Non-Interventional Study Protocol

B3281009

RITUXIMAB BS Intravenous Infusion 100mg・500mg [Pfizer]

Post-marketing Database Study

Statistical Analysis Plan

VERSION: 2

Author: PPD

Date: 28 Jan 2025

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
2 28 Jan 2025	Version 3.0 14 Nov 2024	Based on the results of the feasibility analysis, in order to appropriately evaluate the safety of this drug, the definition of disease code for CD20-positive B-cell non-Hodgkin lymphoma was changed [redacted]	Section 4.2 Changed the definition of disease code for CD20-positive B-cell non-Hodgkin lymphoma.
		Based on the results of the feasibility analysis, the number of patients in the control group is likely to be less than twice the number of the test group at the final analysis. Therefore, [redacted], the matching ratio (test group : control group) was changed from 1:2 to 1:1.	Section 4.8, 5.3, 6.2 Changed the matching ratio (test group : control group) from 1:2 to 1:1. Changed the results of simulation of sample size estimation.
		Clarified the description.	Section 4.6 Updated the operational definition of "Combined use of drugs may induce Liver disorder". Section 8 Added the description of the feasibility analysis that was already conducted. Section 10 Added the description of Appendix 1 of data extraction request form.
		Updated the analysis plan.	Section 7.2 Added the analysis to conduct the subgroup analysis for the age group under 18 (age < 18).
		Corrected description errors.	Section 3, 4.3
1 24 Nov 2023	Original 28 Sep 2023	N/A	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B3281009. 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 incidence of the outcomes for safety specifications in patients in Japan diagnosed with CD20 positive B-cell non-Hodgkin's lymphoma who were treated with Rituximab Pfizer to compare it with outcomes in patients who were treated with Rituxan from 01 January 2020 through 31 December 2024.

Primary objective is to evaluate the incidence of Infections which requires procedures, medication or hospitalization in patients with CD20 positive B-cell non-Hodgkin's lymphoma who were treated with Rituximab Pfizer and to compare it with those in patients who were treated with Rituxan.

Secondary objective is to evaluate the incidence of 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia', Infusion reactions, 'Hepatic function disorder, Jaundice', Cardiac disorder, Gastrointestinal perforation/obstruction, Hypotension and Development of malignant tumor in patients diagnosed with CD20 positive B-cell non-Hodgkin's lymphoma who were treated with Rituximab Pfizer and to compare it with those in patients who were treated with Rituxan.

4. STUDY DESIGN

This is an observational cohort study.

4.1. Study period (Data period)

The study population includes individuals who have a diagnosis of CD20 positive B-cell non-Hodgkin's lymphoma and have been treated to Rituximab Pfizer or the innovator (Rituxan) within a planned 5-year study period between 01 January 2020 through 31 December 2024. For all the cases who meet the inclusion criteria, considering the look back period for 6 months, all the data which are from the oldest to the latest date existing in the database at the timing of extraction will be extracted.

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

Index date is defined as the first recorded Rituximab Pfizer or Rituxan during the 5-year period. In this study, we define 2 analysis sets which are Descriptive Analysis Set and Comparative Analysis Set. The Descriptive Analysis Set is defined as Rituximab Pfizer new user without regard to prior-treatment of any Rituximab products. Considering comparison, the Comparative Analysis Set is defined as the new users of Rituximab Pfizer and Rituxan, excluding prior-treatment of any Rituximab products. Inclusion criteria for each analysis set are as following:

4.2.1. Descriptive Analysis Set

Exposed group:

1. All patients treated with Rituximab Pfizer (B3281009 protocol Appendix 3 Sheet: RTX_pfi) between 01 January 2020 and 31 December 2024. The first prescription date is set as the index date.

2. Having definitive diagnosis code of CD20 positive B-cell non-Hodgkin's lymphoma (B3281009 protocol Appendix 1 Sheet: NHL_CD20_broad) on the index month or within 6 months before index month [-6 month to 0 month (index month)].

3. Having at least one medical record during Look back period (on the index month or within 6 months before index month [-6 month to 0 month (index month)]) and having at least one medical record prior to 7 months before the index month.

4.2.2. Comparative Analysis Set

Exposed group:

1. All patients treated with Rituximab Pfizer (B3281009 protocol Appendix 3 Sheet: RTX_pfi) between 01 January 2020 and 31 December 2024. The first prescription date is set as the index date.

2. Having definitive diagnosis code of CD20 positive B-cell non-Hodgkin's lymphoma (B3281009 protocol Appendix 1 Sheet: NHL_CD20_broad) on the index month or within 6 months before index month [-6 month to 0 month (index month)].

3. Having at least one medical record during Look back period (on the index month or within 6 months before index month [-6 month to 0 month (index month)]) and having at least one medical record prior to 7 months before the index month.

4. Patients without any prior use of Rituximab product before index date (B3281009 protocol Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk).

Control group:

1. All patients treated with Rituxan (B3281009 protocol Appendix 3 Sheet: RTX_original) between 01 January 2020 and 31 December 2024. The first prescription date is set as the index date.

2. Having definitive diagnosis code of CD20 positive B-cell non-Hodgkin's lymphoma (B3281009 protocol Appendix 1 Sheet: NHL_CD20_broad) on the index month or within 6 months before index month [-6 month to 0 month (index month)].

3. Having at least one medical record Look back period (on the index month or within 6 months before index month [-6 month to 0 month (index month)]) and having at least one medical record prior to 7 months before the index month.

4. Patients without any prior use of Rituximab product before index date (B3281009 protocol Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk).

4.3. Exclusion criteria

Patients meeting following criteria will not be included in the study:

- Having any diagnosis code for following diseases on or before index month: CD20 positive Chronic Lymphocytic Leukemia (B3281009 protocol Appendix 1 Sheet: B_CLL), Immune thrombocytopenia, Idiopathic Thrombocytopenic Purpura (B3281009 protocol Appendix 1 Sheet: ITP), Nephrotic Syndrome (B3281009 protocol Appendix 1 Sheet: Nephrosis), Granulomatosis with polyangiitis/Microscopic polyangiitis (B3281009 protocol Appendix 1 Sheet: MPA_GPA), Acquired Thrombotic Thrombocytopenic Purpura (B3281009 protocol Appendix 1 Sheet: TTP_acquired), Systemic Sclerosis (B3281009 protocol Appendix 1 Sheet: SSc), Refractory Pemphigus Vulgaris and Pemphigus Foliaceus (B3281009 protocol Appendix 1 Sheet: PV_PF), Neuromyelitis Optica Spectrum Disorder (B3281009 protocol Appendix 1 Sheet: NMOSD), Liver (B3281009 protocol Appendix 4 Sheet: Liver_transplantation) and Kidney transplantation (B3281009 protocol Appendix 4 Sheet: Kidney_transplantation)

Patients meet following criteria will not be included to the analysis of each outcome:

- Patients having diagnosis for Tuberculosis defined in B3281009 protocol 10.3.1.1 before the index date are excluded from the main analysis of Infection.

- Patients having outcome event of Supraventricular arrhythmia and Ventricular arrhythmia defined in B3281009 protocol 10.3.1.2.8 Cardiac disorder between 90 days and 1 day before the index date are excluded from the analysis of that outcome.

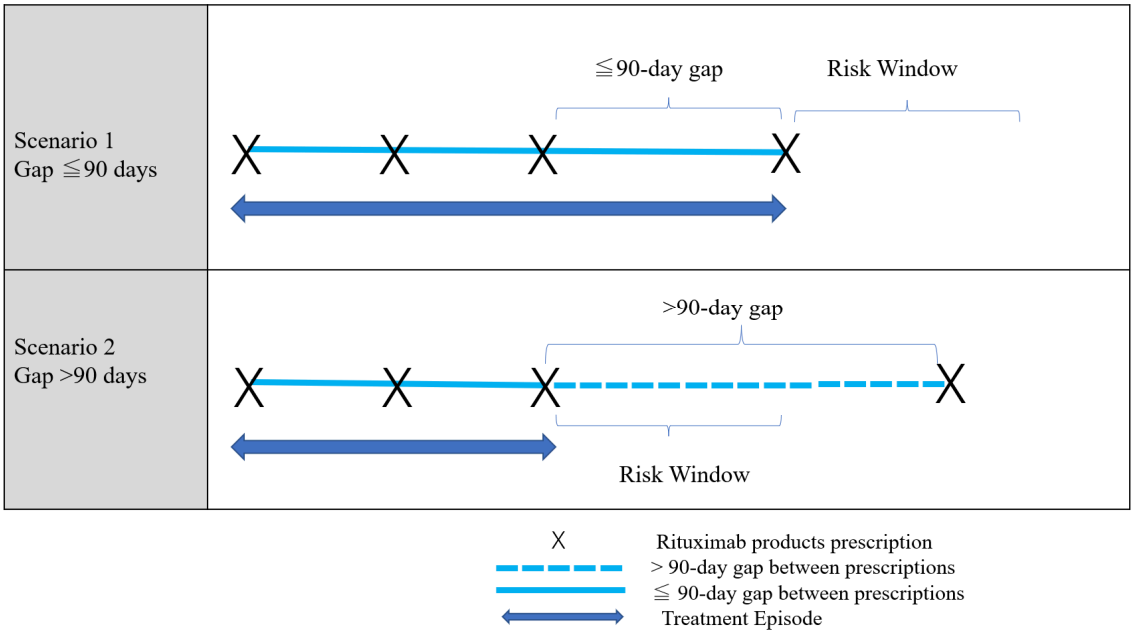
- Patients having outcome event defined in B3281009 protocol 10.3.1.2.11 Development of Malignant Tumor between 5 years (1800 days) and 1 day before the index date are excluded from the analysis of that outcome.

- Patients having outcome event defined in B3281009 protocol 10.3.1.1 and 10.3.1.2 except Supraventricular arrhythmia and Ventricular arrhythmia for Cardiac disorder and Development of Malignant Tumor between 28 days and 1 day before the index date are excluded from the analysis of that outcome.

4.4. Definition of continuous treatment

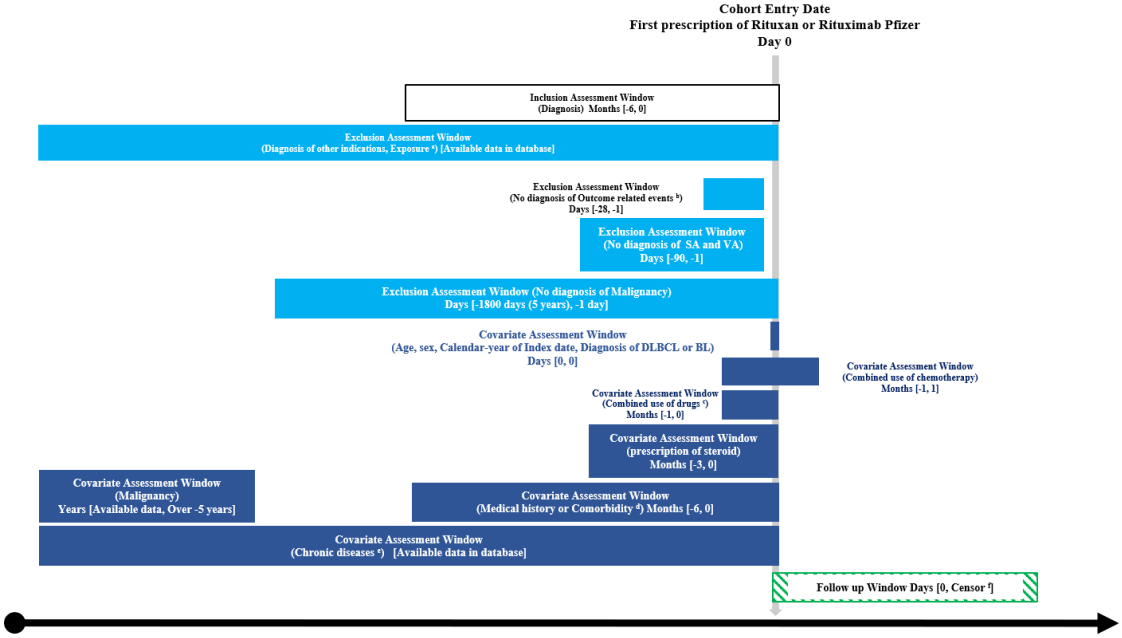
According to the dosage and administration on package insert, for the acute therapy, Rituximab product is administrated once a week up to 8 times and for maintenance therapy, it is administrated every 8 weeks up to 12 times. The acute and maintenance therapy can't be clearly distinguished, therefore we consider if there is less than 90-day gap between prescriptions, it shows that the therapy is continuing in the same episode and if there is more than 90-day gap, it will be defined as the end of treatment. Examples of each scenario are shown in Figure 1.

Figure 1. Examples of exposure episodes



4.5. Flow chart

Figure 2. Exposure-based cohort entry where the cohort entry date is selected after application of exclusion criteria



a. No Rituximab Pfizer for exposure group and not any Rituximab products for Control group
b. Outcomes are defined in Section 10.3.1 and 10.3.2 except Tuberculosis, SA, VA and Malignancy.
c. Combined use of drugs may induce Liver disorder and Antihypertensives
d. Medical history or Comorbidity included: Infection, Lymphopenia, Hypoglobulinemia, Heart disorder (Circulatory disorder), Lung disorder (Respiratory disorder) and Liver disorder
e. Chronic diseases included: Medical History of Rheumatoid arthritis, Bone marrow hypofunction, Bone marrow invasion of malignancy cell, Heart disorder.
f. Earliest of an event, date of switch to another Rituximab product, the end of continuous treatment plus risk window, death, or the end of study period except Malignancy.

DLBCL: Diffuse large B-cell lymphoma
BL: Burkitt lymphoma
VA: Ventricular Arrhythmia
SA: Supraventricular Arrhythmia

4.6. Variables

The following data will be available for the analysis. Study variables, their roles and operational definitions are described in Table 2. One month will be defined as 30 days.

Table 2. Study variables, their roles, and operational definitions

Outcome Variables	Role	Operational definition
Infection	Primary outcome	See B3281009 protocol 10.3.1.1
'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia'	Secondary outcome	See B3281009 protocol 10.3.1.2.1, 10.3.1.2.2, 10.3.1.2.3, 10.3.1.2.4, 10.3.1.2.5
Infusion reactions	Secondary outcome	See B3281009 protocol 10.3.1.2.6
'Hepatic function disorder, Jaundice'	Secondary outcome	See B3281009 protocol 10.3.1.2.7
Cardiac disorder	Secondary outcome	See B3281009 protocol 10.3.1.2.8
Gastrointestinal perforation/obstruction	Secondary outcome	See B3281009 protocol 10.3.1.2.9
Hypotension	Secondary outcome	See B3281009 protocol 10.3.1.2.10
Development of malignant tumor	Secondary outcome	See B3281009 protocol 10.3.1.2.11
Covariates		
Age	Baseline characteristics	Age
Sex	Baseline characteristics	Sex (male, female)
Calendar year of the index date	Baseline characteristics	Calendar year of the index date
Medication therapy (monotherapy or combination chemotherapy)	Prescription on the Index month or within ± 1 Index month [-1 month to +1 month]	See Section 7.1
Long term use of Steroid	Prescription of Steroid on the Index month or 3 months before the Index month [-3 months to 0 month (Index month)]	Therapeutic Category of Drugs in Japan: 245, oral only
Leukopenia, Neutropenia	Definite Diagnosis of Leukopenia, Neutropenia on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: D70 AND recipient code: 2888009, 2880001, 2880005, 8842350, 8842350, 2880006, 2880006
Lymphopenia	Definite Diagnosis of Lymphopenia on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: D728 AND recipient code 2888001

Outcome Variables	Role	Operational definition
Hypoglobulinemia	Definite Diagnosis of Hypoglobulinemia on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: R771 AND recipient code 8837868
Medical history or Comorbidity of Infection	Definite Diagnosis of Infection on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: A00-B99
Medical History or Comorbidity of Rheumatoid Arthritis (RA)	Definite Diagnosis of RA as available data in database	ICD-10 code: M05, M06
Bone marrow hypofunction	Definite Diagnosis of Bone marrow hypofunction as available data in database	ICD-10 code: D619
Bone marrow invasion of malignancy cell	Definite Diagnosis of Bone marrow invasion of malignancy cell as available data in database	ICD-10 code: C795 AND recipient codes: 8844349 and 8844442
Medical history or Comorbidity of Heart Disorder (Circulatory disorder)	Definite Diagnosis of circulatory disorder on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: I00-I99
Medical history or Comorbidity of Lung Disorder (Respiratory disorder)	Definite Diagnosis of the respiratory disorder on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: J00-J99
Medical history or Comorbidity of Liver disorder	Definite Diagnosis of liver disorder on the Index month or 6 months before the Index month [-6 months to 0 month (Index month)]	ICD-10 code: K70-K77
Combined use of drugs may induce Liver disorder	Prescription on the Index month or 1 month before the Index month [-1 month to 0 month (Index month)]	The drugs defined in 'Manuals for handling serious adverse events of drug induced liver disorder' (B3281009 protocol Appendix 5)
Medical history or Comorbidity of Heart disorder	Definite Diagnosis of Heart disorder as available data in database	Cardiac arrhythmia (I49.9), Ischaemic heart diseases (I20-I25), Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)
Diagnosis of DLBCL or BL	Definite Diagnosis of DLBCL or BL in the Index month	ICD-10 code: C833 (excluding recipient code 8847324 and 8847396), C835 (recipient code 8847281 only), C837
Combined use of Antihypertensives	Prescription on the Index month or 1 month before the Index month [-1 month to 0 month (Index month)]	Therapeutic Category of Drugs in Japan: 214
Medical History of Malignancy	Definite Diagnosis of Malignancy over 5 years before the index date	ICD-10 code: C00-C97 Exclude definitive diagnosis code of CD20 positive B-cell non-Hodgkin's lymphoma (ICD10 code: C851 AND Recipient code 8848431) and other lymphoma C85

4.6.1. Risk window for each outcome

Infection, 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia', 'Hepatic function disorder, Jaundice', Cardiac disorder and Gastrointestinal perforation/obstruction are expected to occur after the exposure. The risk window of Rituximab products is set 180 days after the last dose to observe the clearance for twice the time, and consider the half-life (approximately 400 hours). An incident event occurring during the 180-day risk window will be counted in the numerator for the analysis and the person-time will accrue until the first incidence of an event, date of switch to another Rituximab product, the end of continuous treatment plus 180 days risk window, death, loss to follow up (the last date of the disease name data, medical practice data, or hospitalization data on DPC form 1 existing on MDV database) or the end of study period.

Infusion reactions and Hypotension are expected to occur soon after the exposure, therefore the period until the next day after the last dose is set as risk window. An incident event occurring during that period will be counted in the numerator for the analysis and the person-time will be accrued until the first incidence of an event, date of switch to another Rituximab product, the end of risk window which is until next day after last dose, death, or the end of study period.

The observation of a latent outcome event like a malignancy requires additional considerations. A 180-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 last date of the disease name data, medical practice data, or hospitalization data on DPC form 1 existing on MDV database). 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 the day after the initial treatment. Sensitivity analyses will be considered that truncate events during specified risk periods (180 days) associated with information known about the incidence of malignancies.

4.6.2. Covariate, and the defining information

The covariates are considered as below, both common for all outcomes and specific for each outcome which will have impact on the incidence of outcomes. This information will be used for the study analysis as appropriate. Disease code list and drug list are described in Table 2. Study variables, their roles, and operational definitions, respectively. These lists will be updated to latest version at the analysis, if needed.

Common for all outcomes: Demographic (age, sex and calendar year of index date) and medication therapy (monotherapy or combination chemotherapy defined in Section 7.1)

Infection: Long term use of Steroid, Leukopenia, Neutropenia, Lymphopenia, Low serum immunoglobulin level (Hypoglobulinemia), Medical history or Comorbidity of Infection, Medical History of RA

'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia': Bone marrow hypofunction, Bone marrow invasion of malignancy cell

Infusion reactions: Medical history or Comorbidity of the heart or lung disorder (defined as circulatory or the respiratory disorder)

'Hepatic function disorder, Jaundice': Medical history or Comorbidity of liver disorder, Combined use of drugs may induce Liver disorder

Cardiac disorder: Medical history or Comorbidity of Heart disorder

Gastrointestinal perforation/obstruction: Diagnosis of DLBCL or BL

Hypotension: Combined use of Antihypertensives

Development of malignant tumor: Medical History of Malignancy

4.7. Data sources

The source population for the study sample will be patients from MDV database; a hospital-based claims database in Japan that consists of outpatient and inpatient data from hospitals using the 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 has also been certified 'ISO27001'. MDV will extract the data which meet the inclusion and exclusion criteria in Section 4.2 and Section 4.3 by their standard operating procedures and provide them to Pfizer.

4.7.2. Validation

For infection which requires procedures, medication and hospitalization, the primary outcome of this study, outcome definition was developed based on the results from published validation studies (Reference 5,6,7,8 in the B3281009 protocol) and treatment guidelines (Reference 9,10 in the B3281009 protocol).

For some of the secondary outcomes, the published validation studies were available such as Leukocytopenia (Reference 11,12 in the B3281009 protocol), Thrombocytopenia (Reference 13,14,15,16,17,18 in the B3281009 protocol), Infusion reactions (Reference 19,20,21 in the B3281009 protocol), Hepatic function disorder and Jaundice (Reference 22,23,24 in the B3281009 protocol), Cardiac disorder (Reference 25,26,27,28,29 in the B3281009 protocol), Gastrointestinal perforation/obstruction (Reference 30 in the B3281009 protocol), and Development of malignant tumor (Reference 8 in the B3281009 protocol). Therefore, the outcome definitions were developed with those clinical experts based on those results and treatment guideline.

For other secondary outcomes, outcome definitions were based on medical practices provided by clinical experts.

4.8. Study size

Study size was determined based on the primary objective.

The number of exposed to Rituximab Pfizer patients would be expected about 1,000 patients with CD20 positive B-cell non-Hodgkin's lymphoma for infection analysis which are defined with disease name, requiring procedures, medications, hospitalization etc. Based on the results of the feasibility analysis using the data collected from January 2020 to September 2023, the number of comparator (Rituxan) patients is likely to be less than twice the number of the exposed patients at the final

analysis. The following sample size rationale was calculated based on the assumption that the number of patients in Rituxan cohort is less than twice that in Rituximab Pfizer 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 detecting large differences such as 2 or 3 times in terms of risk ratios.

Incidence proportion for infection requiring procedures, medications, hospitalization etc. is assumed 2% based on a 52-week clinical study. Probabilistic properties of the risk ratio and the risk difference with Rituximab Pfizer and Rituxan (1: 1 patients) were evaluated.

Incidence proportion of all causalities for infections was 26.5% in the study B3281006 in patients with CD20 positive LTB-FL. Among these infections, the incidence of all-causality serious adverse events was 2.0%. The objective of the sample size is to evaluate defined outcome with at least 2% or more incidence proportion because outcomes of infection will be defined as infection requiring procedures, medications, hospitalization etc. Therefore, the incidence proportion of infection requiring procedures, medications, hospitalization etc. for the DB study was assumed to be at least 2% for the simulation of sample size estimation. Probabilistic properties of the risk ratio and the risk difference with Rituximab Pfizer and the innovator (1: 1 patients) were evaluated.

For infection requiring procedures, medications, hospitalization etc., with the number of patients equal to 1000 in the Rituximab Pfizer group, if the true incidence proportion in Rituximab Pfizer is 5% (2.5 times higher than the innovator), as shown in Table 3, the estimate of risk ratio is distributed within 1.68 to 4.08 with 90% probability, and exceeds 1.5 and 2.0 with probability of 98.0% and 80.2%, respectively. Moreover, the lower limit of the 95% confidence interval of the risk ratio exceeds 1 with probability of 96.3%. When focusing on the risk difference (Table 4), the estimate of risk difference is distributed within 0.0170 to 0.0430 with 90% probability, and the lower limit of the 95% confidence interval exceeds 0 with probability of 96.3%. In addition, the range where the entire 95% confidence interval is included with 90% probability is 0.0011 to 0.0611, and the width of the range was 0.0600.

Based on the above, it is possible to detect the increase of infection requiring procedures, medications, hospitalization etc. appropriately in the database study including 1000 patients in Rituximab Pfizer group.

Table 3. The probabilistic properties of the risk ratio with Rituximab Pfizer and the innovator (1: 1 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>1.5)[a)] (%)	Pr(RR>2) [a)] (%)	Interval in which RR lies with 90% probability [b)]	
1000	1000	0.03	0.02	1.5	47.9	15.6	(0.9512, 2.5000)	29.2
		0.04	0.02	2.0	85.9	47.5	(1.3043, 3.2899)	75.6
		0.05	0.02	2.5	98.0	80.2	(1.6774, 4.0833)	96.3
		0.06	0.02	3.0	99.8	95.4	(2.0370, 4.8667)	99.7

a) Pr(RR>1.5) and Pr(RR>2) show the probabilities that the estimates for risk ratio exceed 1.5 and 2, 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 Rituximab 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 4. The probabilistic properties of the risk difference with Rituximab Pfizer and the innovator (1: 1 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 included with 90% probability[b), c)]	
Pfizer	Innovator	Pfizer	Innovator	difference			Range	Width of the range
1000	1000	0.03	0.02	0.01	(-0.0010, 0.0210)	29.2	(-0.0154, 0.0365)	0.0519
		0.04	0.02	0.02	(0.0080, 0.0320)	75.6	(-0.0072, 0.0490)	0.0561
		0.05	0.02	0.03	(0.0170, 0.0430)	96.3	(0.0011, 0.0611)	0.0600
		0.06	0.02	0.04	(0.0260, 0.0540)	99.7	(0.0096, 0.0731)	0.0635

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 Rituximab Pfizer and the innovator were 0, they were excluded from the calculation.

5. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

5.1. Descriptive analysis set

The descriptive analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria in Section 4.2.1 and Section 4.3.

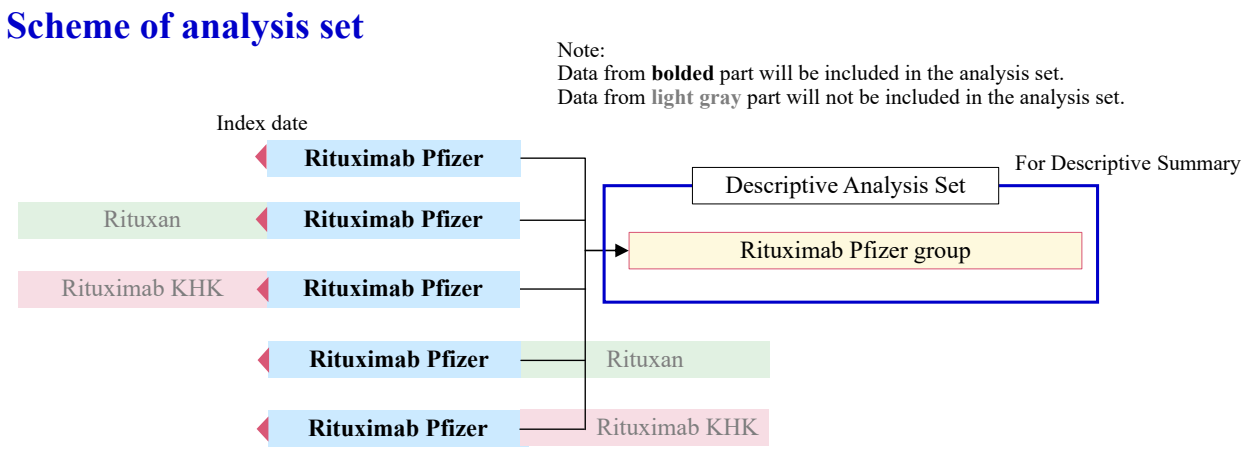
5.2. Comparative analysis set

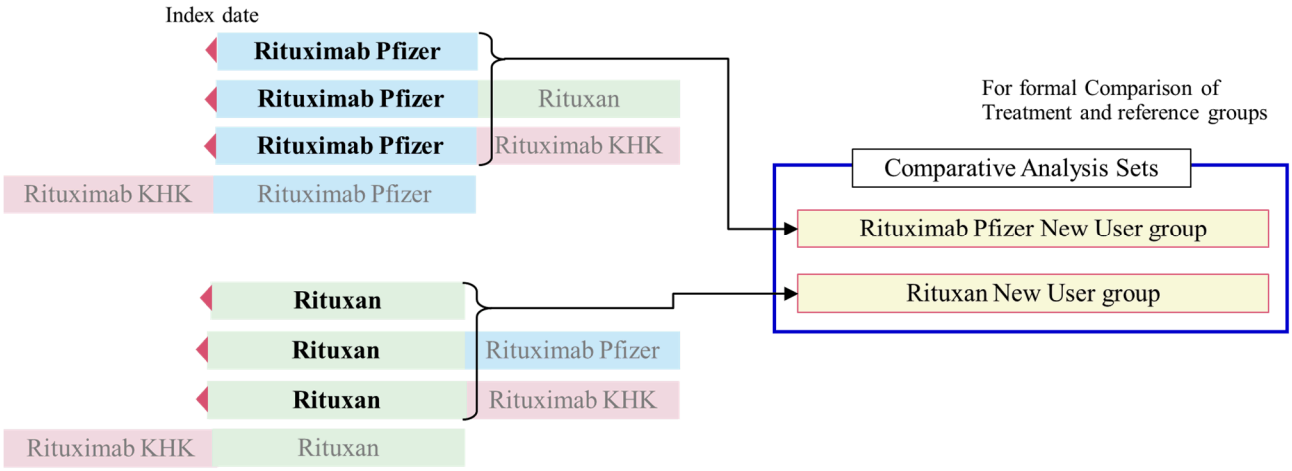
The comparative analysis set will include all patients who are new users among those considered eligible by the inclusion and exclusion criteria in Section 4.2.2 and Section 4.3. Rituximab Pfizer group will include patients who switch to Rituxan or non-Rituximab Pfizer Biosimilar. Rituxan group will include patients who switch to Rituximab Pfizer or non-Rituximab Pfizer Biosimilar.

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 Rituximab Pfizer and Rituxan. Each patient from the Rituximab Pfizer group will be matched to one patients from the Rituxan group based on the propensity score. The propensity score will be based on indicated disease, sex, age at the index date, calendar year of the index date, medical history, and prior medications (Section 4.6.2). Feasibility of the matching scheme will be assessed at the interim analysis.

Figure 3. Scheme 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 Rituximab Pfizer and Rituxan for an interest continuous endpoint; s_p^2, s_R^2: variance of Rituximab Pfizer and Rituxan for an interest continuous endpoint. For propensity score adjusted summary, mean and standard deviation 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 Rituximab Pfizer

and Rituxan for an interest categorial endpoint. For propensity score adjusted summary, proportion and standard deviation 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 other than the development of malignant tumor, the person-time will accrue until the first incidence of an event, the end of each risk window, date of switch treatment, death, loss to follow up (the last date of the disease name data, medical practice data, or hospitalization data on DPC form 1 existing on MDV database) or the end of study period. For the development of malignant tumor 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 Rituxan as the reference group. Crude rate differences will be calculated including 95% confidence intervals (the risk in Rituximab Pfizer - the risk in Rituxan). 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 Rituximab Pfizer and Rituxan; PT_P, PT_R: person-time of observation of Rituximab Pfizer and Rituxan, for the standard error of the logarithm of the incidence rate ratio and the rate difference, respectively[1].

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 (Rituximab Pfizer or Rituxan) 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 (Rituximab Pfizer or Rituxan) 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 Rituxan as the reference group. Hazard ratios and its 95% confidence intervals will be calculated by Cox proportional hazard model with robust variance using treatment (Rituximab Pfizer or Rituxan) 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 (Rituximab Pfizer or Rituxan) 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 (Rituximab Pfizer or Rituxan) 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 = ”Rituximab Pfizer”)
                = 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-one 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 =”Rituximab Pfizer”)
                = covariate1 covariate2;
        Match method = greedy (k=1 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. Definition for monotherapy and combination therapy

If one or more of the predefined drugs excluding prednisolone (Table 4 in the B3281009 protocol) are included on the Index month or within ± 1 Index month [-1 month to +1 month], therapy will be considered "baseline combination chemotherapy" and if not included, therapy will be considered "baseline monotherapy".

After index date, monotherapy and combination therapy will be determined for each Rituximab Pfizer or Rituxan administration. If one or more of the predefined drugs excluding prednisolone (Table 4 in the B3281009 protocol) are included within ±10 days, therapy will be considered combination chemotherapy and if not included, therapy will be considered monotherapy. The date of administration of combination therapy will be defined as the date of Rituximab Pfizer or Rituxan administration.

7.2. Outcome event (Infection and the other outcomes)

Three base analysis sets (Section 5) will be used to evaluate the risks of Rituximab Pfizer. The descriptive analysis set will be defined to evaluate Rituximab Pfizer data as much as possible from the viewpoint of pharmacovigilance. The comparative analysis set and the comparative matched analysis set will be defined to evaluate the relative risk of Rituximab Pfizer to Rituxan. Specifically, hazard ratio, rate ratio, and rate difference will be examined together in a 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 (Infections which requires procedures, medication or hospitalization etc., 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia', Infusion reactions, 'Hepatic function disorder, Jaundice', Cardiac disorder, Gastrointestinal perforation/obstruction, Hypotension, and Development of malignant tumor), a subset of each base analysis set that excludes patients with the same outcome event in accordance with Section 4.3 will be used. Propensity score will be calculated for each outcome event. For assessment of each outcome event, patients will be followed-up according to the definition in Section 4.6.1.

The crude incidence rate of each outcome event will be calculated for Rituximab Pfizer with the descriptive analysis set, and Rituximab Pfizer and Rituxan group with the comparative analysis set and the comparative matched analysis set. These analyses will also be conducted by each baseline monotherapy or baseline combination chemotherapy, and for the age group under 18 (age < 18). Patients who switched from baseline monotherapy to combination chemotherapy or baseline combination chemotherapy to monotherapy in the course of treatment will be considered as censor at the switched time point. In addition, these analyses will also be conducted in case where the switched patients will not be considered as censor at

the switched time point. Analyses where the switched patients are not considered as censor at the switched time point will be mainly used.

For infection which requires procedures, medication or hospitalization etc. and the other outcomes, at the completion of follow-up, 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. These analyses will also be conducted by each baseline monotherapy or combination chemotherapy. Patients who switched from baseline monotherapy to combination chemotherapy or baseline combination chemotherapy to monotherapy in the course of treatment will be considered as censor at the switched time point. In addition, these analyses will also be conducted in case where the switched patients will not be considered as censor at the switched time point. Analyses where the switched patients are not considered as censor at the switched time point will be mainly used.

Although this study is planned to be conducted with 1000 patients in the Rituximab Pfizer group, all the comparative analyses that is planned at the completion of follow-up will be conducted regardless of accumulation of the number of patients. However, if the study size is smaller, the statistical precision of estimation will be lower. Careful interpretation of the results should be required.

Crude hazard ratios and rate ratios will be calculated including 95% confidence intervals with Rituxan 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 KM curve will be used to summarize the time to first event of each outcome.

Two types of analyses based on propensity score will be conducted. First is IPTW method based on the comparative analysis set (primary analysis). Second is the matched analysis based on the comparative matched analysis set. These analyses will take into account the information of baseline monotherapy and baseline combination chemotherapy.

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.

7.2.1. Sensitivity analysis

For Infection, in the same manner of Section 7.2 with the comparative analysis set, because most of the study period are under COVID-19 pandemic situation, sensitivity analysis will also be conducted. Once patients are diagnosed with COVID-19, they will be considered as censor. That is, patients who have the ICD 10 code for COVID-19 (B342, Recipient number

8833876) in the course of exposure episodes will be considered as censor at the time point which have the ICD 10 code for COVID-19.

For malignancy, in the same manner of Section 7.2 with the comparative analysis set, sensitivity analyses will be considered when truncate events during specified risk periods (180 days) are associated with information known about the incidence of malignancies. Patients switching between Rituximab Pfizer and Rituxan will be censored at the time point of switching in this sensitivity analysis (Section 4.6.1).

7.3. 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

7.4. 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 rituximab 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 rituximab product on record, including the time after treatment switching (if any).

Treatment duration of patients switching to other rituximab 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 rituximab product. In addition, for patients switching to other rituximab product after index date (first switching only), the breakdown by pre-switch and post-switch product will be summarized for treatment duration. Rituximab Pfizer, Rituxan, and Rituximab KHK will be specified based on Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk in the B3281009 Protocol.

8. FEASIBILITY ANALYSIS

The feasibility analysis for the evaluation of the IPTW analysis and the matched analysis was conducted by using the data collected from January 2020 to September 2023. To prevent arbitrary planning of the research, only patient characteristics, the IPTW method and the

matching method based on the propensity score was evaluated, and analyses which related to outcome events was not conducted.

9. REFERENCE

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

10. APPENDIX

Appendix 1: Data Extraction Request Form