Non-Interventional Study Protocol
B5371006

Infliximab BS for Intravenous Drip Infusion 100 mg
"Pfizer"
General investigation
(Rheumatoid Arthritis)

Statistical Analysis Plan

Version: 4.0

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 20-Dec-2018 PPD	First version
2.0 07-Jul-2020 PPD	Status of study: Ongoing Based on the objective, etc. of this study, the contents of the study report were examined to add or delete planned tabulations and analyses. The changes are shown below: - 5.4. Subgroups - 8.2.1. Overview of patients - 8.2.2. Patient characteristics and history of treatment - 8.2.3. Safety analysis - 8.2.4. Efficacy analysis - 9. LISTINGS In addition, modifications to the descriptions/wording were made.
3.0 26-May-2021 PPD	Status of study: Ongoing - 5.4. Subgroups The definition of the period to be reviewed for checking presence/absence of past use of infliximab preparations was changed from within 8 weeks to within 9 weeks in consideration for allowance in visit days. - 8.2.2. Patient characteristics and history of treatment To “Administration status of this drug,” tabulations of dosing frequency and summary statistics were added. In addition, modifications to the descriptions/wording were made.
4.0 25-MAY-2023 PPD	Status of study: Ongoing - 5.3. Other Analysis Sets The safety and efficacy analysis sets in the set consisting of consented patients for the dissemination and publication of study results were added. - 8.2. Statistical Analysis The description that the same analyses will also be performed on the set consisting of consented patients (safety and efficacy) was added. - 8.2.1. Overview of patients “Listing of patients excluded from the analysis” was added. - 8.2.3.2. Adverse events This section was added because of addition of the Basic Results form. - 9. LISTINGS “A listing of administration status” was deleted because the administration status can be confirmed in the listing of patients.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the general investigation of Infliximab BS for Intravenous Drip Infusion 100 mg “Pfizer” (generic name, infliximab [genetical recombination] [infliximab biosimilar 3]) (hereinafter referred to as this drug). In this document, texts cited from the protocol of the general investigation are indicated in *italics*.

2.1. Study Design

This study is a multi-center cohort study of patients with rheumatoid arthritis receiving this drug. The observation period is 30 weeks from the day of initial dose of this drug (Day 1) (The period of 30 weeks is defined as up to Day 217 in consideration for allowance in visit days that occur in daily medical practice.). Information up to the day of visit immediately after 8 weeks have elapsed since the last dose during the observation period (day of study completion) will be collected in this study. Adverse events of note in this study are serious infection (pneumonia, Pneumocystis pneumonia, sepsis, opportunistic infection, etc.), tuberculosis, delayed-type hypersensitivity, serious blood disorder, lupus-like syndrome associated with seroconversion of anti-dsDNA antibody, demyelinating disease, hepatic impairment, serious infusion reaction, interstitial pneumonia, rhabdomyolysis, reactivation of hepatitis B, antibody production, malignant tumor, and infection due to inoculation of live vaccines in children.

The target sample size is 300 patients for the safety analysis set. The rationale 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.

2.2. Study Objectives

To collect information on the safety and efficacy of this drug against rheumatoid arthritis 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. At the time of interim analyses, only the analyses necessary for the evaluation report on the risk management plan among the statistical analyses specified in this plan will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypothesis

This study is not a confirmatory investigation. Therefore, any test will be considered as exploratory. The p-value of test results will be evaluated as descriptive statistics. The significance level is not provided, but a threshold may be set afterwards for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as closer as possible to all patients who received this drug. More specifically, the safety analysis set is defined as the patients registered or reported, excluding those who meet at least one 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 of registration (Description in the report: “Registration violation”)

d. Administration of the drug under investigation is not reported at all (Description in the report: “No administration information”)

e. Information on adverse events is not reported at all - No visits after the first prescription day (Description in the report: “No adverse event information - No revisits”)

f. Information on adverse events is not reported at all - There is a visit after the first prescription day but no description of information (Description in the report: “No adverse event information - No description”)

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as the patients in the safety analysis set, excluding those who meet at least one of the following conditions:

g. Efficacy evaluation is not reported at all (Description in the report: “No efficacy information”)

h. Disease is not under investigation (Description in the report; “Disease not under investigation”)

The latest "Criteria for Inclusion in Analysis Sets and Guidance for Data Handling in Drug Use Investigations" will be followed for the details of each criterion.

5.3. Other Analysis Sets

5.3.1. Set consisting of consented patients (safety)

It refers to the set consisting of consented patients for the dissemination and publication of study results among the patients in the safety analysis set.

5.3.2. Set consisting of consented patients (efficacy)

It refers to the set consisting of consented patients for the dissemination and publication of study results among the patients in the efficacy analysis set.

5.4. Subgroups

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

- Presence or absence of past use of infliximab preparations[a] [absent, present, (original product, biosimilar product, other)]

Patients possibly meeting any of the contraindications specified in the package insert of this drug (hereinafter referred to as patients with contraindications) will be extracted based on separately specified criteria and subjected to subgroup analyses of safety.

Subgroup analyses of efficacy will be performed for the following patient characteristics:

- Presence or absence of past use of infliximab preparations [absent, present, (original product, biosimilar product, other)]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

In this study, seriousness and causal relationship of adverse events will be evaluated based on the physician's determination.

- Adverse reactions: Adverse events assessed as related to this drug
- Adverse events: Adverse events of any causality
- Serious adverse events or adverse reactions: Adverse events or adverse reactions assessed as serious

[a]: Patients with past use of infliximab preparations will be further categorized into the following 3 types of patients according to the product used within 9 weeks before the day of initial dose of this drug: original biopharmaceutical product (original product) of this drug, follow-on biosimilar product (biosimilar product) other than this drug, past use not within 9 weeks (other).

- Adverse events of note

  - Serious infection (pneumonia, Pneumocystis pneumonia, sepsis, opportunistic infection, etc.)
  - Tuberculosis
  - Delayed-type hypersensitivity
  - Serious blood disorder
  - Lupus-like syndrome associated with seroconversion of anti-dsDNA antibody
  - Demyelinating disease
  - Hepatic impairment
  - Serious infusion reaction
  - Interstitial pneumonia
  - Rhabdomyolysis
  - Reactivation of hepatitis B
  - Antibody production
  - Malignant tumor
  - Infection due to inoculation of live vaccines in children

  Events handled as adverse events of note will be specified separately.

6.2. Efficacy Endpoints

6.2.1. DAS28 (4/CRP)

This endpoint will be calculated based on the efficacy endpoint using the following formula[1]:

DAS28 (4/CRP) = 0.56 × √(TJC28) + 0.28 × √(SJC28) + 0.36 × LN((CRP) × 10 + 1) + 0.014 × (VAS) + 0.96

TJC28 = tender joint count, SJC28 = swollen joint count, LN = logarithm natural, CRP (mg/dL), VAS = Patient's assessment of overall activity (0 to 100 mm)

6.2.2. Disease Activity based on DAS28 (4/CRP)

Disease activity will be determined based on the calculated DAS28 (4/CRP) using the classification in Table 1.

Table 1. Classification of Disease Activity based on DAS28 (4/CRP)[2]

DAS28 (4/CRP)	Disease activity
> 4.1	High disease activity
2.7 to 4.1	Moderate disease activity
< 2.7	Low disease activity
< 2.3	Remission

6.2.3. Remission based on DAS28 (4/CRP)

Patients achieving remission (<2.3) will be determined based on the disease activity assessed in Section 6.2.2.

6.3. Other Endpoints

Not applicable.

6.4. Covariates

There are no covariates identified from clinical study data, etc. or potential covariates for the safety or efficacy of this drug.

7. HANDLING OF MISSING DATA

If the seriousness, action taken, and outcome of an adverse event are missing, the data will be handled as "unknown" for tabulation. If the causal relationship of an adverse event is missing, the data will be handled as "related" for tabulation.

The strategy for handling data with uncompleted cleaning is described below:

- Item of missing data: The item will be handled as missing (category of categorical variables is "unknown") for both tabulation and listing.
- Item of inconsistent data: The item will be handled as missing for both tabulation and listing. However, a listing of data handling will be prepared separately.
- No signature: Any entry in a case report form without the signature of a contracted physician (including a case report form with the signature of an uncontracted physician only) will be handled as missing for both tabulation and listing.

8. STATISTICAL METHODS AND STATISTICAL ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of continuous data

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

8.1.2. Analysis of categorical data

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

8.1.3. Analysis of binary data

The frequency and proportion of data will be calculated. When the confidence interval of the proportion is calculated, the two-sided 95% confidence interval (exact method) will be calculated.

8.2. Statistical Analysis

Unless otherwise specified, the analyses to be performed on the safety analysis set and the efficacy analysis set will also be performed on the set consisting of consented patients (safety) and the set consisting of consented patients (efficacy).

8.2.1. Overview of patients

- **Patient disposition**

For patients registered, the number of patients registered, the number of patients completing the study, the number of patients in the safety analysis set, and the number of patients in the efficacy analysis set will be tabulated. In addition, the numbers of patients excluded from the safety analysis set and the efficacy analysis set and the number of patients by reason for exclusion will be tabulated.

- **Status of discontinuation/dropout**

For the safety analysis set, the number and proportion of patients at the day of study completion will be calculated by presence or absence of continued treatment with this drug (yes [continued patients] / no [discontinued patients]). In addition, the number of patients not continuing treatment will be tabulated by reason for discontinuation.

- **Listing of patients excluded from each analysis set**

A listing of reasons for excluding patients from the safety analysis and the efficacy analysis will be prepared.

8.2.2. Patient characteristics and history of treatment

- **Patient characteristics**

For the safety analysis set and the efficacy analysis set, the following patient characteristics will be tabulated as described in Section 8.1:

- Gender [male, female]
- Age (continuous)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Weight (continuous)
- BMI (continuous)
- BMI [<18.5, ≥18.5 to <25, ≥25, unknown]

- Diagnosis [rheumatoid arthritis, other]
- Duration of illness (years) (continuous)
- Steinbrocker's classification of disease stage (Stage) [I, II, III, IV]
- Steinbrocker's classification of function (Class) [I, II, III, IV]
- Hepatic impairment [absent, present]
- Severity of hepatic impairment [mild, moderate, severe, unknown]
- Renal impairment[b] [absent, present]
- Tuberculosis test [performed, not performed]
- Results of tuberculosis test [negative, positive, determination suspended, determination not possible]
- Hepatitis virus test [performed, not performed]
- Results of hepatitis virus test [negative, positive]
- Smoking history [non-smoker, smoker, ex-smoker, unknown]
- Family history of malignant tumor (including lymphoma) [absent, present, unknown]
- Past history [absent, present]
- Complication [absent, present]
- Past history: Allergic disease [absent, present]
- Complication: Allergic disease [absent, present]
- Presence or absence of past use of infliximab preparations [absent, present (original product, biosimilar product, other)]

For the safety analysis set, the number and proportion of patients will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for the following:

- Breakdown of past history
- Breakdown of complications

For the safety analysis set and the efficacy analysis set, the number and proportion of patients will be tabulated for the following:

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

- **Presence or absence of pregnancy**

For women in the safety analysis set, the number of patients will be calculated by presence or absence of pregnancy.

- **Administration status of this drug**

[b]: To be determined in accordance with the "Attachment: Procedure for Extraction of Patients with Hepatic/Renal Impairment in Post-marketing Surveillance."

For the safety analysis set, the administration status of this drug will be tabulated for the following:

- Dosing period (days, continuous)
- Dosing frequency (times, continuous)
- Dosing frequency [1, 2, 3, 4, 5, 6, 7, ≥8]
- Initial dose per administration (mg/kg) [<3, 3, >3]
- Initial dose per administration (mg/kg, continuous)
- Maximum dose per administration (mg/kg, continuous)
- Increased dose and shortened dosing period [no for both, increased dose only, shortened dosing period only, yes for both]

The dosing period is defined as the period from the first date of administration to the last date of confirmed administration in this study, including drug withdrawal period.

- **Number of days to study completion**

For the safety analysis set, the number of days to study completion will be tabulated.

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

The study period is defined as the period from the day of initial dose of this drug to the day of study completion.

8.2.3. Safety analysis

Adverse reactions and adverse events occurring between the day of initial dose of this drug (Day 1) and Week 30 (Day 217) will be summarized in listings. For patients withdrawn from the study before Week 30, the data obtained during the observation period (day of visit immediately after 8 weeks have elapsed since the last dose during the observation period [day of study completion]) will be used. If the observation period exceeds 217 days, the data obtained up to Day 217 will be used for tabulation. All events reported in this study will be included in the listings.

8.2.3.1. Adverse reactions

- **All adverse reactions**

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

- **Serious adverse reactions**

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

- **Details of adverse reactions**

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

- Seriousness [serious, non-serious]
- Action taken [discontinued, suspended or dose reduced]
- Outcome [fatal, not resolved/not recovered, resolved/recovered with sequelae, resolving/recovering, resolved/recovered, unknown]

In the tabulation of the number of patients with events, a same adverse reaction (of the same PT) occurring more than once in the same patient will be handled as follows:

- Seriousness: If both serious and non-serious events are reported, the event will be regarded as serious.
- Number of days to onset: Defined as the number of days to the first event.
- Action taken: If multiple types of actions were taken, one will be adopted in the priority order as follows: discontinued, suspended, dose reduced, dose increased, and none.
- Outcome: The outcome of the last occurring event will be used.

- **Adverse events of note**

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

In addition, infusion reaction and hypersensitivity occurring within 2 hours after administration of this drug will be tabulated similarly.

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. For this tabulation, a threshold for incidence will be set as necessary, and only events with an incidence at or above the threshold will be tabulated.

8.2.3.3. Other endpoints

None

8.2.3.4. Subgroup analysis

For each of the factors specified in Section 5.4, the number and proportion of patients with adverse reactions will be tabulated by SOC and PT.

For patients with contraindications, a listing of adverse reactions will be prepared. In addition, the number and proportion of patients with adverse reactions will be tabulated by SOC and PT as necessary.

8.2.3.5. Exploratory analysis

Additional analysis may be performed as necessary. Any exploratory analysis will be reported only when providing results giving important interpretation.

8.2.4. Efficacy analysis

8.2.4.1. DAS28(4/CRP)

For patients with available DAS28 (4/CRP) values both at baseline and on the day of study completion in the efficacy analysis set, summary statistics will be calculated for the DAS28 (4/CRP) at baseline and on the day of study completion. In addition, summary statistics will be calculated for the change from baseline on the day of study completion.

8.2.4.2. Disease activity based on DAS28 (4/CRP)

For patients with available DAS28 (4/CRP) values both at baseline and on the day of study completion in the efficacy analysis set, the number of patients and its proportion will be calculated for the disease activity at baseline and on the day of study completion.

8.2.4.3. Remission rate based on DAS28 (4/CRP)

For patients with available DAS28 (4/CRP) values both at baseline and on the day of study completion in the efficacy analysis set, the number and proportion (remission rate, %) of patients with remission (<2.3) will be calculated along with a 95% confidence interval based on the DAS28 (4/CRP) at baseline and on the day of study completion.

8.2.4.4. Subgroup analysis

For patients with available DAS28 (4/CRP) values both at baseline and on the day of study completion in the efficacy analysis set, summary statistics of the DAS28 (4/CRP) at baseline and on the day of study completion and summary statistics of its change from baseline on the day of study completion will be calculated for each of the factors specified in Section 5.4. In addition, subgroup analyses of the disease activity and remission rate based on DAS28 (4/CRP) will be performed for each factor.

8.2.4.5. Exploratory analysis

Additional analysis may be performed as necessary. Any exploratory analysis will be reported only when providing results giving important interpretation.

9. LISTINGS

The following listings will be prepared:

- Listing of patients
- Listing of patients experiencing adverse reactions
- Listing of patients with contraindications experiencing adverse reactions

- Listing of patients experiencing serious adverse reactions
- Listing of patients experiencing adverse reactions of note
- Listing of patients evaluated for efficacy
- Listing of patients for imaging diagnosis and KL-6 and β-D-glucan test data

In addition, the following table corresponding to the attached form of the evaluation report on the drug risk management plan will be prepared:

- Attached Form 3 (Status of occurrence of adverse reactions/infections in the post-marketing surveillance, etc.)

10. REFERENCES

1. http://www.das-score.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/how-to-calculate-the-das28/alternative-validated-formulae.html
[Accessed 2018 Dec 20]

2. E Inoue, H Yamanaka. Comparison of Disease Activity Score (DAS) 28-erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Annals of the Rheumatic Diseases 2007; 66: 407-409.