Title Page

Title	A Prospective Multi-Center study to observe the **E**ffectiveness on **U**lcerative Colitis and predictive factors of clinical **RE**sponse in **K**orean Patients treated with **A**dalimumab (EUREKA study)
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Research Question and Objectives	To evaluate the real world effectiveness of adalimumab in Korean patients with Ulcerative Colitis (UC) and to explorepotential predictive factors of clinical response.
Country(-ies) of Study	South Korea
Author	[redacted]

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie Korea 6th Fl., Samtan Bldg. 421 YoungDong-Daero, KangNam-Gu, Seoul, Korea

1.0 Table of Contents

2.0 Abbreviations

AAA	Antibodies Against Adalimumab
AE	Adverse Event
ADR	Adverse Drug Reaction
CRA	Clinical Research Associate
CRF	Case Report Form
IBD	Inflammatory Bowel Disease
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal Anti-inflammatory drug
SAE	Serious Adverse Event
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis

3.0 Responsible Parties

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4.0 Abstract

Title:

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

Rationale and Background:

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, 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). 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 tto explore predictive factors of clinical response.

Research Question and Objectives:

To evaluate the real world effectiveness of adalimumab in Korean patients with Ulcerative Colitis (UC) and to explore potential predictive factors of clinical response to adalimumab treatment in patients with UC.

Study Design:

This is a prospective, single country, multi-center study in UC patients treated with adalimumab. 147 subjects will be enrolled at approximately 20 sites. The baseline assessment should be performed prior to the first dose of adalimimab (Visit1). Study visits will be conducted at weeks 8, 16, 24, 32, 40, 48 and 56 in accordance with clinical practice. All subjects will have one Follow-up approximately 70 days after the last dose of adalimumab.

The prescription of adalimumab is at the discretion of the physician in accordance with clinical practice and label, and is made independently from this study and precedes the decision to offer the patient the opportunity to participate in this study.

Primary Endpoint:

- Clinical response at week 8
- Clinical response at week 56 in week 8 responders

Secondary Endpoints:

- Clinical remission at week 8 and 56
- Steroid free remission at week 8 and 56
- Mucosal healing at week 8 and 56
- Change of partial Mayo score from baseline overtime
- The change of the composition of Fecal micro biota from baseline at week 56
- The mean change of Fecal calprotectin level from baseline at week 56

Population:

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

Inclusion Criteria

- Subject must be an adult ≥19 years
- 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
- Subjects must have tuberculosis (TB) Screening Assessment in accordance Korean reimbursement guideline
- Subjects who are started on adalimumab treatment in normal clinical practice setting
- Subject must provide written authorization form to use personal and/or health data prior to the entry into the study

Exclusion Criteria

- Female subjects who are pregnant or breast feeding
- Subject applies with any contraindication to adalimumab
- Subject is participating in other clinical trials

Variables:

- Demographics: Age, Gender, Co-morbidity, disease duration and extent
- UC-related medication
- Full and partial Mayo score
- Endoscopic sub-score for mucosal healing
- General lab test including CRP, albumin and hemoglobin
- Adalimumab related test: trough level and antibody level
- Stool examination: Fecal calprotectin level and Fecal microbiota (16S rRNA gene sequencing)
- Adalimumab administration

Data Source:

The investigator should maintain source documents for each subject in the study, consisting of medical records containing demographic data, and other information to be collected.

Study Size:

With reference to adalimumab real life data in UC, clinical response rate to adalimumab at week 12 was 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.

Data Analysis:

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

-ITT set: The ITT set will include all subjets intended to treat with adalimumab. At week 8, all subjects who have received adalimumab treatment at least once will be includd and at week 56, all subjects who have clinical response at week 8 wiil be included.

-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 eiligibility 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.

General Considerations

As an observational study, the study variables will be analysed and described using descriptive statistics.

Continuous variables will be described, using the mean and 95% confidence intervals For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places. If the observation value is missing value, it will be treated as a missing value in the analysis.

Baseline Characteristics including demographics

Descriptive statistics will be used to present variables regarding demographics and disease/medication related data. Continuous variables will be described with the number of patients, arithmetic mean, standard deviation, median, minimum and maximum. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places.

If the observation value is missing value, it will be treated as a missing value in the analysis. Statistical analyses will be performed using SAS V9.2 or higher.

Milestones: Start of Data Collection: 1Q 2015
End of Data Collection: 2Q 2017
Final Report of Study Results: 4Q 2017

5.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	08Mar2015	Change the collection period for SAE Pregnancy and malignancy text to be added Product complaints text added	Update	Rivese reporting date for drop out subjects and collection period for SAE Add definition of product complaint, justification for not including all AEs, collection period for pregnancy and definition of product complaint
2	26Sep2016	Sample size Reference	Amendment	Change of sample size and reference

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection:	1Q 2015
End of Data Collection:	2Q 2017
Final Report of Study Results:	4Q 2017

7.0 Rationale and Background

7.1 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].

7.2 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.

8.0 Research Question and Objectives

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

9.0 Research Methods

9.1 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. Clinical response is defined as a decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or absolute rectal bleeding sub-score of 0 or 1.

Primary Endpoint:

- The percentage of patients with clinical response at week 8

- The percentage of patients with clinical response at week 56 in week 8 responders

Clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point at week 8.

Durable clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from Baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point at both week 8 and 56.

Secondary Endpoint:

- The percentage of patients with clinical remission at week 8 and 56 (in week 8 sesponders)
  Clinical remission is defined as a total Mayo score <2 points, with no individual sub-score exceeding 1 point

- The percentage of patients with steroid-free remission at week 8 and 56 (in week 8 responders).
  Steroid free remission is defined as patients who are in remission without the use of systemic steroids within the past 12 weeks prior to assessment.

- The percentage of patients with mucosal healing at week 8 and 56 (in week 8 responders).
  Mucosal healing is defined as an endoscopy sub-score of 0 or 1. Endoscopic findings were scored on a scale from 0 to 3 as follows:
  0 = Normal or inactive disease; 1 = Mild disease (erythema, decreased vascular pattern, mild friability); 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions); 3 = Severe disease (spontaneous bleeding, ulceration).
- The change of partial Mayo score from baseline overtime

- The change of the composition of Fecal micro biota from baseline at week 56

- The mean change of Fecal calprotectin level from baseline at week 56

Exploratory data analysis:

In addition to the above secondary end-points, exploratory analysis will be conducted to identify potential predictive factors of clinical effectiveness of adalimumab. These would include age, disease duration, disease extent, ESR and CRP concentrations, level of hemoglobin, albumin level, Fecal calprotectin level, the composition of Fecal microbiota at baseline, and week 8, trough levels of adalimumab at week 8 and TNF antagonist naivety will be considered.

9.2 Setting

9.2.1 Selection of Study Population

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

Inclusion Criteria

- Subject must be an adult ≥19 years
- 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.
- Subject who must have tuberculosis (TB) Screening Assessment in accordance with Korean reimbursement guideline
- Subjects who are started on adalimumab treatment in normal clinical practice setting by their physician.
- Subject must provide written authorization form to use personal and/or health data prior to the entry into the study

Exclusion Criteria

- Female subjects who are pregnant or breast feeding

- Subjects with any contraindication to adalimumab
- Subjects that is participating in other clinical trials

9.2.2 Drop-Out Subjects

Once a subject is dropped out from the study, no further information for that subject will be collected. However, the reason for drop-out will be reported and serious adverse events will be reported to AbbVie until 70 days following the intake of the last dose of adalimumab.

Subjects 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

9.2.3 Investigator Selection Criteria

The gastroenterologist will be selected based on the following criteria:

- Those who work in hospitals that have sufficient numbers of eligible patients.
- Those who agree to devote adequate time to conduct the study in accordance with the protocol.
- Those who are trained in Good clinical practice and commit to reporting any serious adverse events in patients using an AbbVie product to AbbVie in accordance with the protocol.

9.3 Methodology

Clinical variables

Participating subjects will be followed up at week 8, 16, 24, 32, 40, 48 and 56 in

accordance with clinical practice after baseline (window period for each follow up visit will be ±1 week). Demographics, disease and medication related data will be collected at baseline. Also, general laboratory tests will be conducted and Mayo score will be calculated.

Subjects will be administered adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week per the Korean label. Clinical response will be assessed at week 8, and subjects showing 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.

Clinical response is defined as a decrease from baseline in the total Mayo score at least 3 points and at least 30% with an accompanying decrease in rectal bleeding sub-score of at least 1 point or an absolute rectal bleeding sub-score of 0 or 1.

On every follow-up visit, partial Mayo score will be measured to observe the effectiveness of adalimumab and general lab test will be carried out as per Korean clinical practice. Endoscopy will be performed and full Mayo score will be calculated at baseline, week 8, week 56 and inadequate response in accordance with Korean clinical practice.

Laboratory variables

Fecal samples

Fecal calprotectin and the composition of Fecal microbiota (16S rRNA gene sequencing) will be measured at baseline, week 8 and 56. In addition to 16S rRNA gene sequencing for microbiome analysis, stool samples will be frozen and stored in order to facilitate additional testing including metagenomic sequencing for microbiome analysis in the future.

Blood samples

Trough levels of adalimumab will be measured at week 8 and at the time of inadequate

response despite dose escalation. Antibodies against adalimumab (AAA) will be measured at inadequate response despite dose escalation. Inadequate response is defined as: (1) partial Mayo score equal to or above baseline score on 2 consecutive visits at least 14 days apart (for patients with a partial Mayo score of 4-7 at baseline); (2) partial Mayo score ≥7 on 2 consecutive visits at least 14 days apart (for patients with a partial Mayo score of 8 or 9 at baseline). In case of inadequate response, subjects will move to 40 mg every week. Unresponsive subjects to dose escalation will discontinue on their physician's judgement.

In the event of adalimumab discontinuation, the reason for discontinuation will be collected.

In the analyses of each individual predictive factors, subjects of various ages, disease duration, disease extent, ESR and CRP concentrations, level of hemoglobin, albumin level, Fecal calprotectin level and the composition of Fecal microbiota at baseline and week 8, trough levels of adalimumab at week 8 TNF antagonist naivety will be considered.

The following variables will be collected at baseline and every follow-up visit thereafter during the study period.

**Window period for each follow up visit will be ±1 week*

Baseline

1) Demographics: Age, Gender, Weight, Co-morbidity, Date of UC diagnosis, Disease duration and extent
2) UC-related medication and history of other anti -TNF experience
3) Full Mayo score including endoscopic sub-score

4) General lab test: hemoglobin, albumin , ESR and CRP

5) Stool examination: calprotectin level and the composition of Fecal microbiota

6) Adalimumab administration

Week 8 after baseline

1) Full Mayo score including endoscopic sub-score

2) General lab test: hemoglobin, albumin , ESR and CRP

3) Adalimumab related lab test: adalimumab trough level

4) Stool examination: calprotectin level and the composition of Fecal microbiota

5) Adalimumab administration schedule

Week 16, 24, 32, 40 and 48 after baseline

1) Partial Mayo score

Week 56 after baseline

1) Full Mayo score including endoscopic sub-score

2) General lab test: hemoglobin, albumin, ESR and CRP

3) Stool examination: calprotectin level and the composition of Fecal microbiota

Additional data collected

In the event of inadequate response even if dose escalation, as part of the evaluation of patients in accordance with local clinical practice, the following data may be collected:

1) Endoscopy findings

2) Trough level of adalimumab and Antibodies against adalimumab

3) The composition of fecal microbiota

9.4 Data Sources

The investigator should maintain source documents for each subject in the study, consisting of medical records containing demographic data, and other information to be collected.

Case Report Forms will be supplied by AbbVie, and used to transmit the collected information during this study to AbbVie.

Case report forms will include patient demographic information, e.g., gender, age, weight, unique patient study number, family history of UC, co-morbidity and the information to be evaluated according to the study protocol. Case report forms will maintain patient confidentiality, e.g., patient names must not be collected and full date of birth must not be collected (age is acceptable). The investigator or staff under his/her supervision must complete the case report forms, and neither AbbVie nor any agents acting on behalf of AbbVie may complete the case report forms.

9.5 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.

9.6 Data Management

Investigator should complete, sign and date the CRFs accurately. All CRFs must be legible and completed in indelible ballpoint ink. Corrections to the CRFs should be made with a single line, be initialed and dated, with the reason for changes given. Data are not to be obliterated by blacking out, correction fluid, or by erasing the original entry.

At the completion of the study, the completed signed and dated case report forms of all enrolled subjects should be provided to AbbVie by the investigator. ONLY data specified in the protocol should be collected and submitted to AbbVie.

CRAs or their designees will be responsible to review the collected case report forms for completeness and conclusiveness.

9.7 Data Analysis

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

-ITT set: The ITT set will include all subjets intended to treat with adalimumab. At week 8, all subjects who have received adalimumab treatment at least once will be includd and , at week 56, all subjects who have clinical response at week 8 wiil be included.

-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 eiligibility 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.

General Considerations

Continuous variables will be described with the number of subjects, arithmetic mean and standard deviation. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be

rounded to two decimal places. If the observation value is missing value, it will be treated as a missing value in the analysis.

Baseline Characteristics including demographics

Descriptive statistics will be used to present variables regarding demographics and disease/medication related data. Continuous variables will be described with the number of subjects, arithmetic mean and standard deviation. For categorical variables, the frequency and proportion will be presented. The values such as arithmetic mean, standard deviation, and proportion will be rounded to two decimal places.

If the observation value is missing value, NRI and LOCF will be used for a missing value. Statistical analyses will be performed using SAS V9.2 or higher.

Primary Endpoint:

- The percentage of subjects with clinical response at week 8
- The percentage of subjects with clinical response at week 56 in in week 8 responders

; The frequency and proportion of subjects with clinical response at week 8 and 56 will be presented.

Secondary Endpoints:

- The percentage of subjects with clinical remission at week 8 and 56 (in week 8 responders)

; The frequency and proportion of subjects with clinical remission at week 8 and 56 will be presented.

- The percentage of subjects with steroid-free remission at week 8 and 56 (in week 8 responders)

; The frequency and proportion of subjects with steroid-free remission at week 8 and 56 will be presented.

- The percentage of subjects with mucosal healing at week 8 and 56 (in week 8 responders)

; The frequency and proportion of subjects with mucosal healing at week 8 and 56 will be presented.

- The change of partial Mayo score from baseline overtime

; The descriptive statistics (the number of patients, mean, standard deviation, min, max) for partial Mayo score according to study visit and the change from baseline overtime will be presented.

- The change of the composition of Fecal micro biota from baseline at week 56
- The mean change of Fecal calprotectin level from baseline at week 56

9.7.1 Safety Analysis

The serious adverse event · adverse drug reaction will be coded by MedDRA latest version.

The cumulative total number and percentage of subjects reporting serious adverse event · adverse drug reaction will be tabulated. Also, AEs leading to discontinuation of adalimumab will be collected and tabulated.

9.7.2 Exploratory Analysis

In addition to the above secondary end-points, exploratory analysis will focus on identifying potential predictive factors of clinical effectiveness of adalimiumab. These would include age, disease duration, disease extent, ESR and CRP concentrations, level of hemoglobin, albumin level, Fecal calprotectin level and the composition of Fecal

microbiota at baseline and week 8 trough levels of adalimumab at week 8, TNF antagonist naivety will be considered.

9.8 Quality Control

Prior to the initiation of the study, an investigator's meeting or initiation visit will be held with AbbVie personnel or his/her designee, the investigators and their study coordinators. This meeting will include a review of the protocol and CRF completion guideline.

Investigator must assure that the study is conducted in accordance with the protocol and all relevant regulations and CRF is completed accurately.

In general, monitoring for any site is not required, but, for quality assurance, internal consistency check for completeness and consistency of data will be done to ensure the integrity of the information reported.

CRF will be reviewed by CRAs at AbbVie or their designees for completeness and conclusiveness and when necessary, query will be generated and will be resolved by the site staffs.

All data hand-entered in the database will be verified by a double-key entry procedure. Any discrepancies will be reviewed against the hard copy CRF and corrected. After completion of the entry process, computer logic checks will be run. Any necessary corrections will be made to the database and documented.

9.9 Limitations of the Research Methods

NA

9.10 Other Aspects

NA

10.0 Protection of Human Subjects

The study should receive approval from the Institutional Review Board (IRB) of the each institution, and then a written study agreement should be made with institutions before the initiation of the study in each institution.

Patient written authorization form to use and/or disclose personal and/or health data from subjects must be obtained prior to enrolling the subject and the investigator is required to document this authorization.

Subject confidentiality must be maintained at all times; therefore demographics that could identify the patients will not be collected.

Monitoring for any sites is not required. However internal consistency check for completeness and consistency of data will be done to ensure integrity of the information reported.

11.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe, pen).

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant	An event that results in a condition that substantially interferes with the activities of daily living of a study

Disability/Incapacity:	patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

11.1.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 70 days following the intake of the last dose of adalimumab taken during the study.

11.1.5 Serious Adverse Event Reporting

This protocol requires all SAEs as outlined in protocol section 11.1.1 to be actively solicited. The safety profile of adalimumab which has over 3.5 million PYs of post-marketing exposure is stable and well established; non-serious events will not be actively solicited as these events are not likely to contribute to the further understanding of the safety profile of the product. Any non-serious AEs will be collected as spontaneous reports if AbbVie is notified.

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not,

the physician will notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.

AbbVie Safety Korea

[redacted]

11.1.6 Pregnancy Reporting

Pregnancies in patients will be collected from the date of the first dose through 150 days following the last dose of adalimumab taken during the study. In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 11.1.5 within 24 hours of the physician becoming aware of the pregnancy.

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint (see Section 11.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

11.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product and/or device should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

12.0 Plans for Disseminating and Communicating Study Results

At the end of the study, a study report will be written by AbbVie in collaboration with the principal investigator. This report will contain a description of the objectives of the

study, the methodology of the study and its results and conclusions. The completed case report forms and the study report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this study may be published by AbbVie or by any one of the participating investigators after agreement with AbbVie.

13.0 References

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