgroups. T-test or Wilcoxon rank sum test will be performed to determine if there is a difference between the groups within each subgroup.

- Depending on the clinical response at visit 2 (week 8)
- Depending on the clinical response at visit 8 (week 56)
- Depending on the clinical remission at visit 2 (week 8)
- Depending on the clinical remission at visit 8 (week 56)
- Depending on the mucosal healing at visit 2 (week 8)
- Depending on the mucosal healing at visit 8 (week 56)

[a] Fecal calprotectin level: The below the quantification limit (BQL) value of the fecal calprotectin level is <39.000 mg/kg, and when collected like this, it will be analyzed by replacing it with 39.000 mg/kg, and the total number of replacements will be specified.

(9) Mean change in the hemoglobin level at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the hemoglobin level, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit for the following subgroups. T-test or Wilcoxon rank sum test will be performed to determine if there is a difference between the groups within each subgroup.

- Depending on the clinical response at visit 2 (week 8)
- Depending on the clinical response at visit 8 (week 56)
- Depending on the clinical remission at visit 2 (week 8)
- Depending on the clinical remission at visit 8 (week 56)
- Depending on the mucosal healing at visit 2 (week 8)
- Depending on the mucosal healing at visit 8 (week 56)

(10) Mean change in the albumin level at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the albumin level, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit for the following subgroups. T-test or Wilcoxon rank sum test will be performed to determine if there is a difference between the groups within each subgroup.

- Depending on the clinical response at visit 2 (week 8)
- Depending on the clinical response at visit 8 (week 56)
- Depending on the clinical remission at visit 2 (week 8)
- Depending on the clinical remission at visit 8 (week 56)
- Depending on the mucosal healing at visit 2 (week 8)
- Depending on the mucosal healing at visit 8 (week 56)

(11) Mean change in the CRP level at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the CRP level, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit for the following subgroups. T-test or Wilcoxon rank sum test will be performed to determine if there is a difference between the groups within each subgroup.

- Depending on the clinical response at visit 2 (week 8)
- Depending on the clinical response at visit 8 (week 56)

- Depending on the clinical remission at visit 2 (week 8)
- Depending on the clinical remission at visit 8 (week 56)
- Depending on the mucosal healing at visit 2 (week 8)
- Depending on the mucosal healing at visit 8 (week 56)

(12) Mean change in the ESR level at visit 2 (week 8) and visit 8 (week 56) from visit 1 (baseline)

For the ESR level, the descriptive statistics (number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, maximum) will be presented at each visit for the following subgroups. T-test or Wilcoxon rank sum test will be performed to determine if there is a difference between the groups within each subgroup.

- Depending on the clinical response at visit 2 (week 8)
- Depending on the clinical response at visit 8 (week 56)
- Depending on the clinical remission at visit 2 (week 8)
- Depending on the clinical remission at visit 8 (week 56)
- Depending on the mucosal healing at visit 2 (week 8)
- Depending on the mucosal healing at visit 8 (week 56)

(13) Changes in the fecal microbial composition

The analysis of the change in the fecal microbial composition will be conducted separately at the Department of Microbiology of Chung-Ang University.

6.4 Safety Endpoint Analysis Method

6.4.1 Adverse Events (AEs)

The AE status for each of the following items is presented in a summary table. In the summary table, the number of subjects with AE, incidence rate (%), 95% confidence interval for the incidence rate, and number of events will be included.

- AEs that caused discontinuation of the study drug
- Adverse drug reactions (ADRs)[a] that caused discontinuation of the study drug
- Serious adverse events (SAEs) that caused discontinuation of the study drug
- Serious adverse drug reactions (SADRs)[a] that caused discontinuation of the study drug
- SAEs that occurred during the entire study period

For the following items, the AE status will be presented in detail. Using MedDRA, the number of subjects, incidence rate (%), 95% confidence interval for the incidence rate, and number of events will be included by SOC and PT. Here, even if two or more events occurred in one subject, if they fall under one category, they will be analyzed as one subject in the category. Also, one subject may be presented as a duplicate in different AE categories.

- AEs that caused discontinuation of the study drug
- ADRs[a] that caused discontinuation of the study drug
- SAEs that caused discontinuation of the study drug
- SADRs[a] that caused discontinuation of the study drug
- SAEs that occurred during the entire study period

For the AEs that caused discontinuation of the study drug, the number of events for the AE items below will be presented.

- Severity
- Outcome
- Causality

As for “severity” and “causality” among the AE items, the AE status will be presented in detail. Using MedDRA, the number of subjects, incidence rate (%), and number of events will be included by SOC and PT. Here, even if two or more events occurred in one subject, if they fall under one category, they will be analyzed as one subject in the category. Also, one subject may be presented as a duplicate in different AE categories.

Based on the elapsed time since the first administration of the study drug, the AE incidence rate per 100 PTYs[c] will be presented for the items below.

- AEs that caused discontinuation of the study drug
- SAEs that caused discontinuation of the study drug

For the items below, the list for each subject will be presented.

- AEs that caused discontinuation of the study drug
- ADRs[a] that caused discontinuation of the study drug
- SAEs that caused discontinuation of the study drug
- SADRs[a] that caused discontinuation of the study drug
- SAEs that occurred during the entire study period

[a] Adverse drug reaction (ADR): Adverse events with "probable," "possible," "probably not," or "not assessable" causality

[b] PTYs = Sum of the total administration period (days) of all the subjects / 365.25

[c] AE incidence rate per 100 PTY = {(Number of AEs)/(PTYs)}×100

6.5 Exploratory Analysis

(1) Logistic regression

The exploratory analysis will focus on identifying the potential predictors for the clinical effectiveness of adalimumab (persistent clinical response at weeks 8 and 56, clinical response at weeks 8 and 56, clinical remission, clinical response without steroid administration, clinical remission without steroid administration, mucosal healing, and below 250 fecal calprotectin level).

To confirm the predictors, univariate logistic regression will be performed for each factor, and then multiple logistic regressions will be performed for the significant predictors.

Here, the independent variables shown below will be considered predictors, but the variables to be used in the actual analysis can be added or subtracted considering the collected data and characteristics.

- Gender
- Onset age
- BMI
- Disease duration
- Full Mayo score
- Fecal calprotectin level
- UC extent
- CRP
- Albumin
- Trough level of adalimumab
- Concomitant medication for UC
- TNF antagonist naivety
- Dose escalation

(2) Percentage of subjects according to the fecal calprotectin level at baseline, visit 2 (week 8), and visit 8 (week 56)

The frequency and percentage of subjects with a below 250 fecal calprotectin level at baseline, visit 2

(week 8), and visit 8 (week 56) will be presented.

(3) Percentage of subjects according to the CRP level at baseline, visit 2 (week 8), and visit 8 (week 56)

The frequency and percentage of subjects with a CRP level of below 5 mg/L at baseline, visit 2 (week 8), and visit 8 (week 56) will be presented.

(4) Clinical response at each visit depending on the TNF antagonist naivety

The frequency and percentage of subjects who showed a clinical response at visit 2 (week 8) will be presented by classifying the subjects into two groups depending on the TNF antagonist naivety, and the 95% confidence interval for the result will be calculated. Additionally, the frequency and percentage of subjects who showed a persistent clinical response at visit 2 (week 8), visit 4 (week 24), and visit 8 (week 56) will be presented for each group, and the 95% confidence interval for the result will be calculated. Chi-square test or Fisher's exact test will be performed to determine if there is a difference in the clinical response rate between the two groups.

(5) Clinical remission at each visit depending on the TNF antagonist naivety

The frequency and percentage of subjects who showed clinical remission at visit 2 (week 8) will be presented by classifying the subjects into two groups depending on the TNF antagonist naivety. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed clinical remission at visit 4 (week 24) and visit 8 (week 56) will also be presented for each group. Chi-square test or Fisher's exact test will be performed to check if there is a difference in the clinical remission rate between the two groups.

(6) Clinical response without steroid administration at each visit depending on the TNF antagonist naivety

The frequency and percentage of subjects who showed a clinical response without steroid administration at visit 2 (week 8) will be presented by classifying the subjects into two groups depending on the TNF antagonist naivety. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed a clinical response without steroid administration at visit 4 (week 24) and visit 8 (week 56) will also be presented for each group. Chi-square test or Fisher's exact test will be performed to determine if there is a difference in the clinical response rate without steroid

administration between the two groups.

(7) Clinical remission without steroid administration at each visit depending on the TNF antagonist naivety

The frequency and percentage of subjects who showed clinical remission without steroid administration at visit 2 (week 8) will be presented by classifying the subjects into two groups depending on the TNF antagonist naivety. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed clinical remission without steroid administration at visit 4 (week 24) and visit 8 (week 56) will also be presented for each group. Chi-square test or Fisher's exact test will be performed to determine if there is a difference in the clinical remission rate without steroid administration between the two groups.

(8) Mucosal healing at each visit depending on the TNF antagonist naivety

The frequency and percentage of subjects who showed mucosal healing at visit 2 (week 8) will be presented by classifying the subjects into two groups depending on the TNF antagonist naivety. Among the subjects who showed a clinical response at visit 2 (week 8), the frequency and percentage of those who showed mucosal healing at visit 8 (week 56) will also be presented for each group. Chi-square test or Fisher's exact test will be performed to determine if there is a difference in the mucosal healing rate between the two groups.

6.6 Missing Data Handling and Analysis Method

If there are any missing or incomplete data, they shall be handled as shown below.

- If there is any missing value in the demographic data, it shall not be replaced and shall be analyzed as it is.
- For the Mayo score for the evaluation of the clinical response, clinical remission, and mucosal healing among the effectiveness endpoints, if a missing value occurs at a certain point, it shall be handled as shown below.
    - If a missing value occurs at the partial Mayo score (stool frequency, rectal bleeding, physician's global assessment), the most recently obtained value shall be analyzed as if it were obtained at the time (LOCF method).
    - If a missing value occurs at the endoscopic findings subscore in the full Mayo score, it shall not be replaced and shall be analyzed as it is.
- Among the continuous data used in the analysis, the data that include a sign of inequality, symbols, etc. (e.g., "over 20," ">20") shall be excluded from the analysis.

- If only some information of the date used in the continuous data analysis is present and it is therefore not computable, it shall be excluded from the analysis.
- If there is any missing value in the safety data, it shall not be replaced and shall be analyzed as it is.

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