Non-Interventional Study Protocol

B5371010

Infliximab-Pfizer Biosimilar

Post-marketing Database Study

Statistical Analysis Plan

VERSION: 4

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Date: 12-Jul-2024

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 07 Mar 2023	Original 26 Oct 2022	N/A	N/A
2 26 Dec 2023	Version 2.0 30 Oct 2023	Update after the [redacted]	• Interim analysis was removed. Reason: Following a [redacted] on 11-July-2023 that included status of expected number of patients, the plan was revised, and the interim analysis was removed. • Dose of methotrexate and steroid were removed from covariate. Reason: Use of methotrexate and steroid are included as covariate, and thus, dose of methotrexate and steroid were removed from covariate. If any additional analysis for the outcomes is required, consider performing the additional analysis with dose of methotrexate and steroid. • Comparison will be performed even if the target study size is not reached. Reason: Comparison was requested in a [redacted] on 11-July-2023. • Summary of treatment exposure was added. Reason: This summary will be useful for the assessment of treatment groups.
3 24 Apr 2024	Version 3.0 31 Jan 2024	Clarification of the intended analysis.	• In Section 4.6.2, summary by age category was added. • In Section 4.6.2 (Covariate, and the defining information), clarification was added regarding handling of prior medication variables in tabulation and in propensity score calculation.
4 12 Jul 2024	Version 4.0 28 Jun 2024	Update in order to conduct analysis correctly.	• In Section 4.6.2, Biologics was updated from Biologics (excluding Infliximab-Pfizer Biosimilar) to Biologics (excluding any Infliximab products).

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B5371010. This document may modify the plans outlined in the protocol; however, any major modifications of the primary analysis will also be reflected in a protocol amendment.

3. RESEARCH QUESTION AND OBJECTIVES

The research question is to evaluate the important safety outcome events in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.

The primary objective is to evaluate the incidence rate of serious infections overall in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.

Secondary objectives are as follows:

- to evaluate the incidence rate of serious infections in patients in each disease sub-cohort who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.
- to evaluate the incidence rate of tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy overall in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.
- to evaluate the incidence rate of tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy in patients in each disease sub-cohort, who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.

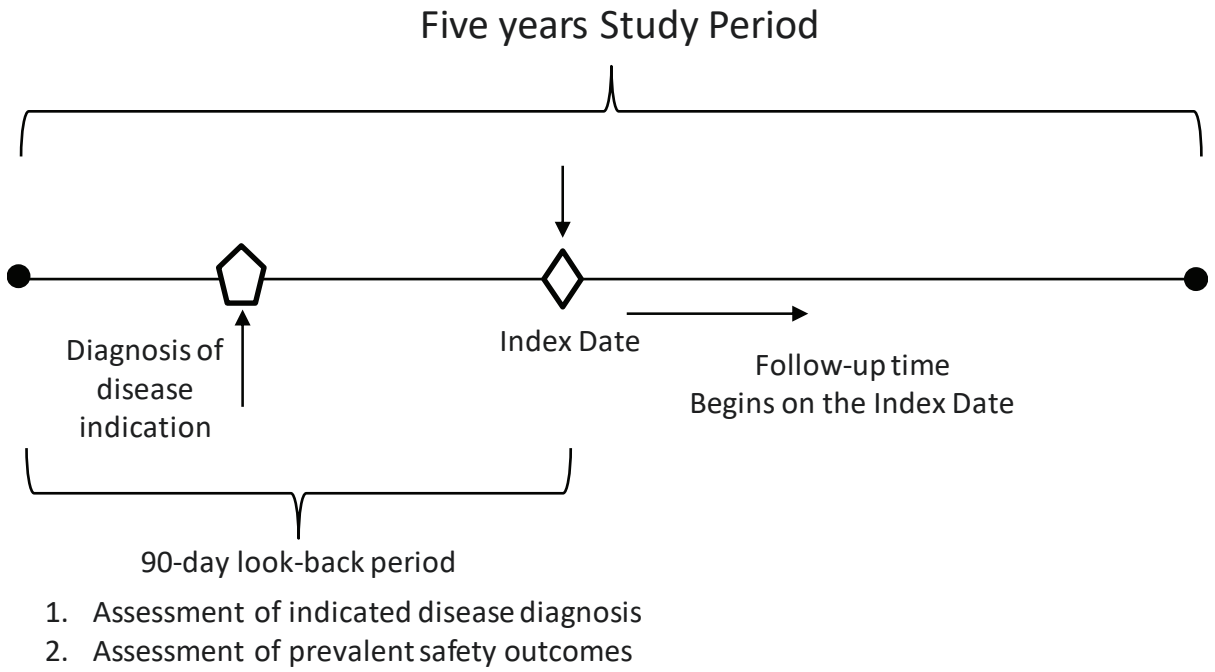
4. STUDY DESIGN

This is an observational cohort study.

4.1. Study period (Data period)

The planned study period is anticipated to be from December 1, 2018 through November 30, 2023. Individuals with the index date (Figure 1 and related explanation) in this study period will be included in the study. This 5-year period might be extended if insufficient number of exposed (Infliximab-Pfizer Biosimilar) patients is available within the initial study period.

Figure 1. Schematic of Cohort Entry



4.2. Definitions of exposure and control, and the defining information

Provisional index date is defined as the first recorded Infliximab-Pfizer Biosimilar or Remicade during the 5-year period (Patients who have any records of Remicade prescription before 01Dec2018 will not be included). The final index date is determined by the 90-day look-back period and the treatment group allocation as follows:

1. All subjects treated with Infliximab-Pfizer Biosimilar that meet the 90-day look-back criteria will be included in the "exposed" group. This definition includes patients switching from non-Pfizer Infliximab Biosimilar or Remicade to Infliximab-Pfizer Biosimilar.

2. All patients not meeting the former criteria but meet the 90-day look-back criteria for Remicade and without prior use of any Infliximab Biosimilar will be included in the "control" group.

No patient will be included in both treatment groups.

4.3. Inclusion criteria

Patients who have any claims record for the above exposure and control must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Have at least 90 days of look-back period

2. Have diagnostic code of indicated diseases (rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis) in the 90-day look-back period. Patients with >1 indication will be summarized as a separate group from each sub-cohort. An inpatient or outpatient visit assigned a diagnosis code consistent with either rheumatoid arthritis, ulcerative colitis, Crohn's disease, or

psoriasis using ICD (International Statistical Classification of Diseases and Related Health Problems) -10 coding:

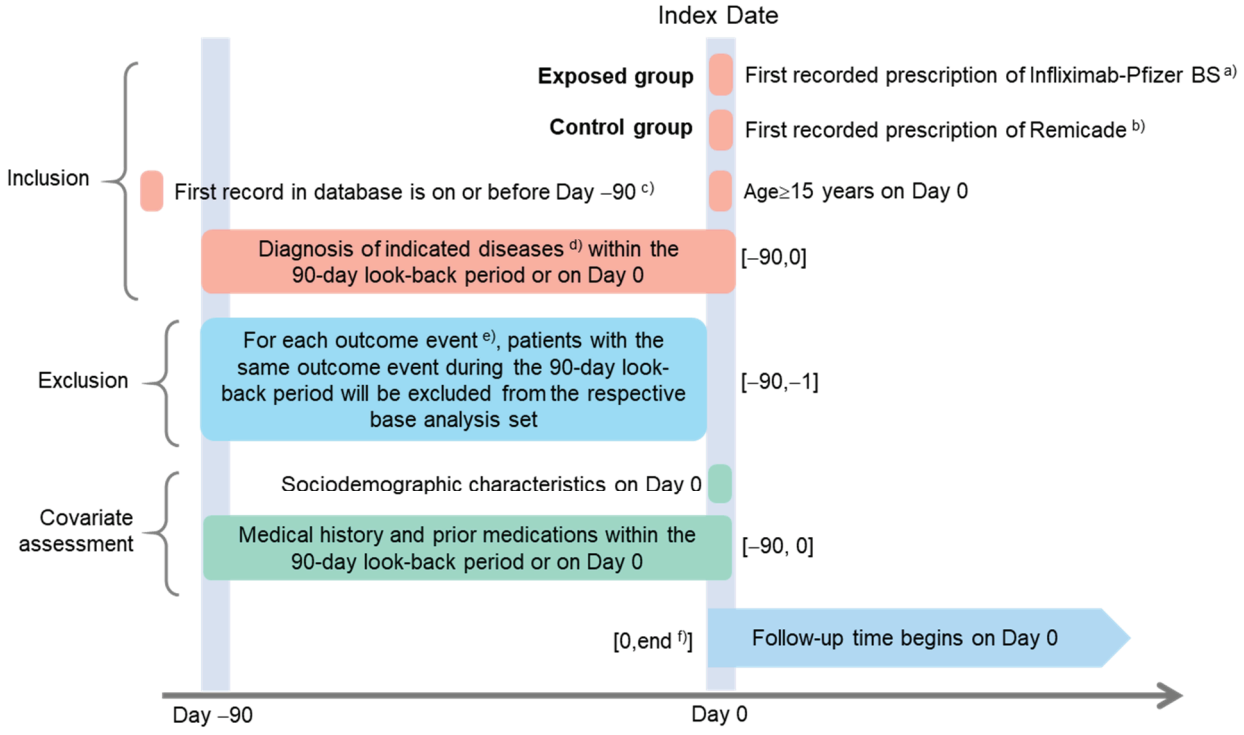
- Rheumatoid arthritis: M05, M06
- Ulcerative colitis: K51
- Crohn's disease: K50
- Psoriasis (Psoriasis vulgaris, Psoriasis arthropica, Pustular psoriasis and Psoriatic erythroderma): L40

3. 15 years of age or older at the time of index date

4.4. Exclusion criteria

Patients with pre-existing safety outcome event during the 90-day look-back period will be excluded from the study cohort for that specific outcome event as this study is observing incident cases. Details for excluding each safety outcome event are shown in Section 7.1.

Figure 2. Schematic of study entry and follow-up



a. Patients treated with Infliximab-Pfizer BS that meet the 90-day look-back criteria will be included in the "exposed" group. This definition includes patients switching from non-Pfizer Infliximab BS or Remicade to Infliximab-Pfizer BS.

b. Patients not meeting criteria a) above but meeting the 90-day look-back criteria for Remicade and without prior use of Infliximab BS will be included in the "control" group.

c. First record for the patient within the study period. This condition assures look-back period of at least 90 days.

d. Indicated diseases: rheumatoid arthritis, ulcerative colitis, Crohn's disease.

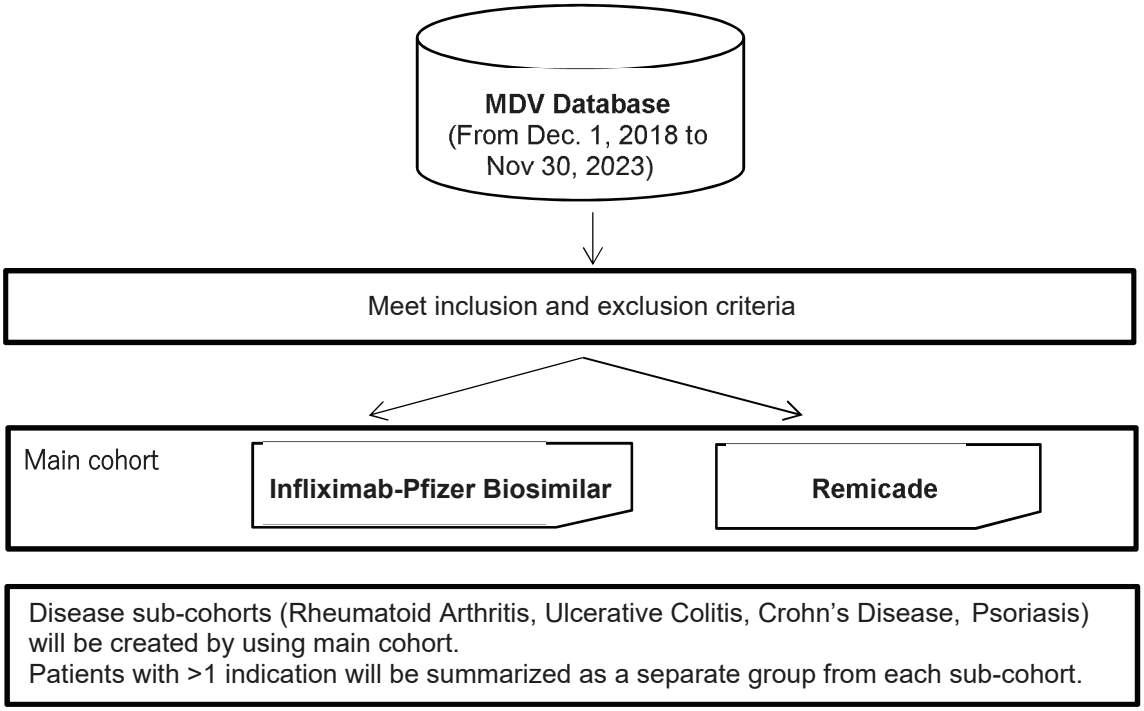
e. Outcome event: serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy

f. Definition of the "end" depends on each outcome event.

4.5. Flow chart

Figure 3 is the flow chart of the study B5371010. Main cohort is defined as overall population who meet the inclusion and exclusion criteria in section 4.3 and 4.4.

Figure 3. Flow chart of the study B5371010



4.6. Variables

4.6.1. Definition of outcomes and defining information

There are five safety outcome events in this study that will be identified using multiple coding systems in the database: serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy.

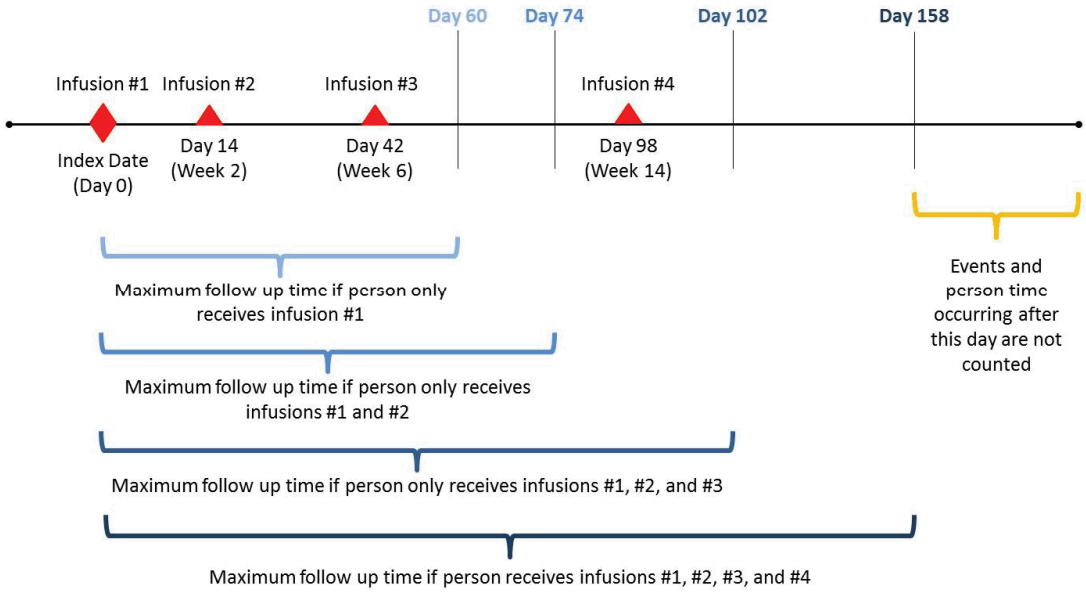
In this database study, based on the incidence rate of the safety specifications in the historical clinical studies (serious infections: 2.8%; tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy: less than 1%), serious infections is set as the primary safety specification, and tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy are set as secondary safety specifications.

Definition of five safety outcome events (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy) are shown in the attachment of the protocol. Outcome events are defined based on medical practice, guidelines, etc.

Outcome (acute) events: serious infections, tuberculosis, serious blood disorder, interstitial pneumonia:

The observation of these outcome events is expected to occur in an acute time period following any exposure. Maximum dosing interval of Remicade is every 8 weeks in the package insert based on overall evaluation of clinical trials (package insert: after the initial dose, dosing at week 2, week 6, and every 8 weeks thereafter). The package insert also indicates that the blood concentration of Remicade was maintained in clinical studies. Furthermore, as a biologic, almost all patients will not use other biologics within 8 weeks after last dose which is approximately 60 days. Therefore, a 60 day risk window after exposure will be utilized from the last dose received. An incident event occurring during the 60 day risk window will be counted in the numerator for the analysis and the person-time will accrue until the first occurrence of an event, the end of the 60 day risk window, date of switch treatment, death, or the end of study period (Figure 4).

Figure 4. Observation Time for Study Patients with Acute Events



Outcome (latent) event: malignancy:

The observation of a latent outcome event like a malignancy requires additional considerations. A 60 day risk window may not be sufficient follow-up time to observe an incident event with long latency. As a result, this study will analyze malignancy differently compared to the acute outcome events by extending follow-up time until the first incident event, death, end of the study period, or loss to follow-up. The primary analysis will utilize an ever-exposed approach whereby a person will always be considered exposed to the initial treatment. All malignancy will be reported in the primary analysis even those that occur after the day of initial treatment.

4.6.2. Covariate, and the defining information

Indicated disease, information on sociodemographic characteristics (sex, age at the index date), medical history (Yes or No in the 90-day look-back period: Cerebrovascular disease, Chronic pulmonary disease, Diabetes, Liver disease, Renal disease, or Dementia), and prior medications (Yes or No in the 90-day look-back period: methotrexate [RA], DMARDs other than methotrexate [RA], Amino salicylate [CD, UC], Immunosuppressant (Steroid), Immunosuppressant (non-steroid), Biologics (excluding any Infliximab products), Janus kinase inhibitor, or Anti-tuberculosis) will be

collected from the database as available. For the tabulation of demographics, age will be also summarized by category (Age <18, 18≤ Age <65, Age ≥65). For the tabulation of prior medications, number and proportion of patients will be calculated for the entire analysis set, as well as for those restricted to the specific indicated disease (i.e., [RA] patients for methotrexate and DMARDs other than methotrexate, and [CD, UC] patients for amino salicylate). For the propensity score model (Section 5.3), indicated disease will be ignored for the prior medication variables (i.e., for all patients, yes/no indicator for each of methotrexate, DMARDs other than methotrexate, and amino salicylate).

Disease code list and drug list were included in the protocol (ATTACHMENT 2. DISEASE CODE LIST, ATTACHMENT 3. DRUG LIST). These lists will be updated to latest version at the analysis, if needed.

4.7. Data sources

The source population for the study sample will be patients from the Medical Data Vision (MDV) database; a hospital-based claims database in Japan that consists of outpatient and inpatient data from hospitals using the diagnosis procedure combination (DPC) system.

4.7.1. Overview of the health information database used in this study

The quality of the data provided is managed by MDV through the oversight of their in-house data maintenance and quality improvement teams. All of these processes are consistently managed in-house. MDV have also been certified 'ISO27001'. MDV will extract the data which met the inclusion and exclusion criteria in section 4.3 and 4.4 by their standard operating procedures and provide them to Pfizer.

4.7.2. Validation

For serious infection, the primary outcome of this study, outcome definition was based on the results from a published validation study[1]. The validation study was planned in [redacted] to evaluate the validity of the algorithm definition for malignant tumor and for serious infections using the MDV database, a Japanese administrative healthcare database. In this study, an optimal algorithm from the validation study was adopted, where the optimality was based on both the positive predictive value and pseudo sensitivity.

For other secondary outcomes (tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy), outcome definitions were based on medical viewpoints with reference to medical practices and clinical guidelines.

4.8. Study size

The number of exposed to Infliximab-Pfizer Biosimilar patients would be expected about 1,000 patients for all 4 indications combined (rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriasis). The number of comparator (Remicade) patients would be expected to be about 9 times as large as the number of exposed patients. The following sample size rationale was calculated based on the assumption that the number of patients in Remicade cohort is at least twice as large as that in Infliximab-Pfizer Biosimilar considering the inclusion and exclusion criteria. Also, the rationale focuses on the precision of estimates achieved with these sample sizes with additional information on possibility of detection large differences such as 2 or 3 times in terms of risk ratios.

Incidence proportion for serious infection is 3% and incidence proportions for the other safety specifications in this database study is 0.5% are assumed based on a 54-week clinical study for Infliximab-Pfizer Biosimilar. It was evaluated the probabilistic properties of the risk ratio and the risk difference with Infliximab-Pfizer Biosimilar and Remicade (1: 2 patients).

For serious infection, when the number of patients is 300 in Infliximab-Pfizer Biosimilar group, if the true incidence proportion of Infliximab-Pfizer Biosimilar is 9% (3 times higher than Remicade), as shown in Table 2, the probabilities that the estimate of risk ratio exceeds 2 and 3 are calculated as 91.5% and 49.3%, respectively. Also, the estimate of risk ratio is distributed within 1.85 to 5.17 with 90% probability. Moreover, the lower limit of the 95% confidence interval of the risk ratio exceeds 1 with probability of 96.1%. When we focus on the risk difference (Table 3), the estimate of risk difference is distributed within 0.0317 to 0.0900 with 90% probability, and the lower limit value of the 95% confidence interval exceeds 0 with probability of 96.1%. In addition, the range where the entire 95% confidence interval is included with 90% probability is 0.0018 to 0.1332, and the width of the range was 0.1314.

For the other events with 0.5% incidence proportion, when the number of patients is 1000 in Infliximab-Pfizer Biosimilar group, if the true incidence proportion of Infliximab-Pfizer Biosimilar is 1.5% (3 times higher than Remicade), as shown in Table 2, the probabilities that the estimate of risk ratio exceeds 2 and 3 are calculated 84.4% and 48.6%, respectively. Also, the estimate of risk ratio is distributed within 1.50 to 6.67 with 90% probability. Moreover, the lower limit of the 95% confidence interval of the risk ratio exceeds 1 with probability of 79.3%. When we focus on the risk difference (Table 3), the estimate of risk difference is distributed within 0.0030 to 0.0170 with 90% probability, and the lower limit value of the 95% confidence interval exceeds 0 with probability of 79.3%. In addition, the range where the entire 95% confidence interval is included with 90% probability is –0.0031 to 0.0281, and the width of the range was 0.0312.

Based on the above, it is possible to detect the increase of the risk appropriately, it is reasonable to estimate to include 1000 patients for all 4 indications combined in the database. Also, it is possible to detect the increase of serious infection appropriately, it is reasonable to be estimated to be included 300 patients for all 4 indications in the database.

Table 2. The probabilistic properties of the risk ratio with infliximab BS Pfizer and the innovator (1: 2 patients) [d)]

The number of patients		True incidence proportion			Estimate of risk ratio (RR)			Probability that the lower limit of the 95% confidence interval of the risk ratio exceeds 1 [c)] (%)
Pfizer	Innovator	Pfizer	Innovator	ratio	Pr(RR>2)[a)] (%)	Pr(RR>3) [a)] (%)	Interval in which RR lies with 90% probability [b)]	
300	600	0.03	0.03	1	3.8	0.5	(0.4615, 1.8889)	3.1
		0.06	0.03	2	48.2	11.0	(1.1429, 3.5556)	56.8
		0.09	0.03	3	91.5	49.3	(1.8490, 5.1667)	96.1
1000	2000	0.03	0.03	1	0.0	0.0	(0.6667, 1.4118)	2.4
		0.06	0.03	2	49.5	1.2	(1.4795, 2.6804)	96.5
		0.09	0.03	3	99.4	49.6	(2.2973, 3.9574)	100.0
		0.005	0.005	1	9.6	2.3	(0.3077, 2.4000)	3.1
		0.010	0.005	2	50.1	17.8	(0.8750, 4.5000)	36.8
		0.015	0.005	3	84.4	48.6	(1.5000, 6.6667)	79.3

a) Pr(RR>2) and Pr(RR>3) shows the probabilities that the estimate for risk ratio exceed 2 and 3, respectively.
b) Interval was defined as 5-percentile and 95-percentile of point estimate.
c) The 95% confidence interval was calculated by using Miettinen-Nurminen method based on score statistics.
d) Based on 10000 times simulations. When the number of cases for infliximab BS Pfizer and the innovator were 0, they were excluded from the calculation. Regarding the confidence interval, even when RR is 0 or infinity, it is excluded from the calculation.

Table 3. The probabilistic properties of the risk difference with infliximab BS Pfizer and the innovator (1: 2 patients) [d)]

The number of patients		True incidence proportion			Interval in which risk difference lies with 90% probability [a)]	Probability that the lower limit of the 95% confidence interval of the risk difference exceeds 0 (%)[b)]	Range in which 95% confidence interval of the risk difference is include with 90% probability[b), c)]	
Pfizer	Innovator	Pfizer	Innovator	difference			Range	Width of the range
300	600	0.03	0.03	0	(–0.0200, 0.0200)	3.1	(–0.0411, 0.0516)	0.0927
		0.06	0.03	0.03	(0.0050, 0.0567)	56.8	(–0.0200, 0.0940)	0.1140
		0.09	0.03	0.06	(0.0317, 0.0900)	96.1	(0.0018, 0.1332)	0.1314
1000	2000	0.03	0.03	0	(–0.0110, 0.0110)	2.4	(–0.0228, 0.0258)	0.0486
		0.06	0.03	0.03	(0.0160, 0.0440)	96.5	(0.0014, 0.0627)	0.0613
		0.09	0.03	0.06	(0.0440 , 0.0760)	100.0	(0.0267, 0.0977)	0.0710
		0.005	0.005	0	(–0.0045, 0.0045)	3.1	(–0.0094, 0.0128)	0.0223
		0.010	0.005	0.005	(–0.0010, 0.0110)	36.8	(–0.0064, 0.0207)	0.0271
		0.015	0.005	0.010	(0.0030, 0.0170)	79.3	(–0.0031, 0.0281)	0.0312

a) Interval was defined as 5-percentile and 95-percentile of point estimate.
b) The 95% confidence interval for risk difference was calculated by using Miettinen-Nurminen method.
c) Lower of the range was defined as 5-percentile of lower limit of 95 % confidence interval on simulations. Upper of the range was defined as 95-percentile of upper limit of 95 % confidence interval on simulations.
d) Based on 10000 times simulations. When the number of cases for infliximab BS Pfizer and the innovator were 0, they were excluded from the calculation.

5. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

5.1. Full analysis set

The full analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria in Section 4.3 and Section 4.4.

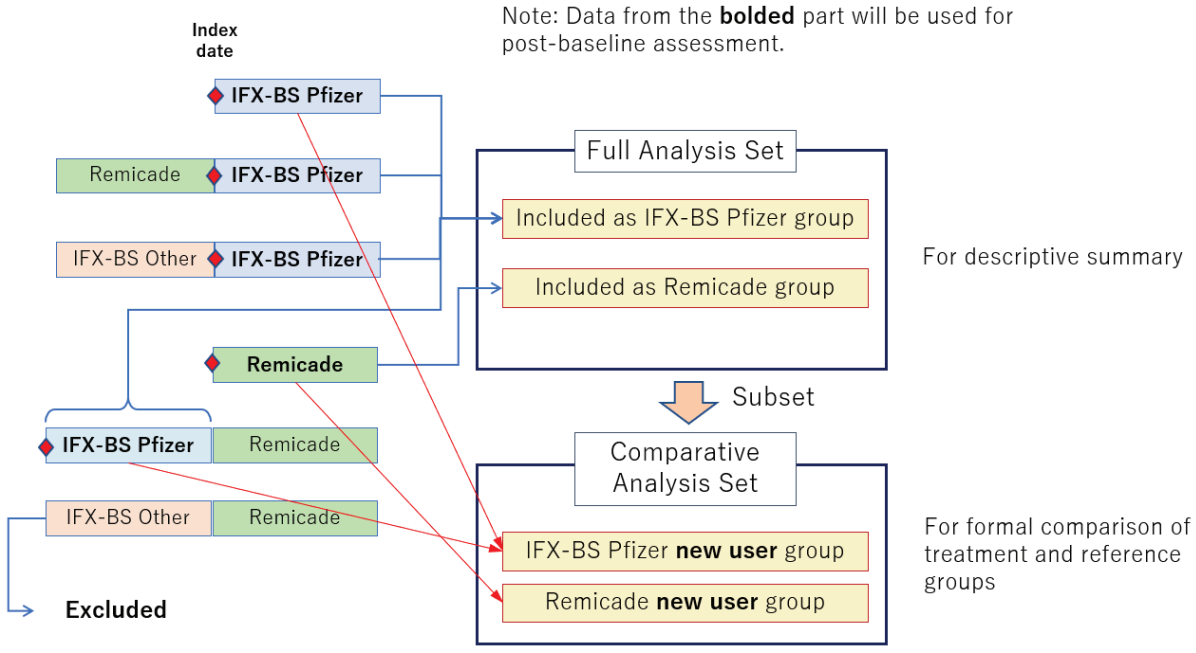
5.2. Comparative analysis set

The comparative analysis set will be a subset of the full analysis set who are new users. That is, patients switching from non-Pfizer Infliximab Biosimilar or Remicade to Infliximab-Pfizer Biosimilar will be excluded. Also, patients switching from any Infliximab Biosimilar to Remicade will be excluded.

5.3. Comparative matched analysis set

The comparative matched analysis set will be a subset of the comparative analysis set that includes all patients matched between Infliximab-Pfizer Biosimilar and Remicade. Each patient from the Infliximab-Pfizer Biosimilar group will be matched to two patients from the Remicade group based on the propensity score. The propensity score will be based on indicated disease, sex, age at the index date, calendar year-month of the index date, medical history, and prior medications (see Section 4.6.2).

Figure 5. Schema of analysis sets



6. GENERAL METHODOLOGY AND CONVENTIONS

SAS sample codes may be updated at the analysis in accordance with updating the procedures.

6.1. Hypothesis and Decision rules

No formal statistical test will be applied.

The primary parameter of interest will be the hazard ratio and its 95% confidence interval from Cox proportional hazard regression models for comparison of event rates in the Inverse Probability of Treatment Weighting (IPTW) analysis.

6.2. General Methods

6.2.1. Analyses for Continuous Endpoints

Continuous endpoints will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, median, minimum and maximum values. Standardized difference will be calculated based on the formula, $(\bar{x}_p - \bar{x}_R)/\sqrt{(s_p^2 + s_R^2)/2}$ where $\bar{x}_p, \bar{x}_R$: mean of Infliximab-Pfizer Biosimilar and Remicade for an interest continuous endpoint; s_p^2, s_R^2: variance of Infliximab-Pfizer Biosimilar and Remicade for an interest continuous endpoint. For propensity score adjusted summary, mean and variance using IPTW will be used.

6.2.2. Analyses for Categorical Endpoints

Categorical endpoints will be presented using summary statistics: counts and percentages. Standardized difference will be calculated based on the formula, $(\hat{p}_p - \hat{p}_R)/\sqrt{\left(\hat{p}_p(1-\hat{p}_p) + \hat{p}_R(1-\hat{p}_R)\right)/2}$ where $\hat{p}_p, \hat{p}_R$: percentage of Infliximab-Pfizer Biosimilar and Remicade for an interest categorial endpoint. For propensity score adjusted summary, mean and variance using IPTW will be used.

The incidence rate will be estimated by counting the number of patients with event in the numerator and dividing by the total person-time of observation in the denominator. For the outcome events: serious infections, tuberculosis, serious blood disorder, and interstitial pneumonia; the *person-time* will accrue until the first occurrence of an event, the end of the 60-day risk window, date of switch treatment, death, or the end of study period. For the malignancy outcome, the *person-time* will accrue until the first incident event, death, end of the study period, or loss to follow-up (Section 4.6.1).

In the crude analysis for assessment of each outcome event, crude rate ratios will be calculated including 95% confidence intervals with Remicade as the reference group. Crude rate differences will be calculated including 95% confidence intervals (the risk of Infliximab-Pfizer Biosimilar - the risk of Remicade). Confidence intervals for rate ratios and rate differences will be calculated based on the formulas, $\sqrt{1/a + 1/b}$ and $\sqrt{a/PT_P{}^2 + b/PT_R{}^2}$ where *a*, *b*: cases of Infliximab-Pfizer Biosimilar and Remicade; PT_P, PT_R: person-time of observation (person-time at risk) of Infliximab-Pfizer Biosimilar and Remicade, for the standard error of the logarithm of the incidence rate ratio and the rate difference, respectively[0].

In the IPTW analysis for assessment of each outcome event, adjusted rate ratios and adjusted rate differences will be calculated based on weights based on the propensity score. Rate ratios and rate differences will be calculated by a Poisson regression model with robust variance accounting for different duration on treatment (person-time at risk). Model-based variance will be considered if the robust variance cannot be calculated. Treatment (Infliximab-Pfizer Biosimilar or Remicade) will be included as a factor.

In the matched analysis for assessment of each outcome event, adjusted rate ratios and adjusted rate differences will be calculated by using the following models. Rate ratios and rate differences will be calculated by a Poisson regression model with robust variance accounting for different duration on treatment (person-time at risk). Model-based variance will be considered if the robust variance cannot be calculated. Treatment (Infliximab-Pfizer Biosimilar or Remicade) will be included as a factor.

In the IPTW analysis and matched analysis of the rate ratio, log link function and offset equal to log of person-time at risk will be used. For the rate difference, the estimated mean and variance-covariance matrix from the rate ratio model will be used to simulate the distribution of the parameters from the bivariate normal distribution, from which the 95% confidence interval of the rate difference will be estimated using the 2.5- and 97.5-percentiles of the simulated rate differences.

Example SAS code for crude analysis:

```
title 'Crude analysis';
data crude;
        crude_ratio = (a / PT_P) / (b / PT_R);
        crude_ratio_L = exp(log(crude_ratio) - probit(0.975) * sqrt(1/ a + 1 / b));
        crude_ratio_U = exp(log(crude_ratio) + probit(0.975) * sqrt(1/ a + 1 / b));

        crude_diff = a / PT_P - b / PT_R;
        crude_diff_L = crude_diff - probit(0.975) * sqrt(a/ (PT_P* PT_P) + b/ (PT_R* PT_R));
```

```
        crude_diff_U = crude_diff + probit(0.975) * sqrt(a/ (PT_P* PT_P) + b/ (PT_R* PT_R));
run;
```

Example SAS code for IPTW analysis:

```
title 'IPTW analysis: GENMOD with no covariate, incidence rate ratio';
ods output GEERCov=ecov    GEEEmpPEst=est ;
proc genmod data = dataset plots=none;
          weight ate ;
         class Drug SubjectID;
         model Outcome = Drug / dist = poisson    link = log    offset = log_duration;
         repeated subject = SubjectID / corrw covb type = ind;
         lsmeans Outcome / diff om e cl exp;
run ;
ods output close ;

title ' IPTW analysis: GENMOD with no covariate, incidence rate difference';
data _NULL_ ; set ecov ; /* ecov contains the empirical variance-covariance matrix */
if rowname="Prm2" then do ;
      call symput("s11",Prm2) ; call symput("s12",Prm3) ; end ;
if rowname="Prm3" then do ;
      call symput("s21",Prm2) ; call symput("s22",Prm3) ; end ;
run ;
data _NULL_ ; set est ; /* est contains the estimated mean */
if level1="TEST" then call symput("mean1",estimate) ;
if level1="CNTL" then call symput("mean2",estimate) ;
run ;

data scov(type=COV) ; /* scov is a standard input for proc simnorm */
length _TYPE_ $4.    _NAME_ $2. S1 S2 8. ;
_TYPE_="COV"     ; _NAME_="S1" ; S1=&s11      ; S2=&s12      ; output ;
_TYPE_="COV"     ; _NAME_="S2" ; S1=&s21      ; S2=&s22      ; output ;
_TYPE_="MEAN"    ; _NAME_=""      ; S1=&mean1 ; S2=&mean2 ; output ;
run ;

proc simnorm data=scov outsim=simdata numreal=1000000 seed=12345 ;
    var s1 s2 ;
run ;
data simdata ; set simdata ;
exps1=exp(s1) ;
exps2=exp(s2) ;
rr=exps1/exps2 ;
```

```
rd=exps1-exps2 ;
run ;

proc univariate data=simdata noprint ;
var rr rd ;
output out=simout pctlpts = 2.5 97.5 pctlpre =rr_ rd_ ;
run;
proc transpose data=est out=est1 ;
where level1 ne '' ;
var estimate ;
id level1 ;
run ;
data simout2 ; merge simout est1 ;
rate_CNTL=exp(CNTL) ;
rate_TEST=exp(TEST) ;
rr=exp(TEST-CNTL) ;
rd=exp(TEST)-exp(CNTL) ;
run ;
proc print data=simout2 ;
var rate_CNTL rate_TEST rr rr_2_5 rr_97_5 rd rd_2_5 rd_97_5 ;
run ;
```

Example SAS code for matched analysis:

```
title 'Matched analysis: GENMOD with no covariate, incidence rate ratio';
ods output GEERCov=ecov    GEEEmpPEst=est ;
proc genmod data = matcheddataset plots=none;
        class Drug MatchID;
        weight _matchwgt_ ;
        model Outcome = Drug / dist = poisson    link = log    offset = log_duration noint;
        repeated subject = MatchID / corrw covb type = ind;
        lsmeans Outcome / diff om e cl exp ;
run ;
ods output close ;
title ' Matched analysis: GENMOD with no covariate, incidence rate difference';
```

Refer to “Example SAS code for IPTW analysis” after the GENMOD procedure.

6.2.3. Analyses of Time to event Endpoints

6.2.3.1. Cox proportional hazard model

A Kaplan-Meier (KM) curve will be produced based on the time to the outcome event of interest (starting from the time of start of index date) for each treatment separately and will

be plotted on the same graph. No statistical testing for differences between treatments will be considered.

Example SAS code for crude analysis:

```
title 'Unadjusted Kaplan-Meier';
ods graphics on;
proc lifetest data=dataset plots=(s);
    time duration_at_risk_Outcome * Outcome(0); /* Status=0 is censor */
    strata Drug;
run;
```

Example SAS code for IPTW analysis:

```
title 'Adjusted Kaplan-Meier: ATE stabilized weighted';
ods graphics on;
proc lifetest data=weighteddataset plots=(s);
    weight _ATEWGT_;
    time duration_at_risk_Outcome * Outcome(0);
    strata Drug ;
run;
ods graphics off;
```

Example SAS code for matched analysis:

```
title 'Adjusted Kaplan-Meier (ATT matching)';
ods graphics on;
proc lifetest data=matcheddataset plots=(s);
   weight _MATCHWGT_;
    time duration_at_risk_Outcome * Outcome(0);
    strata Drug ;
run;
```

6.2.3.2. Cox proportional hazard model

In the crude analysis for assessment of each outcome event, crude hazard ratios will be calculated including 95% confidence intervals with Remicade as the reference group. Hazard ratios and its 95% confidence intervals will be calculated by Cox proportional hazard model with robust variance using treatment (Infliximab-Pfizer Biosimilar or Remicade) as a factor.

For the IPTW analysis for assessment of each outcome event, adjusted hazard ratios will be calculated based on weights based on the propensity score. Hazard ratios will be calculated by Cox proportional hazard model with robust variance. Treatment (Infliximab-Pfizer Biosimilar or Remicade) will be included as a factor.

For the matched analysis for assessment of each outcome event, adjusted hazard ratios will be calculated by using the following models. Hazard ratios will be calculated by Cox proportional hazard model with robust variance. Treatment (Infliximab-Pfizer Biosimilar or Remicade) will be included as a factor.

Example SAS code for crude analysis:

```
title 'Crude analysis: PHREG without covariates, hazard rate ratio';
proc phreg data = dataset covsandwich(aggregate);
        class Drug;
         model duration_at_risk_Outcome * Outcome(0) = Drug / RISKLIMITS=both;
         hazardratio Drug;
         id SubjectID;
run;
```

Example SAS code for IPTW analysis:

```
title 'IPTW analysis: PHREG without covariates, hazard rate ratio';
proc phreg data = weighteddataset covsandwich(aggregate);
        class Drug;
        weight ate ;
         model duration_at_risk_Outcome * Outcome(0) = Drug / RISKLIMITS=both;
         hazardratio Drug;
         id SubjectID;
run;
```

Example SAS code for matched analysis:

```
title 'Matched analysis: PHREG without covariates, hazard rate ratio';
proc phreg data = matcheddataset covsandwich(aggregate);
        class Drug;
         weight matchwgt ;
         model duration_at_risk_Outcome * Outcome(0) = Drug / RISKLIMITS=both;
         hazardratio Drug;id MatchID;
run;
```

6.2.4. Inverse Probability of Treatment Weighting (IPTW) method

The propensity score will be estimated by logistic regression. Stabilized IPTW weight will be calculated based on the estimated propensity score in the common support. This weight corresponds to ATE estimand. Distribution of propensity scores and weights as well as weighted baseline variables will be examined prior to the analyses.

Example SAS code for calculating weight:

```
proc psmatch data = dataset    region = CS;
```

```
        class Drug covariate1;
        psmodel Drug (Treated = ” Infliximab-Pfizer Biosimilar”)
                = covariate1 covariate2;
        assess lps allcov / varinfo nlargestwgt=10
                        plots=(all stddiff(ref=0.1)) weight=atewgt(stabilize=yes);output out =
        weighteddataset   ps = ps   lps=lps   atewgt(stabilize=yes) = ate;
run;
```

6.2.5. Matching with propensity score

One-to-two greedy matching on logit transformed propensity score from the logistic model with a caliper (maximum difference allowed) set to 0.2 of standard deviation. Baseline characteristics will be assessed with the matched dataset. Distribution of propensity scores and as well as matched baseline variables will be examined prior to the analyses.

Example SAS code for matched dataset:

```
proc psmatch data = dataset   region = treat ;
        class Drug covariate1;
        psmodel Drug (Treated = ” Infliximab-Pfizer Biosimilar”)
                = covariate1 covariate2;
        Match method = greedy (k=2 order = random(seed=12345)))
                distance = lps caliper (mult = stddev) = 0.20;
        assess lps allcov / varinfo plots=(all stddiff(ref=0.1));
        output out (obs=match) = matcheddataset   ps = ps   lps = lps
                matchwgt = matchwgt   matchid=MatchID ;
run;
```

7. ANALYSES AND SUMMARIES

7.1. Outcome event (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy)

Three base analysis sets (Section 5) will be used to evaluate the risks of Infliximab-Pfizer Biosimilar to Remicade. Specifically, hazard ratio, rate ratio, and rate difference will be examined together in comprehensive fashion to evaluate the overall safety profile. Any inconsistency in results among the three measures will be examined for its cause.

For assessment of each outcome event (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy), a subset of each base analysis set that excludes patients with the same outcome event during the 90-day look-back period will be used. One set of propensity score will be used for all outcomes.

For each analysis set, the crude incidence rate of each outcome event will be calculated for Infliximab-Pfizer Biosimilar and Remicade group for the main cohort and for each disease sub-cohort (rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis).

The following comparative analyses will be carried out to assess the relative incidence of these events using the comparative analysis set and comparative matched analysis set. Comparative analyses will be conducted regardless of accumulation of the number of patients with an understanding that the statistical precision of estimation will be reduced if the study size is smaller than in the initial plan (i.e., 300 patients for serious infection and 1000 patients for the other outcomes at the conclusion of follow-up who have received Infliximab-Pfizer Biosimilar). In such a case, the interpretation of the results will be made carefully.

Crude hazard ratios and rate ratios will be calculated including 95% confidence intervals with Remicade as the reference group based on Section 6.2. Also, crude rate differences will be calculated including 95% confidence intervals based on Section 6.2. Unadjusted Kaplan-Meier (KM) curve will be used to summarize the time to first event of each outcome. These analyses will be conducted for the main cohort and each disease sub-cohort.

Two types of analyses based on propensity score will be conducted for the main cohort. First is the IPTW analysis based on the comparative analysis set (primary analysis). Second is the propensity score matched analysis based on the comparative matched analysis set.

For the IPTW analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated based on weights based on the propensity score (Section 6.2). Also, adjusted KM will be calculated based on the weights.

For the matched analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated based on propensity score-based matched sets (Section 6.2). Also, adjusted KM will be calculated based on the matched sets.

7.1.1. Sensitivity analysis

For assessment of each outcome event (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy) during the 180-day look-back period in the main cohort will be conducted in the same manner of Section 7.1 with the comparative analysis set as a sensitivity analysis.

For malignancy, in the same manner of Section 7.1 with the comparative analysis set, sensitivity analyses will be conducted that truncate events during specified risk periods (60 days) associated with information known about the occurrence of malignancies.

7.2. Background

Patient flow will be summarized.

Background information as shown in Section 4.6.2 will be summarized by treatment and overall in each analysis sets. Standardized differences will be summarized by Unadjusted with Comparative analysis set, IPTW weighted with Comparative analysis set, Propensity score matched with Comparative matched analysis set.

7.3. Summary of treatment exposure

The number of patients in each treatment group (exposed and control) will be tabulated.

The number of patients switching to other infliximab product after index date (first switching only) will be summarized for each post-switch product (including "no switching") by treatment group.

Treatment duration will be summarized by using the number of patients, mean, standard deviation, median, and ranges (minimum and maximum) by treatment group, where the treatment duration is defined as time from the index date to the last prescription date of any infliximab product on record, including the time after treatment switching (if any).

Treatment duration of patients switching to other infliximab product after index date (first switching only) will be summarized for each post-switch product (including "no switching") by treatment group, where the treatment duration is defined as time from the first to last prescription date of each infliximab product. In addition, for patients switching to other infliximab product after index date (first switching only), the breakdown by pre-switch and post-switch product will be summarized for treatment duration. Infliximab-Pfizer Biosimilar, Remicade, and the other infliximab products will be specified based on Table 4, Table 5, Table 6.

8. INTERIM ANALYSIS

Originally, interim analysis was planned. However, following a CCI [redacted] on 11-July-2023 that included status of expected number of patients, the plan was revised, and the interim analysis was removed.

9. REFERENCE

1. Nishikawa A, Yoshinaga E, Nakamura M, et al. Validation Study of Algorithms to Identify Malignant Tumors and Serious Infections in a Japanese Administrative Healthcare Database, Annals of Clinical Epidemiology 2022;4(1):20–31

Kenneth J. Rothman. Epidemiology. An introduction. 2nd Edition, Oxford University Press, 2012.

Code Lists

Table 4. Code List for Infliximab-Pfizer Biosimilar

Product name	Dosage form	Receipt Code
Non-English text		

Table 5. Code List for Remicade

Product name	Dosage form	Receipt Code
Non-English text		

Table 6. Code List for Infliximab-Biosimilar

Product name	Dosage form	Receipt Code
Non-English text		

Non-Interventional Study Protocol

B5371010

Infliximab-Pfizer Biosimilar

Post-marketing Database Study

Statistical Analysis Plan for

Post hoc Sensitivity Analyses

VERSION: 1.0

Author: PPD (PPD),
PPD (PPD)

Date: 19-Sep-2024

TABLE OF CONTENTS

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0/19 Sep 2024	B5371010 Protocol Ver.4.0 28 JUN 2024	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for *post hoc* sensitivity analyses for Study B5371010.

3. RESEARCH QUESTION AND OBJECTIVES

Overall research question is the same as the protocol (28Jun2024) and the main SAP (12Jul2024). The objectives and rationale for the *post hoc* analyses are shown below.

Objective	Rationale
1. Understand the distribution of index date (year/month) for each treatment group.	Although the index date was included as one of covariates for calculating the propensity score (PS), its distribution was not explicitly summarized in baseline demographics tables or figures.
2. Conduct analysis of each outcome based on the outcome-specific PS.	In the main SAP, only one set of PS was calculated, which was used commonly across all outcomes; this was deemed adequate at the planning stage. However, due to lower-than-expected number of exposed-group patients in the database, the study was stopped prior to meeting the target sample size for the exposed group. This resulted in small number of exposed patients in the Comparative Analysis Set (n=28). For each outcome event, prevalent cases were excluded, which resulted in further reduction of sample size. For example, for the Serious Infection Outcome, 5 prevalent cases were excluded (exclusion rate of 5/28=18%). This may have resulted in insufficient balance between exposed and control groups based on PS [Inverse Probability of Treatment Weighting (IPTW) and matching].

	In addition, index year (year/month) was included in the PS model as a categorical variable in the main SAP, despite the large number of levels. Sensitivity of PS analysis to index year treated as a continuous variable would be informative. Thus, it was deemed informative to have sensitivity analysis to examine the impact of above factors.

4. STUDY DESIGN

This section is unchanged from the protocol and main SAP (See the main SAP subsections 4.1 to 4.8).

5. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

This section is unchanged from the protocol and main SAP (See the main SAP subsections 5.1 to 5.3).

For clarity, the following is reproduced from the main SAP: The PS used in Sections 5.2 (Comparative analysis set) and 5.3 (Comparative matched analysis set) will be based on indicated disease, sex, age at the index date, calendar year-month of the index date, medical history, and prior medications. See Section 6.2.1 below for additional information on the index date.

6. GENERAL METHODOLOGY AND CONVENTIONS

Sample SAS codes shown below may be changed as appropriate at the time of analysis.

6.1. Hypothesis and Decision rules

This section is unchanged from the main SAP.

6.2. General Methods

6.2.1. Analyses for Continuous Endpoints

This section is unchanged from the main SAP, with the following clarification.

It is clarified that index date (year/month) will be converted to number of months from the study period start date (2018/12), which will be analyzed as a continuous variable. For example, index dates of 2018/12, 2019/01, and 2019/06 will be converted to 0, 1, and 6, respectively.

Example SAS code:

```
index_date = input(indexym, YYMMN6.) ;
```

```
index_min = input("201812", YYMMN6.) ;
index_diff = intck("month", index_min, index_date) ;
```

6.2.2. Analyses for Categorical Endpoints

This section is unchanged from the main SAP, with the following additional points.
In the SAS Manual for PSMATCH, it is stated that "For binary classification variables, the mean is taken to be the proportion *p* of units having the first classification level, and the variance is computed as *p(1-p)*." (Accessed on 18SEP2024: https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.3/statug/statug_psmatch_details22.htm)

Thus, in order to use the raw SAS output directly, binary covariates will be re-coded so that the first level is the target level. An example of new coding is shown in the table below. With the new coding, proportion of females, proportion with the indicated disease, proportion with medical history, and proportion with prior medication use will be the default proportions in PROC PSMATCH.

Variables	Current variable names	Levels	Current coding	New coding	New variable names
Sex	sex	Female	2	"1F"	sexF
		Male	1	"2M"	
Indicated disease	i1, …, i4	With disease	"Y"	"1Y"	i1Y, …, i4Y
		Without disease	"N"	"2N"	
Medical history	m1, …, m6	With history	1	"1Y"	m1Y, …, m6Y
		Without history	0	"2N"	
Prior medication	p1, …, p8	With medication	1	"1Y"	p1Y, …, p8Y
		Without medication	0	"2N"	

6.2.3. Analyses of Time to event Endpoints

This section is unchanged from the main SAP.

6.2.4. Inverse Probability of Treatment Weighting (IPTW) method

The propensity score will be estimated by logistic regression. Stabilized IPTW weight will be calculated based on the estimated propensity score in the common support. It is noted that the index date (converted to number of months from 2018/12) is analyzed as a continuous variable as shown in Section 6.2.1. Also, the indicated disease, medical history, and prior medication variables are re-coded as shown in Section 6.2.2.

Example SAS code:

```
proc psmatch data = <dataset>    region = CS ;
    class       drug sexF
                i1Y i2Y i3Y i4Y
                m1Y m2Y m3Y m4Y m5Y m6Y
                p1Y p2Y p3Y p4Y p5Y p6Y p7Y p8Y ;
    psmodel  drug (treated = "Infliximab-Pfizer Biosimilar") = age index_diff ;
    assess     lps allcov / varinfo nlargestwgt=10
               plots=(all stddiff(ref=0.1)) weight=atewgt(stabilize=yes) ;
    output out = weighteddataset    ps = ps    lps=lps    atewgt(stabilize=yes) = ate ;
run ;
```

6.2.5. Matching with propensity score

One-to-two greedy matching on logit transformed propensity score from the logistic model with a caliper (maximum difference allowed) set to 0.2 of standard deviation. Baseline characteristics will be assessed with the matched dataset. Distribution of propensity scores and as well as matched baseline variables will be examined prior to the analyses. It is noted that the index date (converted to number of months from 2018/12) is analyzed as continuous variable as shown in Section 6.2.1. Also, the indicated disease, medical history, and prior medication variables are re-coded as shown in Section 6.2.2.

Example SAS code:

```
proc psmatch data = <dataset>    region = treated ;
    class       drug sexF
                i1Y i2Y i3Y i4Y
                m1Y m2Y m3Y m4Y m5Y m6Y
                p1Y p2Y p3Y p4Y p5Y p6Y p7Y p8Y ;
    psmodel  drug (treated = "Infliximab-Pfizer Biosimilar") = age index_diff ;
    match method = greedy (k=2 order = random(seed=12345))
                        distance = lps caliper (mult = stddev) = 0.20;
    assess lps allcov / varinfo plots=(all stddiff(ref=0.1));
                          output out (obs=match) = matcheddataset    ps = ps    lps = lps
                          matchwgt = matchwgt    matchid = matchID ;
run ;
```

7. ANALYSES AND SUMMARIES

7.1. Outcome events (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy)

For assessment of each outcome event (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy), a subset of each base analysis set that

excludes patients with the same outcome event during the 90-day look-back period will be used. Because this subset can differ across outcomes, separate set of PS will be calculated for each outcome event (this differs from the main SAP which used only one set of PS).

IPTW Analysis: Based on the Comparative Analysis Set for each outcome event (i.e., exclude patients with pre-existing outcome event), PS and the corresponding ATE (Average Treatment Effect) weight is calculated. Based on this weight, adjusted rates for each treatment group, rate difference, rate ratio, and hazard ratio will be calculated. The method of calculation for the adjusted values is the same as in the main SAP.

Matched Analysis: Based on the Comparative Analysis Set for each outcome event (i.e., exclude patients with pre-existing outcome event), PS is calculated, and the Comparative Matched Analysis Set is obtained by matching on the PS. The matching method is the same as in the main SAP. Based on this Comparative Matched Analysis Set, adjusted rates for each treatment group, rate difference, rate ratio, and hazard ratio will be calculated. The method of calculation for the adjusted values is the same as in the main SAP.

7.2. Background

Index date (number of months from the study period start date (2018/12)) will be summarized by treatment group for the Full Analysis Set and the Comparative Analysis Set. Summary statistics include number of patients, mean, standard deviation, median, minimum, and maximum. Also, frequency plot of index date (year/month) will be created.

7.3. Summary of treatment exposure

Not conducted for this SAP.

8. INTERIM ANALYSIS

Not applicable.

9. REFERENCE

None.