Non-Interventional Study Protocol

B5371009

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

General Investigation

(Psoriasis Vulgaris, Psoriasis Arthropathica, Pustular Psoriasis, and Erythrodermic Psoriasis)

Statistical Analysis Plan

Version: 4.0

Author: PPD (Clinical Statistics Group 2)

Date: 25-MAY-2023

TABLE OF CONTENTS

1. Revisions from Previous Version

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 27-DEC-2018 PPD	Original version
2.0 07-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. Efficacy Endpoints -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 25-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 drug use 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 patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, and erythrodermic psoriasis treated with this drug, and will be conducted using an all-case surveillance method. 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 in this study 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, malignancies, and development of infections due to vaccination with live vaccines in children.

Target sample size is to be 100 subjects for safety analysis set (At least 50 patients with psoriasis vulgaris and at least 5 patients with psoriasis arthropathica. Patients with pustular psoriasis and erythrodermic psoriasis will be collected as much as possible.). The rationale is shown below.

<Rationale for the target sample size>

The target sample size was set at 100 taking the feasibility of the study into consideration. The data collected from 100 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 3% or more occurs.

2.2. Study Objective

To collect information on the safety and efficacy of this drug against psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis 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:

- Diagnosis [psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, erythrodermic psoriasis, other]
- 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.

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

- Diagnosis [psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, erythrodermic psoriasis]
- 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

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).

- 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
  - 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

The Psoriasis Area and Severity Index (PASI) score and body surface area involvement (BSA) are efficacy indices commonly used for the target diseases of this study. Efficacy will be evaluated by DAS28 (4/CRP) in addition to PASI score and BSA in psoriasis arthropathica and by global impression of improvement in addition to PASI score and BSA in patients with pustular psoriasis.

6.2.1. Psoriasis Area and Severity Index (PASI) Score

The PASI quantifies the severity of lesions and the percentage of lesion area. It is the total score of the degree of erythema, infiltration/thickening, and scaling (evaluated for each skin finding) in each of the 4 body regions evaluated by the investigator. The score is adjusted for the percentage of lesion area of skin rash in each body region and the percentage of the area of each body region to the whole body. (See 11.1 Appendix 1 for the calculation of PASI score.)

6.2.2. DAS28(4/CRP)

DAS28 (4/CRP) will be calculated from the observed items of DAS28 using the following calculation formula[2]:

$$DAS28(4/CRP) = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.36 \times LN((CRP) \times 10 + 1) + 0.014 \times (VAS) + 0.96$$

TJC28 = tender joint count; SJC28 = swollen joint count; LN= natural log; CRP (mg/dL); VAS= patient's global assessment of activity (0 to 100 mm)

- **Disease activity as measured by DAS28 (4/CRP)**

Disease activity[3] will be determined from DAS28 (4/CRP) values using the classification in Table 2.

Table 2. Classification of Disease Activity by DAS28 (4/CRP)

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

6.2.3. Global Impression of Improvement of Itching

The global impression of improvement of itching will be assessed by the investigator using the following categories:

- Resolved
- Improved
- Unchanged
- Worsened
- Indeterminate

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

If the data of efficacy endpoints are missing at each evaluation time point, the missing data will not be imputed.

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. If there is a field for the date of signature but no date is entered, or if there is an inconsistency in the date of signature entered (e.g., a date that is before the start date of treatment or a date in the future), the entered part of the case report form will be regarded as having no signature.

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 diagnosis in accordance with Section 8.1:

- Sex [male, female]
- Age (continuous)
- Age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years]
- Body weight (continuous)
- BMI (continuous)
- BMI [< 18.5, ≥ 18.5 to < 25, ≥ 25, unknown]
- Diagnosis [psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, erythrodermic psoriasis, other]
- Duration of disease (continuous)
- Hepatic impairment [no, yes]
- Severity of hepatic impairment [mild, moderate, severe, severity unknown]
- Renal impairment[b] [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]
- 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) in the safety analysis set:

- Breakdown of medical history
- Breakdown of complications

The number and proportion of patients for the following will be tabulated in the safety and efficacy analysis sets:

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

- 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**

The following status of administration of this drug in the safety analysis set will be tabulated:

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

In the safety analysis set, the number of days to the completion of the study as shown below will be tabulated:

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

The number of days to the completion of the study will be counted from the start date of treatment 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 (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) will be tabulated. 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 performed by diagnosis.

- **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 performed by diagnosis.

- **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 or dose reduction, and other (none or dose increase).
  - 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 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. PASI Score

In patients in the efficacy analysis set who have the PASI score both at baseline and on the date of completion of the study, summary statistics of the PASI 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 PASI score from baseline to the date of completion of the study in the same manner.

In addition, the percent change (%) in PASI score from baseline to the date of completion of the study will be calculated for each patient, and the number and proportion of patients with ≥ 75% improvement will be calculated as PASI75 with the 95% confidence interval. Similarly, the number and proportion of patients with ≥ 90% improvement will be calculated as PASI90 with the 95% confidence interval.

8.2.4.2. BSA

In patients in the efficacy analysis set who have the BSA both at baseline and on the date of completion of the study, summary statistics of the BSA at baseline and on the date of completion of the study will be calculated. Summary statistics will also be calculated for the change in BSA from baseline to the date of completion of the study in the same manner.

8.2.4.3. DAS28(4/CRP)

In patients with psoriasis arthropathica in the efficacy analysis set who have the DAS28 (4/CRP) both at baseline and on the date of completion of the study, summary statistics of the DAS28 (4/CRP) at baseline and on the date of completion of the study will be calculated. In addition, summary statistics will also be calculated for the change in DAS28 (4/CRP) from baseline to the date of completion of the study in the same manner.

In patients with psoriasis arthropathica in the efficacy analysis set who have the DAS28 (4/CRP) both at baseline and on the date of completion of the study, the number and proportion of patients with each disease activity at baseline and on the date of completion of the study will be calculated. The proportion of patients who achieved remission will be calculated together with the number of patients as the remission rate (%).

8.2.4.4. Global Impression of Improvement of Itching

In patients with pustular psoriasis in the efficacy analysis set, the number and proportion of patients with each global impression of improvement on the date of completion of the study will be calculated. The combined number of patients with "resolved" or "improved" and the proportion will be calculated as the improvement rate (%) together with the number of patients. In this calculation, indeterminate patients will be excluded from the denominator.

8.2.4.5. Subgroup Analysis

Subgroup analyses of PASI score, PASI75, and PASI90 will be performed for each factor specified in Section 5.4. Subgroup analyses of DAS28 (4/CRP) and global impression of improvement of itching will be performed by prior infliximab use.

8.2.4.6. 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 patientsListing 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 events of special interest
- Listing of patients evaluated for efficacy
- 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. PPD Current understanding of the pathology and treatment of psoriasis. Nakayama Shoten Co., LTD. 2012; 61

2. 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]

3. 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.

11. Appendices

11.1. Appendix 1: Calculation of Psoriasis Area and Severity Index (PASI) Score

The calculation method of PASI score[a,b] is shown below.

1. **Severity of lesions:** Erythema, infiltration/thickening, and scaling, which are basic characteristics of psoriatic lesions, are evaluated for the severity of lesions. These 3 major symptoms are assessed individually for 4 body regions: head, upper extremities, trunk, and lower extremities. The degree of erythema, infiltration/thickening, and scaling of each body region is assessed using a 5-point scale: 0= none, 1= mild, 2= moderate, 3= severe, and 4= very severe.

1. Percent BSA involvement: A lesion area score is assigned based on the percentage of lesion area in each of the 4 body regions according to the following lesion area score criteria (Table 1):

Table 1. Lesion Area Score Criteria of Psoriasis Area and Severity Index (PASI)

Percentage of lesion area	Lesion area score
None	0
1-9%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

2. Percentage score for each body region (weighted): Weighting is based on each body region's approximate percent of total body surface area (Table 2).

Table 2. Percentage Score for Each Body Region of Psoriasis Area and Severity Index (PASI) (Weighted)

Body region	Percentage score (weighted)
Head	0.1
Upper extremities	0.2
Trunk	0.3
Lower extremities	0.4

3. According to the following formula, the sum of severity scores for erythema, infiltration/thickening, and scaling of each body region is multiplied by the lesion area score and percentage score to calculate the score for each body region, and then the PASI score is calculated by summing the scores for 4 body regions. The PASI score is expressed to 1st decimal place, and the range of the score is 0.0 to 72.0.

PASI score calculation formula:

PASI=0.1Ah (Eh + Ih + Sh)+0.2Au (Eu + Iu + Su)+0.3At (Et + It + St)+0.4Al (El + Il + Sl)

A = lesion area score, E = erythema score, I = infiltration/thickening score, S = scaling score, h = head, u = upper extremities, t = trunk, l = lower extremities

a : PPD Current understanding of the pathology and treatment of psoriasis. Nakayama Shoten Co., LTD. 2012; 61

b : van de Kerkhof PC. The Psoriasis Area and Severity Index and alternative approaches for the assessment of severity: persisting areas of confusion. British Journal of Dermatology. 1997; 137: 661-662