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

Post-marketing database Study

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Pfizer Japan Inc.

Study information

Title	RITUXIMAB BS Intravenous Infusion 100mg・500mg [Pfizer] Post-marketing database Study
Protocol number	B3281009
Protocol version identifier	Version 3
Date	14 November 2024
Active substance	Rituximab Pfizer
Medicinal product	PF-05280586
Research question and objectives	To evaluate the incidence of the outcomes for the 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
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2. DEFINITION OF TERMS

Not applicable

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
AMI	Acute Myocardial Infarction
BL	Burkitt Lymphoma
COVID-19	Coronavirus Disease 2019
DLBCL	Diffuse Large B-Cell Lymphoma
DPC	Diagnosis Procedure Combination
G-CSF	Granulocyte Colony-Stimulating Factor
GPSP	Good Post-Marketing Study Practice
HF	Heart failure
ICD-10	International Classification of Diseases 10th revision
IPTW	Inverse Probability of Treatment Weighting
ISO	International Organization for Standardization
IV	Intravenous Injection
LTB-FL	Low-Tumor-Burden Follicular Lymphoma
MDV	Medical Data Vision
MHLW	Ministry of Health, Labor and Welfare
RMP	Risk Management Plan
SA	Supraventricular Arrhythmia
SAP	Statistical Analysis Plan
VA	Ventricular Arrhythmia

4. RESPONSIBLE PARTIES

4.1. Responsible person of the study

The Japan Good Post Marketing Study Practice Officer

4.2. Clinical Expert

Name, degree(s)	Job Title	Affiliation
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5. ABSTRACT

- Title: Safety evaluation of Infections after exposure to Rituximab Pfizer in the post-marketing setting using Medical Data Vision database.

- Main authors

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- Rationale and background

Rituximab Pfizer is a follow-on biologic to Rituxan (the innovator). Rituximab Pfizer is a recombinant chimeric monoclonal antibody composed of variable regions derived from mouse anti-human CD20 monoclonal antibody and constant regions derived from human IgG1. Rituximab Pfizer is produced in Chinese hamster ovary cells. Rituximab Pfizer is a glycoprotein (molecular weight: approximately 147,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 213 amino acid residues each. Bio similarities between Rituximab Pfizer and Rituxan have been established through B3281001 and B3281006 and based on the Guidelines for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics from Ministry of Health, Labor and Welfare (PFSB/ELD Notification No. 0304007 dated March 4, 2009), and Rituximab Pfizer is approved as a treatment for CD20 positive B-cell non-Hodgkin's lymphoma.

As the similarity between this product and Rituxan is confirmed in Clinical trials, additional pharmacovigilance activities are required to be conducted for the approval to evaluate the safety for the use of Rituximab Pfizer in clinical settings. Based on the incidence rate of B3281006 study which was conducted for patients with CD20 positive LTB-FL (Low-tumor-burden follicular lymphoma), certain Adverse events are relatively higher (Infection: 26.5%, Serious Infections: 2.0%; Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia: 4.1%) than other safety specifications differentiated in Japan Risk Management Plan(J-RMP) (others: less than 2%). Infections and Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia were initially set as the safety specification of this study and afterwards Infections is set as the primary safety specification as Infection is clinically important and might be the outcome of Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis,

Thrombocytopenia. In this database study, Infection which requires procedures, medication or hospitalization will be focused on as the primary outcomes. 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia' are analyzed as a part of the secondary endpoints. In addition to the above, the outcomes of the following safety specifications will also be defined and they will be evaluated as secondary outcomes: Infusion reactions, 'Hepatic function disorder', Jaundice, Cardiac disorder, Gastrointestinal perforation/obstruction, Hypotension and Development of malignant tumor.

- Research question and objectives

The research question is to evaluate the incidence of the outcomes for above 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.

- Study design

An observational cohort study using a hospital-based claims database in Japan will be performed. (Figure 3) For each outcome except for malignancy, infusion reaction and hypotension, the follow-up window continues until the first incidence of an event, date of switch to another Rituximab product, the end of continuous treatment plus risk window (180 days after the last dose), 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 infusion reaction and hypotension, the follow-up window continues until the first incidence of an event, date of switch to another Rituximab product, the end of continuous treatment plus risk window (until the next day after the last dose), death or the end of study period. For malignancy, the follow-up window continues until the first incident event, 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 end of the study period.

- Population

  The study population includes individuals who have a diagnosis of CD20 positive B-cell non- Hodgkin's lymphoma and have been treated with Rituximab Pfizer or the Rituxan within the planned 5-year study period 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.

- Variables

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 the Rituximab Pfizer exposed group despite of taking any Rituximab products before exposure to Rituximab Pfizer. Considering comparison, the Comparative Analysis Set includes the new users of Rituximab Pfizer and Rituxan. Inclusion criteria for each analysis set are as following:

Descriptive Analysis Set

Exposed group:

1. All patients treated with Rituximab Pfizer (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 the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad) on the index month (the claim month of index date) 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.

Comparative Analysis Set

Exposed group

1. All patients treated with Rituximab Pfizer (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 the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad) on the index month (the claim month of index date) 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 (Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk).

Control group:

1. All patients treated with Rituxan (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 the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad) on the index month or within 6 months before index date [-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 (Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk).

Outcome events: To capture each outcome events of Safety Specification, they are defined with disease, medication or procedures.

Covariates: Information on sociodemographic characteristics (sex, age and calendar year at the index date), medical history and premedication are going to be collected from the database and each assessment windows are determined depends on the characteristics of covariates.

- 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.

- Study size

The number of exposed to Rituximab Pfizer would be expected to 1,000 patients. The number of comparator (Rituxan) patients would be expected to be about 9 times as large as the patients exposed to Rituximab Pfizer.

- Data analysis

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.

- The descriptive analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria.
- The comparative analysis set will include all patients who are new users among those considered eligible by the inclusion and exclusion criteria. 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 Biosimilar or non-Rituximab Pfizer Biosimilar.
- 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 incidence rate 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) 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. The incidence rate will be estimated by counting the number of subjects with event in the numerator and dividing by the total person-time of observation in the denominator. These analyses will also be conducted by each monotherapy (Rituximab Pfizer or Rituxan) or combination chemotherapy (including Rituximab Pfizer or Rituxan). If one or more of the predefined drugs excluding prednisolone are included (Appendix 6), therapy will be considered combination chemotherapy and if not included, therapy will be considered monotherapy. Patients who switched from monotherapy to combination chemotherapy or 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. Crude hazard ratios and 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). These analyses will also be conducted by each monotherapy (Rituximab Pfizer or Rituxan) or combination chemotherapy (including Rituximab Pfizer or Rituxan). Patients who switched from monotherapy to combination chemotherapy or 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.

Two types of analyses based on propensity score will be conducted. First is the Inverse Probability of Treatment Weighting (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 monotherapy and 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. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate differences will be calculated by Poisson regression model accounting for different duration on treatment.

For the matched analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated using the following models. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate differences will be calculated by Poisson regression model accounting for different duration on treatment.

The feasibility analysis for the evaluation of the IPTW analysis and the matched analysis was conducted during the course of the study 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.

- Milestones

The study period is from 01 January 2020 through 31 December 2024. The start of data collection for the final analysis is on 31 January 2025 (the date when data extraction begins). The end of data collection is on 30 April 2025 (the date when the analytic dataset is completely available). The final study report submission will be on 31 January 2026. The data extraction for Feasibility analysis was conducted on 25 December 2023.

6. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Ver 3.0	14 November 2024	substantial	Section 10.2.2.1 Section 10.2.2.2	Change in the definition of the disease code for CD20-positive B-cell non-Hodgkin lymphoma	As a result of the feasibility study, in order to properly evaluate the risks of this drug, the scope of the applicable disease codes was expanded in [redacted]
			Section 10.5 Section 10.7	Changing the matching ratio (treatment group: control group) from 1:2 to 1:1	As a result of the feasibility study, it was anticipated that the number of patients in the control group at the final analysis would fall below twice that of the test drug group, contrary to the initial assumptions made during the trial planning. Therefore, [redacted], the matching ratio (test drug group: control group) was changed from 1:2 to 1:1.
			ANNEX 1	Updated Appendix 1 in accordance with change in the definition of the disease code for CD20-positive B-cell non-Hodgkin lymphoma	As the code List for diseases is updated
		administrative	Abstract	Reflecting the above changes and changing the person in charge	

			All sections All sections	Updated to protocol template Description adjustment to clarify	
Ver 2.0	17 January 2024	substantial	Section 10.3 Section 17 ANNEX 1 Appendix 1 Appendix 2	Clarified the code list information Appendix 5 Deleted the duplicate code 8847396 and added 8847324 Added EPS Corporation Added Appendix 5 and 6 Updated Chart and List Deleted Table 4	As the code list is developed and added as Appendix 5 Error correction As Selected and newly contracted to outsource the analysis. As the code lists are developed and added to Appendix Due to update of Internal Organizational system for Post-marketing Surveillance As the code list is developed and added as Appendix 6

7. MILESTONES

Milestone	Planned date
Timing to finalize the study protocol	30 September 2023
Start of data collection	31 January 2025
End of data collection	30 April 2025
Final study report	31 January 2026

8. RATIONALE AND BACKGROUND

Rituximab Pfizer is a follow-on biologic to Rituxan (the innovator). Rituximab Pfizer is a recombinant chimeric monoclonal antibody composed of variable regions derived from mouse anti-human CD20 monoclonal antibody and constant regions derived from human IgG1. Rituximab Pfizer is produced in Chinese hamster ovary cells. Rituximab Pfizer is a glycoprotein (molecular weight: approximately 147,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 213 amino acid residues each. Bio similarities between Rituximab Pfizer and Rituxan have been established through B3281001 and B3281006 and based on the Guidelines for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics from Ministry of Health, Labor and Welfare (PFSB/ELD Notification No. 0304007 dated March 4, 2009), and Rituximab Pfizer is approved as a treatment for CD20 positive B-cell non-Hodgkin's lymphoma.

As the similarity between this product and Rituxan is confirmed in Clinical trials, additional pharmacovigilance activities are required to be conducted for the approval to evaluate the safety for the use of Rituximab Pfizer in clinical settings. Based on the incidence rate of B3281006 study which was conducted for patients with CD20 positive LTB-FL (Low-tumor-burden follicular lymphoma), certain Adverse events are relatively higher than other safety specifications differentiated in J-RMP (Infection: 26.5%, Serious Infections: 2.0%; 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia': 4.1%; others: less than 2%). Infections and 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia' were initially set as the safety specification of this study and afterwards, Infections is set as the primary safety specification as Infection is clinically important and might be the outcome of Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia. In this database study, Infection which requires procedures, medication or hospitalization will be focused on. 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia' is analyzed as a part of the secondary endpoints. In addition to the above, the outcomes of the following safety specifications will also be defined, and they will be evaluated as secondary outcomes:

Infusion reactions, 'Hepatic function disorder, Jaundice', Cardiac disorder, Gastrointestinal perforation/obstruction, Hypotension and Development of malignant tumor.

This study will be conducted based on the following Good Post-Marketing Study Practice (GPSP) Ordinance:

"MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated 20 Dec 2004), "Enforcement of the MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated 20 Dec 2004), "Questions and Answers (Q & A) on the MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Medical Products" (Office Memorandum, dated 25 Mar 2005), "Guidelines on the Method for Conducting Post-marketing Study, etc. of Prescription Drugs" (PFSB/ELD Notification No. 1027001, dated 27 Oct 2005), "Enforcement of the MHLW Ordinance on the Standards for Post-marketing Safety Control of Medicinal Products, Quasi-medicinal Products, Cosmetics, and Medical Devices and Enforcement of the MHLW Ordinance on the Partial Revision of the MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 0311-7, dated 11 Mar 2013), "MHLW Ordinance on the Amendments of Related Cabinet Orders in accordance with the Law Partially Revising the Pharmaceutical Affairs Law, etc. and Enforcement of the Law Partially Revising the Pharmaceutical Affairs, Law, etc. and on the Amendments of Related Cabinet Orders in accordance with the Enforcement of the Cabinet Order on Transitional Measures" (Article 14, Partial Revision of the MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Medical Devices) (MHLW Ministerial Ordinance No. 87, dated 30 Jul 2014), "MHLW Ordinance for Partial Amendments of the MHLW Ordinance on the Standards for Post-Marketing Surveillances and Clinical Trials of Medical Products (Partial Amendments of the MHLW Ordinance on the Standards for Post-Marketing Surveillances and Clinical Trials of Medical Products)" (MHLW Ordinance No. 116, dated 26 Oct 2017), "Promulgation of the MHLW Ordinance for Partial Amendments of the MHLW Ordinance on the Standards for Post-Marketing Surveillances and Clinical Trials of Medical Products (Related to the MHLW Ordinance on the Standards for Post- Marketing Surveillances and Clinical Trials of Medical Products)" (PSEHB Notification No. 1026-1, dated 26 Oct 2017), "MHLW Ordinance on the Amendments of Related Cabinet Orders in accordance with enforcement of the Law Partially Revising the Law on Ensuring Quality, Efficacy, and Safety of Pharmaceutical Products and Medical Devices (Partial Revision of the MHLW Ordinance on the Standards for Post-marketing Studies and Clinical Trials of Pharmaceutical Products)" (MHLW Ordinance No. 155, dated 31 Aug 2020), About the confirmation method of the implementation status of the Post-marketing Database Studies using the DB survey management tool in the compliance inspection of pharmaceutical products and regenerative medical products (PMDA/CRS Notification No. 1111002, dated 11 Nov 2021), "Points to note on the Reliability assurance for Post-marketing Database Studies Medical Products" (PSEHB Notification No. 0221-1, dated 21 Feb 2019), "Questions and Answers (Q & A) on the Reliability assurance for Post-marketing Database Studies

Medical Products" (Office Memorandum, dated 19 Jun 2019), "Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases" (PMDA) (dated 31 Mar 2014), "Basic principles on the utilization of health information databases for Post-Marketing Surveillance of Medical Products" (PSEHB/PED Notification No. 0609-8, PSEHB/SD Notification No. 0609-4, dated 9 Jun 2019), "Contents and format of a study protocol for Post-marketing Database Study" (PMDA) (dated 23 Jan 2018), "Risk Management Plan Policy" (PFSB/SD Notification No. 0411-1 / -2, dated 11 Apr 2012), "Procedures for Developing Post-marketing Study Plan (originally published as Procedures for Developing Post-marketing Study Plan by PMDA in January 2018)" (PSEHB/PED Notification No. 0314-4, PSEHB/SD Notification No. 0314-4, dated 14 Mar 2019), "Development and Publication of Risk Management Plan" (Joint PSEHB/DED Notification No. 0318-2 and PSEHB/SD Notification No. 0318-1, dated 18 Mar 2022), "Questions and Answers (Q & A) on Risk Management Plans" (Office Memorandum, dated 18 Mar 2022), and "Pharmacovigilance Planning" (PFSB/ELD Notification No. 0916001, PFSB/SD Notification No. 0916001, dated 16 Sep 2005).

9. RESEARCH QUESTION AND OBJECTIVES

9.1. Safety Specifications(J-RMP)

Important Identified Risks: "Infections, 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia', Infusion reactions, 'Hepatic function disorder, Jaundice', Cardiac disorder, Gastrointestinal perforation/obstruction, Hypotension"

Important Potential Risks: "Development of malignant tumor"

Important Missing Information: "None"

9.2. Research question (study objective)

Research question for this study is to evaluate the incidence of the outcomes for above safety specifications in patients diagnosed with CD20 positive B-cell non- Hodgkin's lymphoma who were treated with Rituximab Pfizer to compare it to those 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.

10. RESEARCH METHODS

10.1. Study design

An observational cohort study using a hospital-based claims database in Japan will be performed. (Figure 3) The primary and secondary outcomes are evaluated 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.

10.2. Setting

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. Data collection of MDV database started from April 2008. As of January 2023, the MDV database included information on more than 42 million patients from 475 hospitals which covers approximately 27% of acute-care hospitals using the DPC system. Data variables include hospitalization and discharge information, patient information, inpatient and outpatient medications, medical practices, inpatient and outpatient diagnoses, and laboratory results.

10.2.1. 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.

10.2.2. 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 with the exposure group despite of taking any Rituximab products before exposure to Rituximab Pfizer. Considering comparison, the Comparative Analysis Set includes the new users of Rituximab Pfizer and Rituxan. Inclusion criteria for each analysis set are as following:

10.2.2.1. Descriptive Analysis Set

Exposed group:

1. All patients treated with Rituximab Pfizer (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 the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad)[1,2] 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.

10.2.2.2. Comparative Analysis Set

Exposed group:

1. All patients treated with Rituximab Pfizer (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 the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad)[1,2] 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 (Appendix 3 Sheet: RTX_pfi, RTX_original, RTX_khk).

Control group:

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

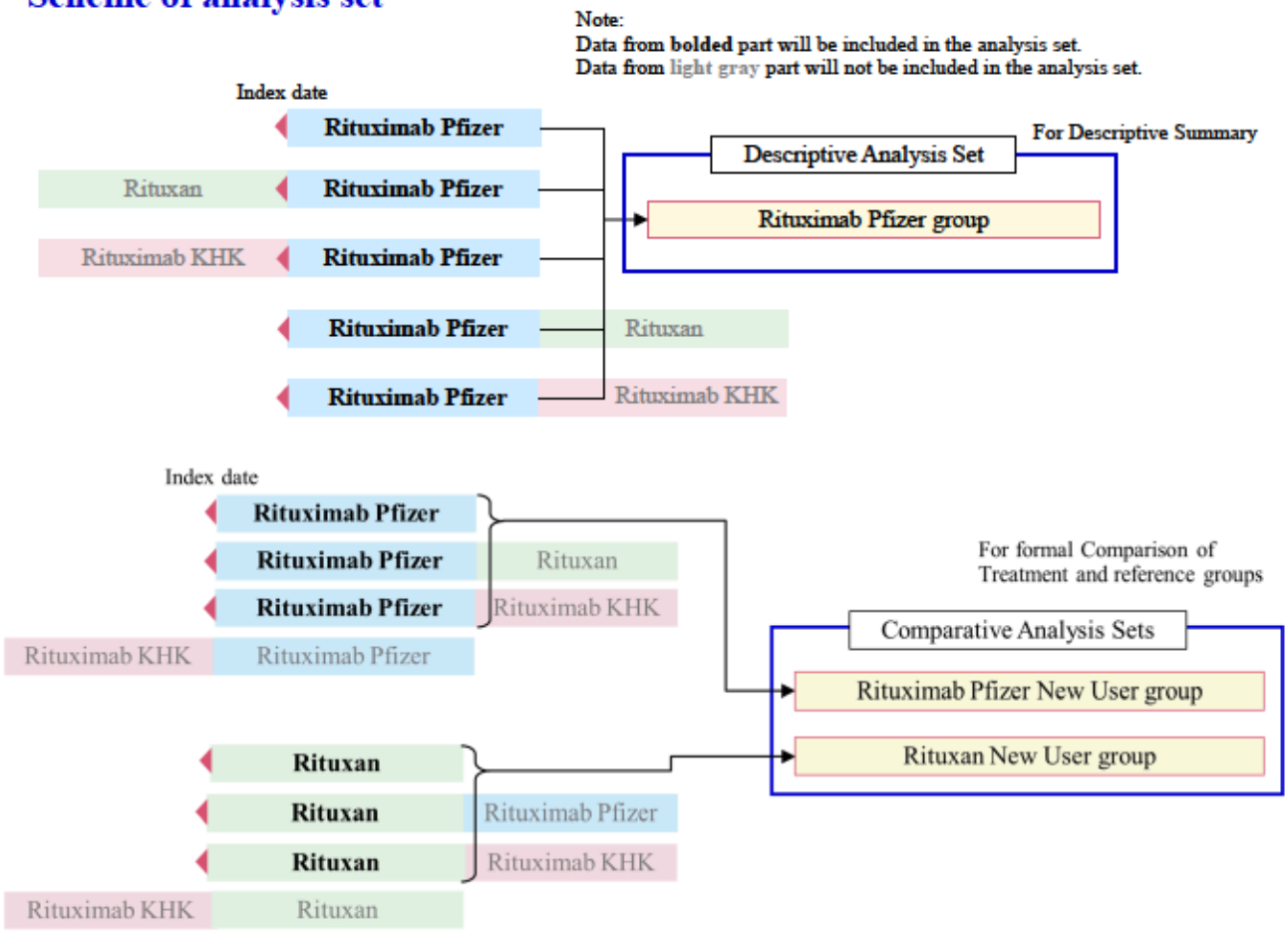
2. Having the defined diagnosis code of CD20 positive B-cell non- Hodgkin's lymphoma (Appendix 1 Sheet: NHL_CD20_broad) on the index month or within 6 months before index month [-6 month to 0 month (index month)].

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 s before the index month.

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

Figure 1. Scheme of Analysis sets

Scheme of analysis set



10.2.3. 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 (Appendix 1 Sheet: B_CLL), Immune thrombocytopenia, Idiopathic Thrombocytopenic Purpura (Appendix 1 Sheet: ITP), Nephrotic Syndrome (Appendix 1 Sheet: Nephrosis), Granulomatosis with polyangiitis/ Microscopic polyangiitis (Appendix 1 Sheet: MPA_GPA), Acquired Thrombotic Thrombocytopenic Purpura (Appendix 1 Sheet: TTP_acquired), Systemic Sclerosis (Appendix 1 Sheet: SSc), Refractory Pemphigus Vulgaris and Pemphigus Foliaceus (Appendix 1 Sheet: PV_PF), Neuromyelitis Optica Spectrum Disorder (Appendix 1 Sheet: NMOSD), Liver (Appendix 4 Sheet: Liver_transplantation) and Kidney transplantation (Appendix 4 Sheet: Kidney_transplantation)

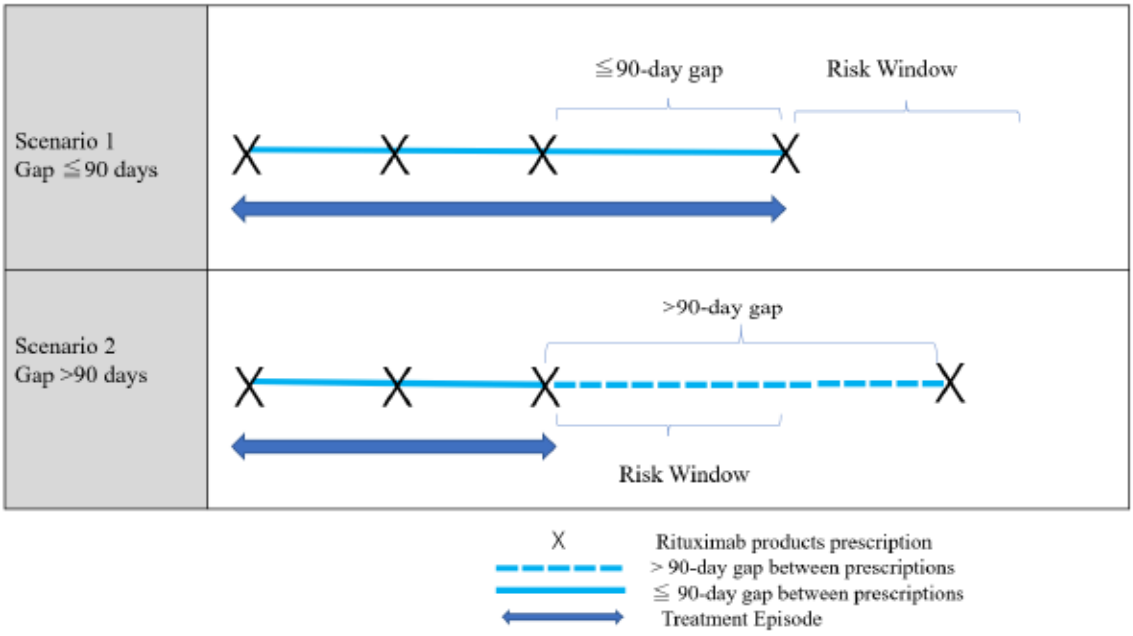
Patients meet following criteria will not be included to the analysis of each outcome:

- Patients having diagnosis for Tuberculosis defined in 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 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 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 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.

10.2.4. Definition of continuous treatment

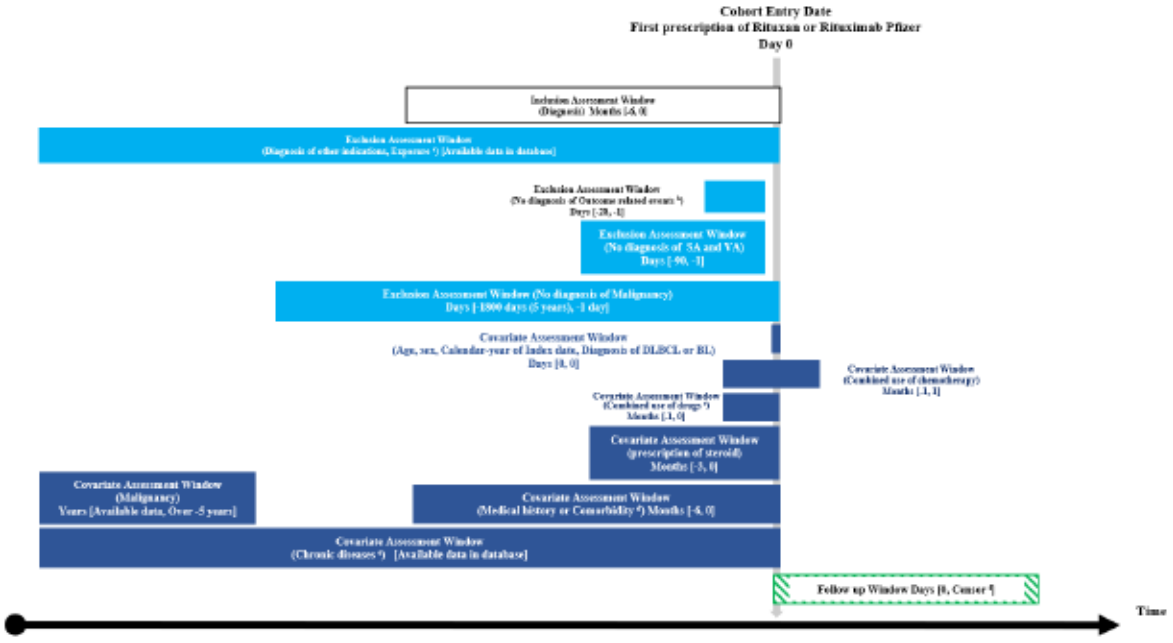
According to the dosage and administration on package insert, for the acute therapy, Rituximab product is administrated once a week up to 8 times and for maintenance therapy, it is administrated every 8 weeks up to 12 times. The acute and maintenance therapy can't be clearly distinguished, therefore 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 2.

Figure 2. Examples of exposure episodes



10.2.5. Flow chart

Figure 3. 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

10.3. Variables

The following data will be available for the analysis. Study variables, their roles and operational definitions are described in Table 1.

Table 1 Study variables, their roles, and operational definitions

Variable	Role	Operational definition
Exposure Variables		
Rituximab Use	Main Exposure	See 10.2.2
Outcome variables		

Variable	Role	Operational definition
Infection	Primary outcome	See 10.3.1.1
'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia'	Secondary outcome	See 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 10.3.1.2.6
'Hepatic function disorder, Jaundice'	Secondary outcome	See 10.3.1.2.7
Cardiac disorder	Secondary outcome	See 10.3.1.2.8
Gastrointestinal perforation/obstruction	Secondary outcome	See 10.3.1.2.9
Hypotension	Secondary outcome	See 10.3.1.2.10
Development of malignant tumor	Secondary outcome	See 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 10.7
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

Variable	Role	Operational definition
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
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' [3] (Appendix 5).

Variable	Role	Operational definition
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 8847396 and 8847324), 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

10.3.1. Definition of outcomes and defining information

10.3.1.1. Primary Outcome: Infection which requires procedures, medication or hospitalization

Infection is defined be the composite criteria.

[Infection requiring hospitalization]

Hospitalization due to Infection specified in the code list (excluding Tuberculosis, Herpes zoster, Cytomegalovirus infection, and Candida infection) (Appendix 2). From DPC form 1, a hospitalization date when Infection code is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date.

[Tuberculosis]

Identify events as below and set the earliest date as the outcome incidence date.

• Patients who have Tuberculosis record specified in the code list (Appendix 1 Sheet: TB) and given concomitant prescribing of Isoniazid (Appendix 3 Sheet: INH) and Rifampicin (Appendix 3 Sheet: RFP) or Pyrazinamide (Appendix 3 Sheet: PZA) within the three months before and after the month Tuberculosis recorded. The date of drug prescription is defined as the event incidence date.

[Herpes zoster]

Identify events by the following Composite:

• The record of hospitalization according to Herpes zoster specified in the code list (Appendix 1 Sheet: VZV). From DPC form 1, a hospitalization date when Herpes zoster code is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

• Patients who have the record of Herpes zoster specified in the code list and a prescription of any of Aciclovir (Appendix 3 Sheet: ACV), Valaciclovir (Appendix 3 Sheet: VACV), Famciclovir (Appendix 3 Sheet: FCV), Amenamevir (Appendix 3 Sheet: AMNV), and Vidarabine (except for topical treatment) (Appendix 3 Sheet: Ara_A) in the same month. The date of drug prescription is defined as the event incidence date. Aciclovir must be greater than 200 mg/day.

[Cytomegalovirus infection]

Identify events by the following Composite: Identify events as follows:

• Hospitalization due to Cytomegalovirus infection specified in the code list (Appendix 1 Sheet: CMV). From DPC form 1, a hospitalization date when Cytomegalovirus infection code is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

• Patients who have a record of Cytomegalovirus infection specified in the code list and prescription with either Ganciclovir (Appendix 3 Sheet: GCV), Valganciclovir (Appendix 3 Sheet: VGCV), or Foscarnet (Appendix 3 Sheet: FOS) in the same month. The date of drug prescription is defined as the event incidence date.

[Candidiasis]

Identify events as follows:

・Patients who have the record of Candidiasis specified in the code list (Appendix 1 Sheet: Candida) and prescription of any one of Micafungin (Appendix 3 Sheet: MCFG), Caspofungin (Appendix 3 Sheet: CPFG), Amphotericin B liposome (Appendix 3 Sheet: L_AMB), and Voriconazole (Appendix 3 Sheet: VRCZ) in the same month. The date of drug prescription is defined as the event incidence date.

10.3.1.2. Secondary Outcomes

Each outcome is defined as below.

10.3.1.2.1. Pancytopenia (Aplastic anemia)

Identify event incidence date by the following Composite:

・Hospitalization due to Aplastic anemia. From DPC form 1, a hospitalization date when the Aplastic anemia code (Appendix 1 Sheet: AA) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date.

OR

・When treatment was performed by Granulocyte Colony Stimulating Factor (G-CSF) product (Appendix 3 Sheet: GCSF), red blood cell transfusion (Appendix 3 Sheet: RBC), or platelet transfusion (Appendix 3 Sheet: PC) in the same month of the record of the aplastic anemia. The earliest date of intervention is defined as the outcome incidence date.

OR

・When the date of incidence of each outcome of Anemia, 10.3.1.2.2 Leukopenia, and 10.3.1.2.5 Thrombocytopenia was identified and all of them occurred in the same month. Among the incidence dates of these outcomes identified in the same month, the earliest date will be the incidence date of pancytopenia.

To cover Pancytopenia, we define Anemia as well for a part of its outcome definition. Identify event incidence day by the following Composite:

・Hospitalization due to Anemia. From DPC form 1, a hospitalization date when Anemia code (Appendix 1 Sheet: Anemia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

• When the red blood cell transfusion (Appendix 3 Sheet: RBC) is conducted in the same month as the diagnosis of Anemia was recorded. Red blood cell transfusion date will be the event incidence date.

10.3.1.2.2. Leukocytopenia

Identify event incidence date by the following Composite:

·Hospitalization due to Leukopenia. From DPC form 1, a hospitalization date when Neutropenia code (Appendix 1 Sheet: Leukopenia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

·When G-CSF product (Appendix 3 Sheet: GCSF) is prescribed in the same month when Leukopenia is recorded. The date of drug prescription is defined as the event incidence date.

10.3.1.2.3. Neutropenia

Identify event incidence date by the following Composite:

·Hospitalization due to Neutropenia. From DPC form 1, a hospitalization date when Neutropenia code (Appendix 1 Sheet: Neutropenia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

·When G-CSF product (Appendix 3 Sheet: GCSF) is prescribed in the same month when neutropenia is recorded. The date of drug prescription is defined as the event incidence date.

10.3.1.2.4. Agranulocytosis

Identify event incidence date by the following Composite:

·Hospitalization due to Agranulocytosis. From DPC form 1, a hospitalization date when Agranulocytosis code (Appendix 1 Sheet: Agranulocytosis) is included in diagnostic information/main injury disease (payload code A006010), diagnostic

information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

·When G-CSF product (Appendix 3 Sheet: GCSF) is prescribed in the same month when Agranulocytosis are recorded. The date drug prescription is defined as the event incidence date.

10.3.1.2.5. Thrombocytopenia

Identify event incidence date by the following Composite:

·Hospitalization due to Thrombocytopenia. From DPC form 1, a hospitalization date when Thrombocytopenia code (Appendix 1 Sheet: Thrombocytopenia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the event incidence date.

OR

·When the thrombocytopenia was calculated in the same month that the platelet transfusion (Appendix 3 Sheet: PC (Platelet Concentrate)) was performed. The date of Platelet transfusion is performed is defined as the event incidence date.

10.3.1.2.6. Infusion Reaction

Identify events using the following algorithm. The earliest date of related medical activities is defined as the date of outcome incidence.

1. Anaphylaxis/Allergy (Appendix 1 Sheet: Allergy), Angioedema (Appendix 1 Sheet: Angioedema), Shock (Appendix 1 Sheet: Shock), Hypotension (Appendix 1 Sheet: Hypotension), Fever/ Chills (Appendix 1 Sheet: Fever), Headache (Appendix 1 Sheet: Headache), Nausea (Appendix 1 Sheet: Nausea), Malaise (Appendix 1 Sheet: Malaise), Rash (Appendix 1 Sheet: Rash), Bronchospasm (Appendix 1 Sheet: Bronchospasm), Ventricular Fibrillation (Appendix 1 Sheet: VF), Acute Respiratory Distress Syndrome (Appendix 1 Sheet: ARDS), Acute Myocardial Infarction (AMI) (Appendix 1 Sheet: AMI), and Pneumonia (Appendix 1 Sheet: Pneumonia_IR) are recorded in the same month as the Rituximab product prescription.

2. Patients who meet criteria 1 above with Epinephrine (Appendix 3 Sheet: Epinephrine), short acting beta-agonists (Appendix 3 Sheet: SABA), Vasoconstrictive (Intravenous Injection (IV)) drug (Appendix 3 Sheet: Vasoconstrictive), Glucagon (Appendix 3

Sheet: Glucagon) administration (if β-blocker prescription is available within 90 days), 2 or more Histamine 1 blocker (Appendix 3 Sheet: H1_blocker) administrations, 2 or more Infusion drug product (Appendix 3 Sheet: Infusion) administrations, 2 or more Glucocorticoid (except topical medication) (Appendix 3 Sheet: GC) administrations or Oxygen (Appendix 4 Sheet: Oxygen) administrations on the same or following day of the Rituximab product prescription .

10.3.1.2.7. Hepatic function disorder, Jaundice

Identify event incidence date using the following methods.

・Patients with the diagnosis record of Toxic liver disease (Appendix 1 Sheet: Toxic_liver_disease), Liver failure (Appendix 1 Sheet: Liver_failure), Inflammation liver disease/unspecified (Appendix 1 Sheet: Inflammatory_liver_disease), Central hemorrhagic liver necrosis (Appendix 1 Sheet: Central_hemo_liver_necrosis), Jaundice (Appendix 1 Sheet: Jaundice) and Serum chemistry (Appendix 4 Sheet: Serum_chemistry) done in the same month. The onset date of any medical treatments identified in this bullet is defined as the event incidence date.

10.3.1.2.8. Cardiac Disorder

Define the events by the following Composite.

[Supraventricular Arrhythmia (SA)]

Define events by the following Composite:

・Hospitalization due to SA. From DPC form 1, a hospitalization date when SA code (Appendix 1 Sheet: Supraventricular_arrhythmia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date.

OR

・ When either Anticoagulant prescription (Appendix 3 Sheet: Anticoagulant), Arrhythmia drug prescription (Appendix 3 Sheet: Antiarrhythmic), Defibrillation (Appendix 4 Sheet: Defibrillation), or Ablation (Appendix 4 Sheet: Ablation) is conducted in the same month as the diagnostic code of Supraventricular arrhythmia is recorded. The date of medical treatment will be the outcome incidence date.

[Ventricular Arrhythmia (VA)]

Define events by the following Composite:

・Hospitalization due to VA. From DPC form 1, a hospitalization date when VA code (Appendix 1 Sheet: Ventricular_arrhythmia) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as an outcome incidence date.

OR

・When either prescription of arrhythmia drug (Appendix 3 Sheet: Antiarrhythmic), defibrillation (Appendix 4 Sheet: Defibrillation), or Ablation (Appendix 4 Sheet: Ablation) is conducted in the same month as diagnostic code of Ventricular arrhythmia is recorded. The earliest date when the medical procedures are recorded is defined as the outcome incidence date.

[AMI/Angina pectoris]

Define events by the following Composite.

・Hospitalization due to AMI. From DPC form 1, a hospitalization date when the AMI code (Appendix 1 Sheet: AMI) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date.

OR

・When either Percutaneous coronary intervention (Appendix 4 Sheet: PCI) or Coronary Artery Bypass Grafting (Appendix 4 Sheet: CABG) is performed. The date of medical treatment will be the outcome incidence date.

[Heart failure (HF)]

Define events by the following Composites:

・Hospitalization due to HF. From DPC form 1, a hospitalization date when HF code (Appendix 1 Sheet: HF) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as an outcome incidence date.

OR

・When either Diuretic(IV) (Appendix 3 Sheet: Diuretic), Nitrates (IV) and Nicorandil (Appendix 3 Sheet: Nitrate), Carperitide (Appendix 3 Sheet: Carperitide), Catecholamine Cardiotonic (Appendix 3 Sheet: Catecholamine) , Digitalis (Appendix 3 Sheet: Cardiotonic), PDEIII inhibitors /Calcium sensitizers (Appendix 3 Sheet: PDEIII_inhibitor) or Adenylate cyclase activators (Appendix 3 Sheet: AC_activator) is prescribed in the same month as the disease name of HF was recorded. The date when the drug was prescribed will be the outcome incidence date.

10.3.1.2.9. Gastrointestinal perforation/obstruction

Identify each outcome by the following Composite.:

[Gastrointestinal perforation]

・Hospitalization due to Gastrointestinal perforation. From DPC form 1, a hospitalization date when Gastrointestinal perforation code (Appendix 1 Sheet: GI_perforation) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date.

OR

・When the Surgery (Appendix 4 Sheet: Surgery) is performed in the same month of the diagnostic code of Gastrointestinal perforation is recorded. The date when the surgery is performed will be the outcome incidence date.

[Gastrointestinal obstruction]

・ Hospitalization due to Gastrointestinal obstruction. From DPC form 1, a hospitalization date when Gastrointestinal obstructions (Appendix 1 Sheet: Intestinal_obstruction) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resources (payload code A006030) is defined as the outcome incidence date.

OR

・Either Surgery (Appendix 4 Sheet: Surgery) or Gastric continuous drainage (Appendix 4 Sheet: Ga_drainage) was performed in the same month when the diagnostic code of Gastrointestinal obstruction is recorded. The date when the surgery is performed will be the outcome incidence date.

10.3.1.2.10. Hypotension

Identify events by the following algorithm. The earliest date of related medical activities is defined as the outcome incidence date.

1. Both Shock (Appendix 1 Sheet: Shock) and Hypotension (Appendix 1 Sheet: Hypotension) are recorded in the same month as the Rituximab product prescription.

2. Patients who meet criteria 1 above with epinephrine (Appendix 3 Sheet: Epinephrine), short acting beta-agonists (Appendix 3 Sheet: SABA), Vasoconstrictive (IV) (Appendix 3 Sheet: Vasoconstrictive), glucagon (Appendix 3 Sheet: Glucagon) administration (if β-blocker prescription is available within 90 days), 2 or more H1 blocker (Appendix 3 Sheet: H1 blocker) administrations, 2 or more infusion drug product (Appendix 3 Sheet: Infusion) administrations, 2 or more glucocorticoid (except topical medication) (Appendix 3 Sheet: GC) administrations or oxygen (Appendix 4 Sheet: Oxygen) administrations on the same or following day of the Rituximab product prescription.

10.3.1.2.11. Development of malignant tumor

Identify events by the following Composite. The events are evaluated for each malignant tumor code.

·Malignant tumor (Appendix 1 Sheet: Cancer) is recorded, and Surgery (Appendix 1 Sheet: Surgery) is performed in the same month, or within the same hospitalization period. The date of surgery is defined as the outcome incidence date.

OR

·Malignant tumor is recorded and anti-tumor drug therapy is performed in the same month. The date of prescription of chemotherapy (Appendix 3 Sheet: Chemotherapy) will be the outcome incidence date.

OR

·Malignant tumor is recorded and radiation therapy is performed in the same month. The date of Radiation (Appendix 4 Sheet: Radiation) performed is defined as the outcome incidence date.

OR

·Malignant tumor is recorded, and hematopoietic stem cell transplantation is performed in the same month. The date of hematopoietic stem cell transplantation (Appendix 4 Sheet: HSCT) will be the outcome incidence date.

OR

·Malignant tumor is recorded more than once within 2 months. The day in a following month among the two specified claims months is the outcome incidence date.

OR

·Hospitalization due to Malignant tumor. From DPC form 1, a hospitalization date when Malignant tumor code (Appendix 1 Sheet: Cancer) is included in diagnostic information/main injury disease (payload code A006010), diagnostic information/hospitalization trigger (payload code A006020), and diagnostic information/medical resource (payload code A006030) is defined as the outcome incidence date. However, purpose and clinical course (payload code A000060) are "diagnosis and investigation only" and "educational hospitalization" will be excluded.

10.3.1.3. 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 [4]). 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.

10.3.2. 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 1 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 10.7)

Infection: Long term use of Steroid, Leukopenia, Neutropenia, Lymphopenia, Low serum immunoglobulin level (Hypoglobulinemia), Medical history or Comorbidity of Infection, Medical History of Rheumatoid Arthritis (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: Combined use of Chemotherapy, Diagnosis of DLBCL or BL

Hypotension: Combined use of Antihypertensives

Development of malignant tumor: Medical History of Malignancy

10.4. 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. The detailed information is described in Section 10.2.

10.4.1. 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 10.2.2 and Section 10.2.3 by their standard operating procedures and provide them to Pfizer.

10.4.2. 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[5,6,7,8] and treatment guidelines[9,10].

For some of the secondary outcomes, the published validation studies were available such as Leukocytopenia[11,12], Thrombocytopenia[13,14,15,16,17,18], Infusion reactions[19,20,21], Hepatic function disorder and Jaundice[22,23,24], Cardiac disorder[25,26,27,28,29], Gastrointestinal perforation/obstruction[30], and Development of malignant tumor[8] therefore, the outcome definition 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.

10.5. 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 2, 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 3), 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 2. 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 3. 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.

10.6. Data management

The quality of the provided data is managed under the internal procedures of MDV which is aligned with GPSP requirement. The frequency for medical information DB is done by monthly for the updates and the format is based on the claimed data or DPC template which is stated by the government. All the data is provided to MDV once the data is anonymized at the sites.

10.7. Data analysis

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 comprehensive fashion to evaluate the overall safety profile. Any inconsistency in results among the three measures will be examined for its cause.

- The descriptive analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria in Section 10.2.2.1 and Section 10.2.3.
- The comparative analysis set will include all patients who are new users among those considered eligible by the inclusion and exclusion criteria in Section 10.2.2.2 and Section 10.2.3. 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.
- 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 10.3.2). Feasibility of the matching scheme will be assessed at the interim analysis.

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 10.2.3 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 10.3.1.3. In addition, for Infection, 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.

The 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. The incidence rate will be estimated by counting the number of subjects with event in the numerator and dividing by the total person-time of observation in the denominator. These analyses will also be conducted by each monotherapy (Rituximab Pfizer or Rituxan) or combination chemotherapy (including Rituximab Pfizer or Rituxan). If one or more of the predefined drugs excluding prednisolone are included (Appendix 6), therapy will be considered combination chemotherapy and if not included, therapy will be considered monotherapy. Patients who switched from monotherapy to combination chemotherapy or 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 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. 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 10.3.1.3).

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. Crude hazard ratios and 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). Hazard ratios and its 95% confidence intervals will be calculated by Cox proportional hazard model using treatment (Rituximab Pfizer or Rituxan) as a factor. 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[31]. These analyses will also be conducted by each monotherapy (Rituximab Pfizer or Rituxan) or combination chemotherapy (including Rituximab Pfizer or Rituxan). Patients who switched from monotherapy to combination

chemotherapy or 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.

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 monotherapy and 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 as same as the score used in the matched analysis. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate differences will be calculated by Poisson regression model accounting for different duration on treatment. In each of these analyses, treatment (Rituximab Pfizer or Rituxan) will be included as a factor. Distribution of propensity scores and weights will be examined prior to the analyses.

For the matched analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated using the following models. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate differences will be calculated by Poisson regression model accounting for different duration on treatment. In each of these analyses, treatment (Rituximab Pfizer or Rituxan) will be included as a factor.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

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.

10.8. Quality control

This study is a retrospective cohort study using quality-controlled data in a pre-existing database, and primary data collection will not be conducted. The quality of the data provided is managed by MDV through the oversight of their in-house data maintenance and quality improvement teams. All these processes are consistently managed in-house. MDV also has been certified as 'ISO27001'. Each document or dataset developed through this study will be stored for the duration required by GPSP.

10.9. Limitations of the research methods

Several limitations should be considered when interpreting the findings from this study. Following limitations are likely to apply to both exposure and control groups equally. Hence, confounding effects are expected to be limited in this study under an assumption of non-differential misclassification in compared groups.

Limitations due to MDV database:

- As the laboratory data of MDV is not available for use in Post marketing DB studies yet because of the data reliability and the limited number of sites which provide the laboratory data, outcome and covariates which should be defined with laboratory test data such as 'Pancytopenia, Leukocytopenia, Neutropenia, Agranulocytosis, Thrombocytopenia' or the 'Hepatic function disorder', are defined with disease names or other medication records in this study. Therefore, events which require hospitalization or treatments are captured on the other hand not all the outcomes will be captured as if event is mild and treatments are not required, it may not be recorded in the database.

- Claims data between hospitals for a patient are not able to be linked in MDV database because patient information is anonymized in a hospital. Claims data of a patient is only traced within the hospital. Therefore, not all the medication history or outcomes will be captured if a patient transfer to a different hospital.

- The data available in MDV is limited to DPC hospitals. Therefore, the disease, exposure, and outcome assessment may not be generalizable to all of Japan.

- No differentiation can be made between hospitals with MDV data. Therefore, adjustment cannot be made even if there are unmeasured confounding factors of hospitals.

- It is not possible to collect the vaccination data which may impact the incidence of Infection such as Herpes zoster, pneumococcus and BCG for tuberculosis or COVID-19 vaccine as it is impossible to collect the data from the other institution where the previous medication is provided.

Limitations of this study specifically:

- The combination chemotherapy impacts the incidence of some outcomes however each regimen is difficult to detect in the database by defining the combination of the drugs included in each regimen as the timing or arrangement of administration may differ depends on the institution or physicians. Therefore, instead of detecting the regimens, if either drug included in regimen is prescribed, it is considered as combination chemotherapy.

- It is not feasible to develop the definition of covariates for Infusion reaction, which are Tumor cells more than 25,000～50,000/μL in blood, presence of splenomegaly and B-cell

non-Hodgkin's lymphoma in the pharyngeal and palatine tonsil region as they are not the data recorded in claims data.

- 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.

10.10. Other aspects

Not applicable

11. PROTECTION OF HUMAN PARTICIPANTS

11.1. Patient information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

11.2. Patient consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

11.3. Institutional review board (IRB)/Ethics committee (EC)

In this study, the review by the Institutional Review Board (IRB)/Ethics Committee (EC) is not essential.

11.4. Ethical conduct of the study

This study is included in the scope of application of the "Good Post-Marketing Study Practice" (Ordinance of Ministry of Health, Labour and Welfare No. 90 of July 30, 2014) and will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information obtained in this study shall be used to report Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), Pfizer Inc. which is the corporate parent of marketing authorization holder (or sponsor) of this study, and the group companies, or regulatory agency in other countries. And also, it shall be used for application of re-examination (including Japan Periodic Safety Report), re-evaluation, preparation of material for proper use information of this drug, publications and activities for information service. Also, Pfizer could disclose the study results to provide information for proper use, as needed, on www.clinicaltrials.gov (ClinicalTrials.gov), as presentations at academic conferences, as manuscripts, and so on.

Data obtained in this study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act; pertinent to which, data may be publicly posted in MHLW's "Pharmaceutical and Medical Device Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp) as an aggregated data or other relevant information. Furthermore, results may also be disclosed if the MHLW is required to disclose such information in accordance with the "Act on Access to Information Held by Administrative Organs" (Law No. 42 dated May 14, 1999); provided that in no personal information be subject to such disclosure, nor will it be posted or disclosed in any form or shape.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR REPORTING OF STUDY IMPLEMENTATION STATUS AND EVALUATION OF OBTAINED RESULTS TO THE PMDA

Review and report annually and at the time of submission of the final report.

15. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

Review the J-RMP including the following contents at the scheduled timing of milestones.

1) Review the necessity for changing the contents of risk minimization activities for the current safety specifications.

2) Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications (continuation of the study, implementation of additional study, etc.).

3) Review the necessity for formulating risk minimization measures for new safety specifications.

16. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

Regarding the organizational system in the study, refer to the APPENDIX 1. Organizational system for Post-marketing Surveillance

17. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS

Company name: Pfizer R&D Japan
Address: Shinjuku Bunka Quint Bldg., 3-22-7, Yoyogi, Shibuya-ku, Tokyo
Scope of the outsourced operations: Draft of study planning and operations etc.

Company name: Real World Data, Co., Ltd.
Address: Shiseido Kyoto Bldg. 4F, 480, Aburanokojidori, Kizuyabashi-sagaru, Kitafudondocho, Shimogyo-ku, Kyoto-shi, Kyoto
Scope of the outsourced operations: Medical inputs for developing outcome definitions and code lists.

Company name: EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Scope of the outsourced operations: Statistical analysis

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19. LIST OF TABLES

20. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Appendix 1: Code List for Diseases

Appendix 2: Code List for Infections

Appendix 3: Code List for Drugs

Appendix 4: Code list for Procedures

Appendix 5 Code List for Drugs may induce Liver disorder

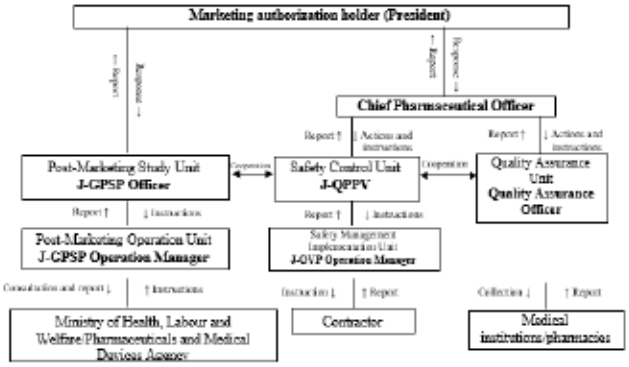
Appendix 6 Code List for Drugs included in chemotherapy regimen

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

APPENDIX 1. ORGANIZATIONAL SYSTEM FOR POST-MARKETING SURVEILLANCE

Organizational structure chart



List of relevant departments

Unit	Unit	Department in charge
Safety Control Unit	Quality Assurance Division(*)	
	Quality Assurance Division	Safety Assurance Group
	Quality Assurance Division Drug Safety Unit	General Manager (J-QPPV) Product Safety Vigilance Department
		Drug Safety Coordination Department
	Medical Division	Medical Quality Oversight Department
Quality Assurance Unit	Manufacturing Unit	Quality Operations (Tokyo)
	Quality Assurance Division(**)	
	Medical Division	Medical Quality Oversight Department
Post-Marketing Study Unit	Assistant to the Member of the Board, Pfizer Japan Inc. (R&D)	(J-GPSP Officer)
	Quality Assurance Division Drug Safety Unit	Product Safety Vigilance Department
	Medical Division	Medical Quality Oversight Department
	Medical Division	Medical Affairs(***)
Safety Management Implementation Unit	Refer to the List of Duties of the J-GVP Operation Managers and his/her appointers.	
Post-Marketing Operation Unit	Refer to the List of J-GPSP Operation Managers and his/her appointers.	

As of September 29, 2023

[Definitions]

(*): Person who performs GVP operations

(**): Person who performs GQP operations

(***): Only in cases other than post-marketing clinical studies related to re-examinations/re-evaluations