Non-Interventional Study Protocol

B5371008

Infliximab BS for I.V. Infusion 100 mg [Pfizer]

General Investigation

(Crohn's Disease and Ulcerative Colitis)

Statistical Analysis Plan

Version: 4.0

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Date: 19-MAY-2023

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1. Revisions from Previous Version

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 11-JAN-2019 PPD	Original version
2.0 08-JUL-2020 PPD	Status of investigation: Ongoing The contents of the study report were reviewed based on the objective of the study, and planned tabulations and analyses were added or deleted. The changed sections are shown below. -5.4. Subgroups -6.2.2.1. Ulcerative Colitis Patient Rating Scales (Mayo Score and Partial Mayo Score) -8.2.1. Overview of Patients -8.2.2. Patient Demographics and Treatment History -8.2.3. Safety Analysis -8.2.4. Efficacy Analysis -9. Listings Other description adjustments were made.
3.0 26-MAY-2021 PPD	Status of investigation: Ongoing -5.4. Subgroups The definition of the category of “yes” for prior infliximab use was changed from 8 weeks to 9 weeks in consideration of the difference between scheduled and actual visit dates. -8.2.2. Patient Demographics and Treatment History The tabulation of frequency of dosing and summary statistics was added to the status of administration of this drug. Other description adjustments were made.
4.0 19-MAY-2023 PPD	Status of investigation: Ongoing -5.3. Other Analysis Populations The safety and efficacy analysis sets in the population that gave consent to dissemination/publication, etc. of study results were added. -8.2. Statistical Analyses A description to perform the same analyses for the consented populations (safety and efficacy) was added. -8.2.1. Overview of Patients A list of patients excluded from analyses was added. -8.2.3.2. Adverse Events This section was added to add the Basic Results form. -9. Listings The list of administration status was deleted because the administration status can be checked in the patient listing.

2. Introduction

This statistical analysis plan describes a statistical analysis plan for the general investigation of Infliximab BS for I.V. Infusion 100 mg [Pfizer] (generic name, Infliximab [Genetical Recombination] [Infliximab Biosimilar 3]) (hereinafter referred to as this drug). In this plan document, sentences cited from the protocol are shown in *italics*.

2.1. Study Design

This study is a multicenter cohort study to be conducted in Crohn's disease patients and ulcerative colitis patients treated with this drug. The study method is an all-case investigation not only in patients who used this drug at contract sites after the date of approval, but also those who used this drug before the conclusion of contract with contract sites (including retrospective patients). The observation period will be 30 weeks from the start date of treatment with this drug (Day 1) (the 30-week period is defined as the period up to Day 217 to account for the difference between scheduled and actual visit dates that occurs in routine clinical practice). In this study, information will be collected from the last dose during the observation period to the date of visit immediately after 8 weeks have passed (the date of completion of the study). Adverse events of special interest include serious infections (pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection, etc.), tuberculosis, delayed type hypersensitivity, serious blood disorders, lupus-like syndrome with seroconversion of anti-dsDNA antibodies, demyelinating disorders, hepatic impairment, serious infusion reactions, interstitial pneumonia, rhabdomyolysis, reactivation of hepatitis B, antibody formation, stenosis intestinal/stenosis/obstruction (Crohn's disease), malignancies, and development of infections due to vaccination with live vaccines in children.

Target sample size is to be 300 subjects for safety analysis set (Of these, at least 100 each should be those with Crohn's disease or ulcerative colitis.). The rationale for the target sample size is shown below.

<Rationale for the target sample size>

The data collected from 300 subjects to whom this drug is administered should enable to detect and verify, with a probability of 95%, at least 1 subject in whom each adverse event with an incidence of 1% or more occurs.

The incidences of infusion reaction, hypersensitivity, and hepatic impairment are expected to be higher than those of other events based on the results of clinical studies. Assuming that the incidences of infusion reaction, hypersensitivity, and hepatic impairment in drug use investigations are 5%, 10%, and 5%, respectively, the probability that accumulation of 300 patients allows collection of each event in 10 or more patients is approximately 94% or more for each event.

The frequencies of serious infusion reaction and delayed-type hypersensitivity are presumed to be low because serious infusion reaction was observed in 1 patient but delayed-type hypersensitivity was not observed in a global phase 3 study of this drug. Therefore, in this study, information on the occurrence of infusion reaction and hypersensitivity will be widely collected to tabulate their incidences and perform factorial analyses, and these events will also be evaluated from the standpoints of seriousness and whether they were treated.

The target sample size of at least 100 patients each with Crohn's disease or ulcerative colitis for a total of 300 patients was selected taking the feasibility of patient registration into consideration in view of the number of patients in actual clinical practice.

2.2. Study Objective

To collect information on the safety and efficacy of this drug against Crohn's disease or ulcerative colitis under actual status of use.

3. Interim and Final Analyses

In this study, interim analyses for the evaluation report on the Risk Management Plan will be performed periodically. Among the statistical analyses specified in this plan, only those items necessary for the evaluation report on the Risk Management Plan will be analyzed at the time of interim analysis. In addition, the final analysis will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. Hypothesis and Decision Rules

4.1. Statistical Hypothesis

Since this study is not a confirmatory study, tests will be positioned as exploratory tests. The p-value of the test result will be evaluated as a descriptive statistic. The significance level will not be specified, but a threshold may be set post-hoc for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable.

5. Analysis Sets

5.1. Safety Analysis Set

The safety analysis set will be the full analysis set that is as close as possible to all patients who received this drug. More specifically, the safety analysis set is defined as the population of registered or reported patients excluding those who meet any of the following conditions:

a. The case report form could not be collected at all (description in the report: "case report form not collected").

b. There was a violation or deficiency in the contract (description in the report: "contract violation/deficiency").

c. There was a violation in registration (description in the report: "registration violation").

d. Administration of the study drug was not reported at all (description in the report: "no administration information").

e. Information on adverse events was not reported at all - no visits after the first prescription day (description in the report: "No adverse event information - no re-visits").

f. Information on adverse events was not reported at all - there was a visit after the first prescription day but no description (description in the report: "no adverse event information - no description").

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as the population of patients in the safety analysis set excluding those who meet any of the following conditions:

g. Efficacy evaluation was not reported at all (description in the report: “no efficacy information”).

h. Disease not subject to the study (description in the report: “disease not subject to the study”).

For details of each criterion, the latest "Guidance on Criteria for Inclusion in Analysis Sets and Handling of Data in Drug Use Investigations" should be followed.

5.3. Other Analysis Sets

5.3.1. Consented Population (Safety)

The consented population (safety) is defined as the population of patients in the safety analysis set who have given consent to the dissemination and publication of study results.

5.3.2. Consented Population (Efficacy)

The consented population (efficacy) is defined as the population of patients in the efficacy analysis set who have given consent to the dissemination and publication of study results.

5.4. Subgroups

Subgroup analyses of safety will be performed for the following patient demographics:

- Target disease [Crohn's disease, ulcerative colitis]
- Prior infliximab use [no, yes, (original product, biosimilar products, other)][a]

Patients who may be contraindicated according to the package insert of this drug (hereinafter referred to as contraindicated patients) will be extracted based on separately specified criteria, and a subgroup analysis of safety will be performed.

a：Patients with prior infliximab use will be further tabulated for the following 3 types: the original bio-pharmaceutical of this drug (original product) used within 9 weeks before the date of initial administration of this drug, biosimilar products other than this drug (biosimilar products), and patients with prior infliximab use but not within 9 weeks (other).

Subgroup analysis of efficacy will be performed for the following patient demographic:

- Prior infliximab use [no, yes, (original product, biosimilar products, other)]

6. Endpoints and Covariates

6.1. Safety Endpoints

In this study, the investigator's judgment will be used to evaluate the seriousness and causal relationship with adverse events.

- Adverse drug reactions: Adverse events assessed as related
- Adverse events: All-causality adverse events
- Serious adverse events or adverse drug reactions: Adverse events or adverse drug reactions assessed as serious.
- Adverse events of special interest:
  - Serious infections (pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection, etc.)
  - Tuberculosis
  - Delayed type hypersensitivity
  - Serious blood disorder
  - Lupus-like syndrome with seroconversion of anti-dsDNA antibodies
  - Demyelinating disorders
  - Hepatic impairment
  - Serious infusion reactions
  - Interstitial pneumonia
  - Rhabdomyolysis
  - Reactivation of hepatitis B
  - Antibody formation
  - Stenosis intestinal/stenosis/obstruction (Crohn's disease)
  - Malignancies
  - Development of infections due to vaccination with live vaccines in children

Events to be handled as adverse events of special interest will be separately specified.

6.2. Efficacy Endpoints

Efficacy endpoints are presented by target disease (Crohn's disease and ulcerative colitis).

6.2.1. Crohn's Disease

6.2.1.1. Crohn's Disease Assessment Scale (CDAI score)

The Crohn's Disease Activity Index (CDAI) score will be the total score as assessed by the investigator at each evaluation time point.

- **CDAI remission and response**

A CDAI score of < 150 will be considered CDAI remission.[1] CDAI response[1] is defined as a decrease of ≥ 25% and ≥ 70 points in CDAI score after treatment with this drug compared with the CDAI score before treatment.

6.2.1.2. Endoscopic findings in patients with Crohn's disease (SES-CD)

Endoscopic findings in patients with Crohn's disease will be evaluated according to the evaluation items of Simple Endoscopic Score for Crohn's disease (SES-CD) for each sit e to be checked.

For each of the 5 sites to be checked (ileum, right colon, transverse colon, left colon, and rectum), endoscopic findings (size of ulcer surface [0 to 3 points], area of ulcer [0 to 3 points], area of lesion [0 to 3 points], and presence of stenosis [0 to 3 points]) will be individually scored according to the following criteria, and the total thereof will be defined as SES-CD score.[2] The SES-CD score ranges from 0 to 56. The sites of confirmation and criteria for endoscopic findings are shown below.

Sites to be checked: Ileum, right colon, transverse colon, left colon, and rectum

Endoscopic findings:

a. *Size of ulcer surface (0, none; 1, aphthous ulcer [0.1 to 0.5 cm]; 2, large ulcer [0.5 to 2 cm]; 3, very large ulcer [> 2 cm])*
b. *Area of ulcer (0, none; 1, < 10%; 2, 10% to 30%; 3, > 30%)*
c. *Area of lesion (0, none; 1, < 50%; 2, 50% to 75%; 3, > 75%)*
d. *Presence of stenosis (0, none; 1, 1 site, passable; 2, multiple sites, passable; 3, not passable)*

6.2.1.3. Efficacy Laboratory Measurements

CRP and fecal calprotectin will be used as laboratory findings for efficacy in Crohn's disease.

6.2.2. Ulcerative Colitis

6.2.2.1. Ulcerative Colitis Patient Rating Scales (Mayo Score and Partial Mayo Score)

The Mayo score[3] consists of 4 domains, each scored as a 0- to 3-point subscore, with higher scores indicating more severe disease activity. The 4 domains are the number of bowel movements subscore (0 to 3), rectal bleeding subscore (0 to 3), endoscopic finding subscore (0 to 3), and physician's global assessment subscore (0 to 3).

The method of calculating the Mayo score[3] is the sum of all subscores in the 4 domains, with a range of 0 to 12 points. The partial Mayo score is the sum of the subscores for the 3 domains excluding endoscopy, with a range of 0 to 9 points.

The 4 domains and scores are shown below.

- *Number of bowel movements[*1] :*

  0 = comparable to the number of bowel movements per day in a normal state
  1 = larger than the number of bowel movements per day in a normal state by 1 to 2
  2 = larger than the number of bowel movements per day in a normal state by 3 to 4
  3 = larger than the number of bowel movements per day in a normal state by 5 or more

- *Rectal bleeding[*2] :*

  0 = no blood
  1 = small amount of blood, equal to or less than a half of the number of bowel movements
  2 = evident blood, essentially every time
  3 = essentially blood only

- *Endoscopic finding:*

  0 = normal or remission phase
  1 = mild (redness, decrease in visible vascular pattern, mild vulnerability)
  2 = moderate (marked redness, disappearance of visible vascular pattern, vulnerability, erosion)
  3 = severe (spontaneous bleeding, ulcer)

- *Physician's global assessment[*3] :*

  0 = normal
  1 = mild
  2 = moderate
  3 = severe

*[*1] : Each patient serves as a control for the patient to assess the level of abnormality in the number of bowel movements. The number of bowel movements in a normal state is defined as the number of bowel movements in a state without relapse.*
*[*2] : The bleeding score on each day represents the severest bleeding on the day.*

*[*3] : Physician's global assessment is made taking into consideration other 3 criteria, patient's abdominal discomfort, overall physical condition and physical findings, and patient's general condition.*

- **Mayo score**

Disease activity based on the Mayo score at each evaluation time point will be classified according to the following table.

Mayo Score Disease Activity Classification

Score	Disease Activity
0 - 2	remission (provided that no subscore for each single parameter is greater than 1)
3 - 5	mild activity
6 – 10	moderate activity
> 10	severe activity
Reference: https://www.igibdscores.it/en/info-mayo-full.html (accessed date: 08-Jul-2020)	

- **Mayo score remission, mucosal healing, and Mayo score response**

Mayo score remission, mucosal healing, and Mayo score response will be determined in patients with a calculated Mayo score. The criteria for Mayo score remission, mucosal healing, and Mayo score response[4] are shown below.

Criteria for Mayo Score Remission, Mucosal Healing, and Mayo Score Response

Item	Criteria
Remission	Mayo score ≤ 2 with no individual subscore of > 1
Mucosal healing	Endoscopy finding subscore of ≤ 1
Response	When the following 2 conditions are met: • Reduction in Mayo score by ≥ 30% and ≥ 3 points reduction from baseline • Reduction in the rectal bleeding subscore of ≥ 1 from baseline or a rectal bleeding subscore of ≤ 1

- **Partial Mayo score**

Disease activity based on the partial Mayo score at each evaluation time point will be classified according to the following table.

Partial Mayo Score Disease Activity Classification

Score	Disease Activity
< 2	remission
2 - 4	mild activity
5-7	moderate activity
> 7	severe activity
Reference: https://www.igibdscores.it/en/score-mayo-partial.html (accessed date: 08-Jul-2020)	

- **Partial Mayo score remission and partial Mayo score response**

The criteria for partial Mayo score remission and partial Mayo score response are shown for patients with a calculated partial Mayo score.

Criteria for Partial Mayo Score Remission and Partial Mayo Score Response

Item	Criteria
Remission	Partial Mayo score of < 2
Response	≥ 2-point reduction from baseline

6.2.2.2. Efficacy Laboratory Measurements

CRP and fecal calprotectin will be used as laboratory findings for efficacy in ulcerative colitis.

6.3. Other Endpoints

Not applicable.

6.4. Covariates

There are no covariates identified from clinical study data to date or potential covariates for the safety and efficacy of this drug.

7. Handling of Missing Data

If the seriousness, actions taken, and outcome of adverse events are missing, they will be handled as "unknown" in tabulation. If the causal relationship with an adverse event is missing, it will be handled as "related " in tabulation.

The policy for handling uncleaned data is described below.

- Items with missing data: The data will be handled as missing (category of classification variable is "unknown") in both tabulation and listing.

- Items with inconsistent data: The inconsistent portion will be handled as missing in both tabulation and listing. However, a list of data handling will be prepared separately.

- No signature: Data entered in the case report form without the signature of contracting investigator (including those signed only by physicians other than contracting investigator) will be handled as missing in both tabulation and listing.

8. Statistical Methods and Analysis

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, maximum, and minimum) will be calculated.

8.1.2. Analysis of Categorical Data

The frequency (e.g., number of patients) and proportion of each category will be calculated.

8.1.3. Analysis of Binary Data

Frequency and its proportion will be calculated. If the confidence interval of proportion is calculated, a two-sided 95% confidence interval (exact method) will be calculated.

8.2. Statistical Analysis

Unless otherwise specified, analyses in the safety analysis set and the efficacy analysis set will also be performed on the consented population (safety) and the consented population (efficacy).

8.2.1. Overview of Patients

- **Patient composition**

The number of registered patients, patients who completed the study, patients included in the safety analysis set, and patients included in the efficacy analysis set will be tabulated for registered patients. In addition, the number of patients excluded from the safety and efficacy analysis sets and the number of patients by reason for exclusion will be tabulated.

- **Status of discontinuation/withdrawal**

In the safety analysis set, the number and proportion of patients will be calculated by presence/absence of continued administration of this drug (yes [continued patients]/no [discontinued patients]) on the date of completion of the study. In addition, the number of patients by reason for discontinuation will be tabulated for patients without continued administration.

- **List of patients excluded from the analysis set**

Lists of reasons for exclusion of patients excluded from the safety and efficacy analysis set will be prepared.

8.2.2. Patient Demographics and Treatment History

- **Patient demographics**

In the safety analysis set and efficacy analysis set, the following patient demographics will be tabulated for the overall population and by Crohn's disease and ulcerative colitis in accordance with Section 8.1:

Overall:

- Sex [male, female]
- Age (continuous)
- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Children [infants (< 1 year), toddlers (≥ 1 to < 7 years), and children (≥ 7 to < 15 years)]
- Body weight (continuous)
- BMI (continuous)
- BMI [< 18.5, ≥ 18.5 to < 25, ≥ 25, unknown]
- Target disease [Crohn's disease, ulcerative colitis, other]
- Hepatic impairment [no, yes]
- Severity of hepatic impairment [mild, moderate, severe, severity unknown]
- Renal impairment[a] [no, yes]
- Tuberculosis test [implemented, not implemented]
- Tuberculosis test results [negative, positive, pending, indeterminate]
- Hepatitis virus test [implemented, not implemented]
- Hepatitis virus test results [negative, positive]
- Smoking history [non-smoker, smoker, former smoker, unknown]
- Family history of malignancies (including lymphoma) [no, yes, unknown]
- Medical history [no, yes]
- Complications [no, yes]
- Medical history: Allergic disease [no, yes]
- Complications: Allergic disease [no, yes]
- Prior infliximab use [no, yes, (original product, biosimilar products, other)]

Crohn's disease:

- Sex [male, female]
- Age (continuous)
- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Children [infants (< 1 year), toddlers (≥ 1 to < 7 years), and children (≥ 7 to < 15 years)]

a: It will be determined in accordance with "Appendix: Procedure for Extracting Patients with Hepatic/Renal Impairment in Post-Marketing Surveillance."

- Body weight (continuous)
- BMI (continuous)
- BMI [< 18.5, ≥ 18.5 to < 25, ≥ 25, unknown]
- Duration of disease (continuous)
- Current state [initial onset, relapse]
- (In the case of relapse) Number of relapses in the past year (continuous)
- Number of days from current relapse (continuous)
- Range of lesion [small intestine type, small intestine and large intestine type, large intestine type, special type]
- Disease stage [active phase, remission phase]
- Severity [mild, moderate, severe]
- External fistula [no, yes]
- Hepatic impairment [no, yes]
- Severity of hepatic impairment [mild, moderate, severe, severity unknown]
- Renal impairment [no, yes]
- Tuberculosis test [implemented, not implemented]
- Tuberculosis test results [negative, positive, pending, indeterminate]
- Hepatitis virus test [implemented, not implemented]
- Hepatitis virus test results [negative, positive]
- Smoking history [non-smoker, smoker, former smoker, unknown]
- Family history of malignancies (including lymphoma) [no, yes, unknown]
- Medical history [no, yes]
- Complications [no, yes]
- Medical history: Allergic disease [no, yes]
- Complications: Allergic disease [no, yes]
- Prior infliximab use [no, yes, (original product, biosimilar products, other)]

Ulcerative colitis:

- Sex [male, female]
- Age (continuous)
- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Children [infants (< 1 year), toddlers (≥ 1 to < 7 years), and children (≥ 7 to < 15 years)]
- Body weight (continuous)
- BMI (continuous)
- BMI [< 18.5, ≥ 18.5 to < 25, ≥ 25, unknown]
- Duration of disease (continuous)
- Current state [initial onset, relapse]
- (In the case of relapse) Number of relapses in the past year (continuous)
- Number of days from current relapse (continuous)
- Range of lesion [pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]
- Disease stage [active phase, remission phase]
- Severity [mild, moderate, severe]

- Hepatic impairment [no, yes]
- Severity of hepatic impairment [mild, moderate, severe, severity unknown]
- Renal impairment [no, yes]
- Tuberculosis test [implemented, not implemented]
- Tuberculosis test results [negative, positive, pending, indeterminate]
- Hepatitis virus test [implemented, not implemented]
- Hepatitis virus test results [negative, positive]
- Smoking history [non-smoker, smoker, former smoker, unknown]
- Family history of malignancies (including lymphoma) [no, yes, unknown]
- Medical history [no, yes]
- Complications [no, yes]
- Medical history: Allergic disease [no, yes]
- Complications: Allergic disease [no, yes]
- Prior infliximab use [no, yes, (original product, biosimilar products, other)]

The number and proportion of patients for the following will be tabulated by system organ class (SOC) and preferred term (PT) for the overall population and by Crohn's disease and ulcerative colitis in the safety analysis set:

- Breakdown of medical history
- Breakdown of complications

The number and proportion of patients for the following will be tabulated for the overall population and by Crohn's disease and ulcerative colitis in the safety and efficacy analysis sets:

- Breakdown of concomitant medications
- Breakdown of non-drug concomitant therapies
- Breakdown of prior medications

- **Pregnancy status**

For women included in the safety analysis set, the number of patients will be calculated by pregnancy status.

- **Status of administration of this drug**

In the safety analysis set, the status of administration of this drug will be tabulated as follows for the overall population and by Crohn's disease and ulcerative colitis:

- Duration of treatment (days, continuous)
- Number of doses (1,2, 3, 4, 5, 6, 7, ≥ 8)
- Number of doses (times, continuous)
- Initial single dose (mg/kg) [< 5, 5, > 5 to < 10, 10, > 10]
- Initial single dose (mg/kg, continuous)
- Maximum single dose (mg/kg, continuous)

The following status of administration of this drug in patients with Crohn's disease in the safety analysis set will be tabulated:

- Dose increase and shortening of treatment duration [neither, only dose increase, only shortening, both]

The duration of treatment will be from the day of initial dose to the last confirmed day of treatment in this study, including treatment-free interval.

- **Number of days to the completion of the study**

The number of days to the study completion date will be tabulated for the overall population and by Crohn's disease and ulcerative colitis in the safety analysis set.

- Number of days to the completion of the study (continuous)
- Number of days to the completion of the study [< 30 weeks (210 days), ≥ 30 weeks (210 days)]

The study period will be from the date of commencement of treatment with this drug to the date of completion of the study.

8.2.3. Safety Analysis

Adverse drug reactions and adverse events that occur between the start date of treatment with this drug (Day 1) and Week 30 (Day 217) will be tabulated. For patients who discontinued the study before Week 30, data up to and during the observation period (the date of visit immediately after 8 weeks from the date of the last dose during the observation period [the date of completion of the study]) will be used. If the observation period exceeds 217 days, data up to 217 days will be used for tabulation. Listings will include all events reported in this study.

8.2.3.1. Adverse Drug Reactions

- **All adverse drug reactions**

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT. The same tabulation will be made by Crohn's disease and ulcerative colitis.

- **Serious adverse drug reactions**

The number and proportion of patients with serious adverse drug reactions will be tabulated by SOC and PT. The same tabulation will be made by Crohn's disease and ulcerative colitis.

- **Details of adverse drug reactions**

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT for each of the following:

- Seriousness [serious, non-serious]

- Treatment [discontinuation, temporary suspension or dose reduction]
- Outcome [fatal, not recovered, recovered with sequelae, recovering, disappeared, recovered, unknown]

If the same adverse drug reaction (with the same PT) occurs more than once in the same patient, it will be handled as follows in the tabulation of the number of patients with events:

- Seriousness: If both serious and non-serious events are reported, it will be serious.
- Number of days to onset: It should be the number of days to the first event.
- Action taken: If multiple types of actions were taken, 1 type will be adopted in the following order of priority: discontinuation, temporary suspension, dose reduction, dose increase, and none.
- Outcome: It should be the outcome of the last event.

- **Adverse events of special interest**

The number and proportion of patients with adverse events of special interest will be tabulated by SOC and PT.

Infusion reaction and hypersensitivity that occur within 2 hours after treatment with this drug will also be tabulated in the same manner.

8.2.3.2. Adverse Events

- **Serious adverse events**

The number and proportion of patients with serious adverse events will be tabulated by SOC and PT.

- **Non-serious adverse events**

The number and proportion of patients with non-serious adverse events will be tabulated by SOC and PT. In this tabulation, a threshold for incidence will be set as necessary, and only events with an incidence of at least the threshold will be tabulated.

8.2.3.3. Other Endpoints

Not applicable.

8.2.3.4. Subgroup Analysis

The number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT for each factor specified in Section 5.4.

A list of adverse drug reactions will be prepared for contraindicated patients. In addition, the number and proportion of patients with adverse drug reactions will be tabulated by SOC and PT as necessary.

8.2.3.5. Exploratory Analysis

Additional analyses may be performed as necessary. Exploratory analyses will be reported only when results that provide important interpretation are obtained.

8.2.4. Efficacy Analysis

8.2.4.1. Efficacy in Patients with Crohn's Disease

8.2.4.1.1. CDAI Score

In patients with Crohn's disease in the efficacy analysis set who have the CDAI score both at baseline and on the date of completion of the study, summary statistics of the CDAI score at baseline and on the date of completion of the study will be calculated. Summary statistics will also be calculated for the change in CDAI score from baseline to the date of completion of the study.

In patients with Crohn's disease in the efficacy analysis set who have the CDAI score both at baseline and on the date of completion of the study, the number and proportion of patients with CDAI response on the date of completion of the study will be calculated as the CDAI response rate with the 95% confidence interval. In addition, the number and proportion of patients with CDAI remission at baseline and on the day of completion of the study will be calculated as the CDAI remission rate with the 95% confidence interval.

8.2.4.2. Efficacy in Patients with Ulcerative Colitis

8.2.4.2.1. Partial Mayo Score

In patients with ulcerative colitis in the efficacy analysis set who have the partial Mayo score both at baseline and on the date of completion of the study, summary statistics of the partial Mayo score at baseline and on the date of completion of the study will be calculated. Summary statistics will also be calculated for the change in partial Mayo score from baseline to the date of completion of the study.

Changes in disease activity based on the partial Mayo score at baseline and on the date of completion of the study will be derived, and the number and proportion of patients in remission will be calculated as the partial Mayo remission rate with the 95% confidence interval. In addition, the proportion of patients with response after treatment will be calculated as a response rate with the 95% confidence interval.

8.2.4.2.2. Mayo Score

In patients with ulcerative colitis in the efficacy analysis set who have the Mayo score both at baseline and on the date of completion of the study, summary statistics of the Mayo score at baseline and on the date of completion of the study will be calculated. Summary statistics will also be calculated for the change in Mayo score from baseline to the date of completion of the study.

8.2.4.3. Subgroup Analysis

For Crohn's disease, summary statistics will be calculated for the CDAI score at baseline and on the date of completion of the study by factor specified in Section 5.4. Summary statistics of the change in CDAI score from baseline to the date of completion of the study will be calculated by factor specified in Section 5.4. Subgroup analyses will also be performed for CDAI response and remission rates.

For colitis ulcerative, summary statistics of the partial Mayo score at baseline and on the date of completion of the study will be calculated by factor specified in Section 5.4. In addition, summary statistics of the change in partial Mayo score from baseline to the date of completion of the study will be calculated by factor specified in Section 5.4. Subgroup analyses will also be performed for partial Mayo score remission and response rates.

8.2.4.4. Exploratory Analysis

Additional analyses may be performed as necessary. Exploratory analyses will be reported only when results that provide important interpretation are obtained.

9. Listings

The following listings will be prepared:

- Listing of patients
- Listing of patients with adverse drug reactions
- Listing of contraindicated patients with adverse drug reactions
- Listing of patients with serious adverse drug reactions
- Listing of patients with adverse drug reactions among adverse events of special interest
- Listing of patients evaluated for efficacy (to be prepared by Crohn's disease and ulcerative colitis)
- Patient listing of diagnostic imaging, and KL-6 and β-D-glucan

In addition, the following table corresponding to the appendix form of the evaluation report on the Risk Management Plan will be prepared:

- Appendix Form 3 (Occurrences of Adverse Drug Reactions/Infections in Post-Marketing Surveillance, etc.)

10. References

1. REMICADE for I.V. Infusion 100 Reexamination Report (Crohn's Disease). 26-DEC-2014; 9

2. Daperno M, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc*. 2004; 60(4): 505-512

3. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. *N Engl J Med* 1987; 317: 1625-1629

4. REMICADE for I.V. Infusion 100 Review Report (1) (Ulcerative Colitis). 16-APR-2010; 10