Infliximab-Pfizer Biosimilar Post-Marketing Database Study

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Pfizer Japan Inc.

Study information

Title	Infliximab-Pfizer Biosimilar Post-Marketing Database Study
Protocol number	B5371010
Protocol version identifier	Version 4
Date	28 June 2024
Active substance	Infliximab-Pfizer Biosimilar
Medicinal product	PF-06438179
Research question and objectives	The research question is to evaluate the important safety outcome events in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade from December 1, 2018 through November 30, 2023. The primary objective is to evaluate the incidence rate of serious infections overall in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade. Secondary objectives are as follows, ● to evaluate the incidence rate of serious infections in patients in each disease subcohort who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade. ● to evaluate the incidence rate of tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy overall in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade. ● to evaluate the incidence rate of tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy in patients in each disease subcohort, who have received Infliximab-Pfizer

	Biosimilar compared to those patients who have received Remicade.
Author	PPD PhD PPD PPD Pfizer R&D Japan PPD , PhD PPD PPD Pfizer R&D Japan PPD PhD PPD PPD Pfizer R&D Japan

1. TABLE OF CONTENTS

2. DEFINITION OF TERMS

Not applicable

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
BCG	Bacille de Calmette et Guérin
CD	Crohn's Disease
DMARDS	Disease Modifying Anti-Rheumatic Drugs
DPC	Diagnosis Procedure Combination
EC	Ethics Committee
ICD	International Classification of Diseases
IgG1	Immunoglobulin G1
IPTW	Inverse Probability of Treatment Weighting
IRB	Institutional Review Board
ISO	International Organization for Standardization
MDV	Medical Data Vision
MHLW	Ministry of Health, Labour and Welfare
PFSB	Pharmaceutical and Food Safety Bureau
PMDA	Pharmaceuticals and Medical Devices Agency
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
TNFα	Tumor Necrosis Factor Alpha
UC	Ulcerative Colitis

4. RESPONSIBLE PARTIES

The Japan Good Post Marketing Study Practice Officer

5. ABSTRACT

Title: Infliximab-Pfizer Biosimilar Post-Marketing Database Study

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Rationale and Background:

Based on results from the clinical development program, safety specifications for additional pharmacovigilance activities have been identified. Additional pharmacovigilance activities will be performed through comparisons of the occurrence of the safety specifications especially for serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy between Infliximab-Pfizer Biosimilar and the innovator (Remicade) by using an electronic health care database. Since it has not been reported that the safety is significantly different between the indications of Remicade, the evaluation will be mainly performed in the overall four diseases, and the evaluation of each disease will be also performed in disease subcohorts.

Research Question and Objectives:

The research question is to evaluate the important safety outcome events in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade from December 1, 2018 through November 30, 2023.

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

Secondary objectives are as follows,

- to evaluate the incidence rate of serious infections in patients in each disease subcohort who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.

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

- to evaluate the incidence rate of tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy in patients in each disease subcohort, who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade.

Study Design: This is an observational cohort study.

Population: The study population includes individuals who have a diagnosis of rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis and have been exposed to Infliximab-Pfizer Biosimilar or the innovator (Remicade) with a planned study period between December 1, 2018 and November 30, 2023.

Outcome events: Serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, malignancy

Data Source: 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 Infliximab-Pfizer Biosimilar patients would be expected about 1,000 patients for all 4 indications (rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriasis). The number of comparator (Remicade) patients would be expected to be about 9 times as large as the number of exposed patients.

Data Analysis:

Three analysis sets will be defined as follows to evaluate the relative risks of Infliximab-Pfizer Biosimilar to Remicade.

- The full analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria in Section 10.2.3 and Section 10.2.4.

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

- The comparative matched analysis set will be a subset of the comparative analysis set that includes all patients matched between Infliximab-Pfizer Biosimilar and Remicade. Each patient from the Infliximab-Pfizer Biosimilar group will be matched to two patients from the Remicade group based on the propensity score.

For each analysis set, the incidence rate of each outcome event (serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy) will be calculated for Infliximab-Pfizer Biosimilar and Remicade group for the main cohort and for

each disease subcohort (rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis). The incidence rate will be estimated by counting the number of events in the numerator and dividing by the total person-time of observation in the denominator.

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 Remicade as the reference group. Crude rate differences will be calculated including 95% confidence intervals (the risk of Infliximab-Pfizer Biosimilar - the risk of Remicade).

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. Second is the method based on matched analysis based on the comparative matched analysis set.

For the IPTW analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated based on weights based on the propensity score. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate difference will be calculated by a Poisson regression model accounting for different duration on treatment.

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

Milestones: The study period is from 1 December 2018 through 30 November 2023. The start of data collection for the final analysis is on 1 December 2023 (the date when data extraction begins). The end of data collection is on 28 February 2024 (the date when the analytic dataset is completely available). The final study report submission will be on 31 July 2025.

6. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Ver. 4	28 June 2024	Substantial	10.3.2. Covariate, and the defining information	Descriptive update from Biologics (excluding Infliximab-Pfizer Biosimilar) to Biologics (excluding any Infliximab products)	In order to conduct analysis correctly
			ATTACHMENT 1. OUTCOME DEFINITIONS 3. Serious blood disorder Table A1-3-1. Basic Conditions and Additional Conditions for Blood Disorder (Pancytopenia) to be Used in this Study Additional Condition 4	Correction of drug name and drug code	Description updates due to typo
			ATTACHMENT 2. DISEASE CODE LIST Table A2-1. Disease Code List for Infection	Update of disease code list	CCI [redacted]
			ATTACHMENT 2. DISEASE CODE LIST Table A2-5. Disease Code List for Malignancy	Update of disease code list	
			ATTACHMENT 3. DRUG LIST Table A3-5. List of Biologics	Removal of Infliximab from the list to align with the descriptive update in 10.3.2	In order to conduct analysis correctly
Ver. 3	31 January 2024	Administrative	17. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of the outsource vendor	Selected the vendor for statistical analysis

			APPENDIX. ORGANIZATIONAL SYSTEM FOR POST-MARKETING SURVEILLANCE	Update of the organization structure	Administrative change
			Other	Update of the footer information	Revision of the protocol template
Ver. 2	30 October 2023	Substantial	Study information	Descriptive update to Align with cover title	Administrative change
			3. LIST OF ABBREVIATIONS	Descriptive update(Addition and deletion)	Administrative change
			5. ABSTRACT Title	Descriptive update to Align with cover title	Administrative change
			5. ABSTRACT Data Analysis and Milestones	Descriptive update for changes in the analysis plan and milestone	CCI [redacted]
			7. MILESTONES	Deletion of planned interim analysis date	
			10.3.2. Covariate, and the defining information	Descriptive update for changes in the analysis plan	
			10.6. Data analysis	Descriptive update for changes in the analysis plan	
			10.8. Limitations of the research methods	Addition of the description that comparisons will be made regardless of the number of accumulated cases, and limitation regarding the interpretation of the results of comparison in the case where the comparison is conducted without achieving the target sample size.	
			11.3. Institutional review board (IRB)/Ethics committee (EC)	Descriptive update for the section title and expression.	Description updates
			ATTACHMENT 3. DRUG LIST	Descriptive update for changes in the analysis plan and milestone	Description updates
Ver. 1	26 October 2022	NA	NA	NA	NA

7. MILESTONES

Milestone	Planned date
Timing to finalize the study protocol	26 October 2022
Start of data collection for final analysis	1 December 2023
End of data collection for final analysis	28 February 2024
Final study report	31 July 2025

8. RATIONALE AND BACKGROUND

Infliximab-Pfizer Biosimilar is a follow-on biologic to Remicade (the reference product). It consists of a chimeric immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to the human tumor necrosis factor alpha (TNFα). Biosimilarities between Infliximab-Pfizer Biosimilar and Remicade have been established through analytical, structural and functional tests and non-clinical and clinical studies in accordance with the *Guidelines for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics* from Ministry of Health, Labour and Welfare *(PFSB/ELD Notification No. 0304007 dated March 4, 2009)*, therefore, the treatment for rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriasis has been approved on 2 July 2018 and launched 10 December 2018, the treatment for refractory uveoretinitis has been approved on 22 April 2020 and the treatment for ankylosing spondylitis has been approved on 14 October 2020.

During the review process of J-NDA approval, it was pointed out from the regulatory authority that it is important to confirm a broad safety profile in clinical practice for biosimilars in drug use investigations etc. as information available based on clinical studies by approval is limited. Clinical studies were conducted to show similarity between Infliximab-Pfizer Biosimilar and Remicade-EU in patients with RA, however there is no safety data in patients with indications other than RA in clinical study. Therefore, it was also pointed out that concerning indications of infliximab for which clinical studies have not been conducted, it is important to prove not only the safety but also the efficacy by conducting drug use investigations, etc. Therefore, Pfizer planned drug use investigations to confirm the safety and efficacy and this database study to confirm the safety for rheumatoid arthritis, ulcerative colitis, Crohn's disease, and psoriasis as shown in the RMP. Among safety specifications of additional pharmacovigilance activities for the four indications, Pfizer selected serious infections, tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy as safety specifications evaluated in pharmacovigilance activities using a hospital based claims database since it was considered feasible to collect information in the database study and would be valuable to provide the information with both Infliximab-Pfizer Biosimilar and Remicade. Since it has not been reported that the safety is significantly different between the indications of Remicade, the evaluation will be mainly performed in the overall four diseases (indicated conditions; rheumatoid arthritis, ulcerative colitis,

Crohn's disease, and psoriasis), and the evaluation of each disease will also be performed in disease subcohorts as secondary objective.

According to the Notification for 'Procedures for developing Post-marketing Study Plan' (Pharmaceuticals and Medical Device Agency 23 Jan 2018), when there are multiple research questions for a single product, studies are selected depending upon each approach. In these instances, feasible studies to respond to multiple research questions may be investigated as needed, taking into account the feasibility of implementing the respective studies together. To make it feasible to deal with multiple research questions together by one study, this database study will be conducted to evaluate one representative safety specification as the primary outcome event which is the most appropriate to compare with Remicade based on the possibility of collecting the sufficient number of occurrences and evaluate the other outcome events as a secondary objective.
These outcome events will be measured in both Infliximab-Pfizer Biosimilar and Remicade exposed-patients, and the occurrence of these events are expected to be similar. There are five safety specifications for this database study, but serious infections, which can expect the greatest number of subjects based on historical studies, will be the primary safety specification, and others will be secondary specifications from the viewpoint of comparability.

This study will be conducted based on the following 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 Postmarketing 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" (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" (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

Important Identified Risks: serious infections, tuberculosis, serious blood disorder, interstitial pneumonia

Important Potential Risks: malignancy

Important Missing Information: None

9.2. Research question and study objective

The research question is to evaluate the important safety outcome events in patients with rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis who have received Infliximab-Pfizer Biosimilar compared to those patients who have received Remicade from December 1, 2018 through November 30, 2023.

In this database study, based on the incidence rate of the safety specifications in the historical clinical studies (serious infections: 2.8%; tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy: less than 1%), serious infections is set as the primary safety specification, and tuberculosis, serious blood disorder, interstitial pneumonia, and malignancy are set as secondary safety specification to show no significant difference in safety concerns between Infliximab-Pfizer Biosimilar and Remicade.

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

Secondary objectives are as follows,

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

10. RESEARCH METHODS

10.1. Study design

To meet the study objectives, an observational cohort study using a hospital-based claims database in Japan will be performed (Figure 2).

10.2. Setting

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. Data collection of MDV database started from April 2008. As of August 2020, the MDV database included information on more than 32 million patients from 419 hospitals which covers

approximately 24% 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. Currently, more than 150 studies have already been published which includes more than 10 safety evaluating studies.

10.2.1. Study period (data period)

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

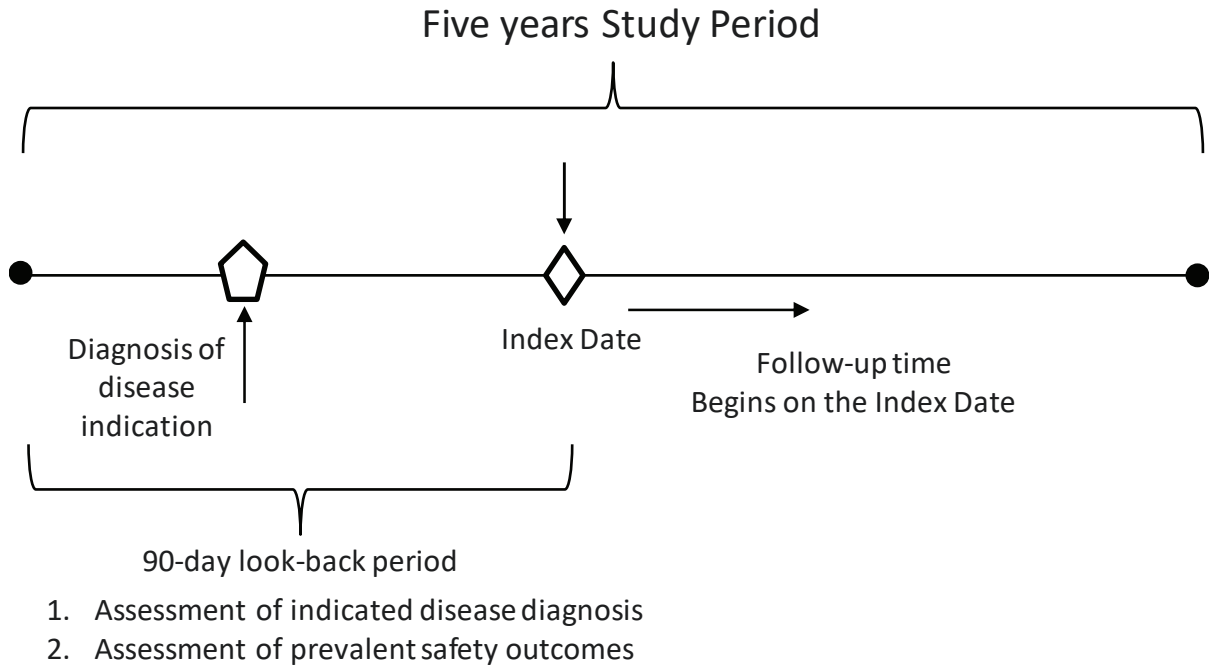

Figure 1. Schematic of Cohort Entry

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

Provisional index date is defined as the first recorded Infliximab-Pfizer Biosimilar or Remicade during the 5-year period. The final index date is determined by the 90-day look-back period and the treatment group allocation as follows:

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

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

No patient will be included in both treatment groups.

10.2.3. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

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

2. Have diagnostic code of indicated diseases (rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis) in the 90-day look-back period. Patients with >1 indication will be summarized as a separate group from each sub-cohort. An inpatient or outpatient visit assigned a diagnosis code consistent with either rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis using ICD-10 coding:

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

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

10.2.4. Exclusion criteria

Patients with pre-existing safety outcome event during the 90-day look-back period will be excluded from the study cohort for that specific outcome event as this study is observing incident cases(see Section 10.6).

10.2.5. Flow chart

Figure 2 is the flow chart of the study B5371010. Main cohort is defined as overall population who meet the inclusion and exclusion criteria in section 10.2.3 and 10.2.4.

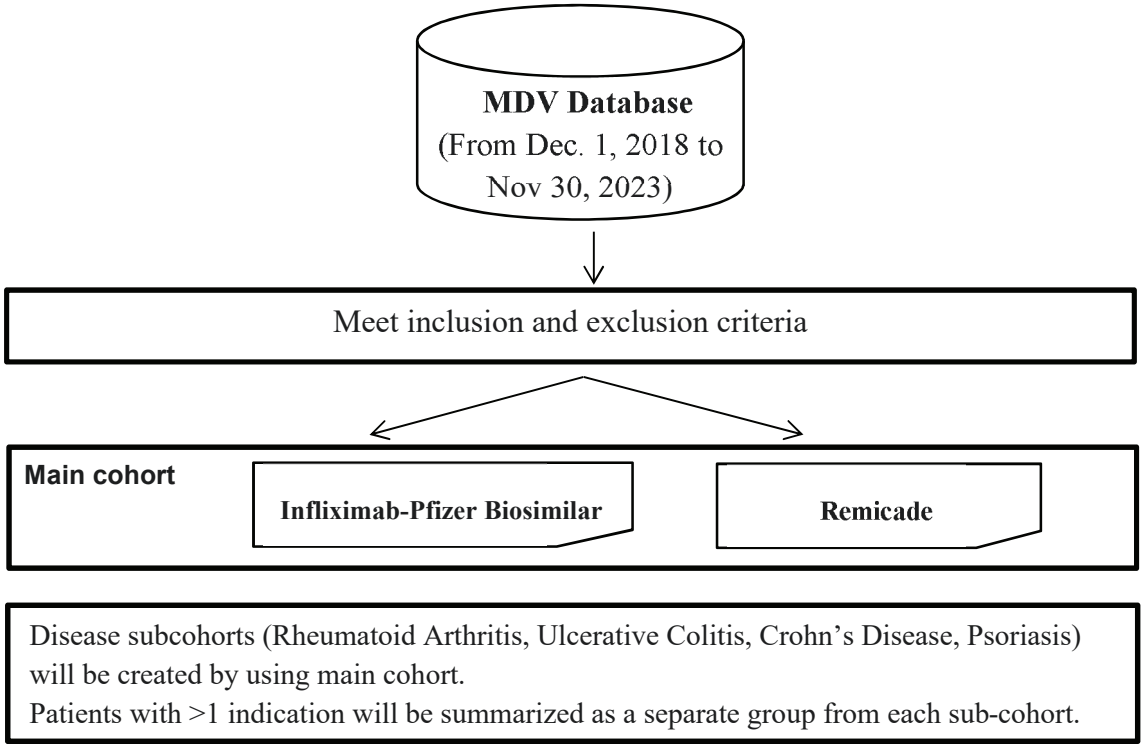

Figure 2. Flow chart of the study B5371010

10.3. Variables

10.3.1. Definition of outcomes and defining information

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

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

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

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

The observation of these outcome events is expected to occur in an acute time period following any exposure. Maximum dosing interval of Remicade is every 8 weeks in the package insert based on overall evaluation of clinical trials. The package insert also indicates that the blood concentration of Remicade was maintained in clinical studies. Furthermore, as a biologic, almost all patients will not use other biologics within 8 weeks after last dose which is approximately 60 days. Therefore, a 60 day risk window after exposure will be utilized from the last dose received. An incident event occurring during the 60 day risk window will be counted in the numerator for the analysis and the person-time will accrue until the first occurrence of an event, the end of the 60 day risk window, date of switch treatment, death, or the end of study period (Figure 3).

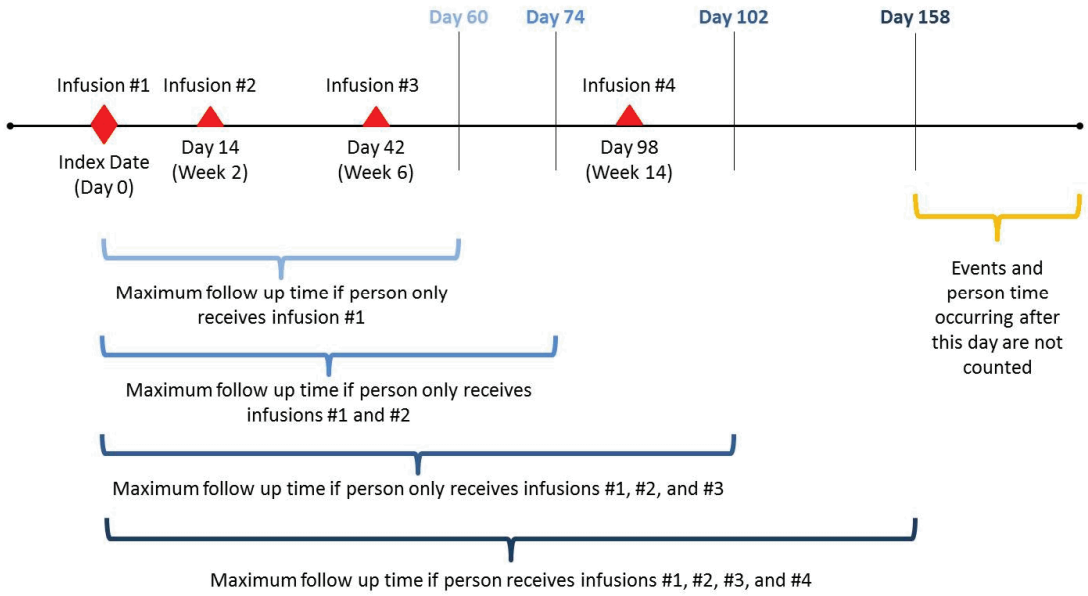

Figure 3. Observation Time for Study Patients with Acute Events

Outcome (latent) event: malignancy:

The observation of a latent outcome event like a malignancy requires additional considerations. A 60 day risk window may not be sufficient follow-up time to observe an incident event with long latency. As a result, this study will analyze malignancy differently compared to the acute outcome events by extending follow-up time until the first incident event, death, end of the study period, or loss to follow-up. The primary analysis will utilize an ever-exposed approach whereby a person will always be considered exposed to the initial treatment. All malignancy will be reported in the primary analysis even those that occur after the day of initial treatment. Sensitivity analyses will be considered that truncate events during specified risk periods (60 days) associated with information known about the occurrence of malignancies. Patients switching between Infliximab-Pfizer and Remicade is likely to be excluded from this sensitivity analysis.

10.3.2. Covariate, and the defining information

Indicated disease, Information on sociodemographic characteristics (sex, age at the index date), medical history (Yes or No in the 90-day look-back period: Cerebrovascular disease, Chronic pulmonary disease, Diabetes, Liver disease, Renal disease, or Dementia), and prior medications (Yes or No in the 90-day look-back period: Methotrexate [RA], DMARDS other than methotrexate [RA], Amino salicylate [CD, UC], Immunosuppressant (Steroid), Immunosuppressant (non-steroid), Biologics (excluding any Infliximab products), Janus kinase inhibitor, or Anti-tuberculosis) will be collected from the database as available. This information will be used for the study analysis as appropriate. Disease code list and drug list are included in ATTACHMENT 2. DISEASE CODE LIST and ATTACHMENT 3. DRUG LIST, respectively. These lists will be updated to latest version at the analysis, if needed.

10.4. 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. 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 have also been certified 'ISO27001'. MDV will extract the data which met the inclusion and exclusion criteria in section 10.2.3 and 10.2.4 by their standard operating procedures and provide them to Pfizer.

10.4.2. Validation

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

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

10.5. Study size

The number of exposed to Infliximab-Pfizer Biosimilar patients would be expected about 1,000 patients for all 4 indications (rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriasis). The number of comparator (Remicade) patients would be expected to be about 9 times as large as the number of exposed patients. The following sample size rationale was calculated based on the assumption that the number of patients in Remicade cohort is at least twice as large as that in Infliximab-Pfizer Biosimilar considering the inclusion and exclusion

criteria. Also, the rationale focuses on the precision of estimates achieved with these sample sizes with additional information on possibility of detection large differences such as 2 or 3 times in terms of risk ratios.

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

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

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

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

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

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

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

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

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

a) Interval was defined as 5-percentile and 95-percentile of point estimate.

b) The 95% confidence interval for risk difference was calculated by using Miettinen-Nurminen method.

c) Lower of the range was defined as 5-percentile of lower limit of 95 % confidence interval on simulations. Upper of the range was defined as 95-percentile of upper limit of 95 % confidence interval on simulations.

d) Based on 10000 times simulations. When the number of cases for infliximab BS Pfizer and the innovator were 0, they were excluded from the calculation.

10.6. Data analysis

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

- The full analysis set will include all patients who are considered eligible by the inclusion and exclusion criteria in Section 10.2.3 and Section 10.2.4.

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

- The comparative matched analysis set will be a subset of the comparative analysis set that includes all patients matched between Infliximab-Pfizer Biosimilar and Remicade. Each patient from the Infliximab-Pfizer Biosimilar group will be matched to two patients from the Remicade group based on the propensity score. The propensity score will be based on indicated disease, sex, age at the index date, calendar year-month of the index date, medical history, and prior medications (see Section 10.3.2).

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

For each analysis set, the incidence rate of each outcome event will be calculated for Infliximab-Pfizer Biosimilar and Remicade group for the main cohort and for each disease subcohort (rheumatoid arthritis, ulcerative colitis, Crohn's disease, or psoriasis). 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. For the outcome events: serious infections, tuberculosis, serious blood disorder, and interstitial pneumonia; the *person-time* will accrue until the first occurrence of an event, the end of the 60-day risk window, date of switch treatment, death, or the end of study period. For the malignancy outcome, the *person-time* will accrue until the first incident event, death, end of the study period, or loss to follow-up (Section 10.3.1).

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 Remicade as the reference group. Crude rate differences will be calculated including 95% confidence intervals (the risk of Infliximab-Pfizer Biosimilar - the risk of Remicade). Hazard ratios and its 95% confidence intervals will be calculated by Cox proportional hazard model using treatment (Infliximab-Pfizer Biosimilar or Remicade) 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 Infliximab-Pfizer Biosimilar and Remicade; PT_P, PT_R: person-time of observation of Infliximab-Pfizer Biosimilar and Remicade, for the standard error of the logarithm of the incidence rate ratio and the rate difference, respectively[2].

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 method based on matched analysis based on the comparative matched analysis set.

For the IPTW analysis, adjusted hazard ratios, rate ratios, and rate differences will be calculated based on weights based on the propensity score as same as the score used in the matched analysis. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate difference will be calculated by a Poisson regression model accounting for different duration on treatment. In each of the previous analyses, treatment (Infliximab-Pfizer Biosimilar or Remicade) 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 by using the following models. Hazard ratios will be calculated by Cox proportional hazard model. Rate ratios and rate difference will be calculated by a Poisson regression model accounting for different duration on treatment. In each of the previous analyses, treatment (Infliximab-Pfizer Biosimilar or Remicade) 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.

10.7. 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 of these processes are consistently managed in-house. MDV have also been certified ‘ISO27001’.

10.8. Limitations of the research methods

This study has several limitations.

First, the potential data source, MDV, is an acute-care hospital-based database. Therefore, severe cases of disease are more likely to be captured than mild or moderate cases of disease which can be treated in other non-hospital settings. As a result, the disease, exposure, and outcome assessment may not be generalizable to all of Japan. Second, patients may seek care outside the hospital where the primary disease diagnosis and treatment occurred; thus, not all

outcomes will be recorded. This is likely to result in an underestimate in the absolute incidence for all outcomes but is likely to be non-differential when comparing Infliximab-Pfizer Biosimilar to Remicade. Third, MDV has inpatient and outpatient prescription information, but dosing information may not be accurate. Fourth, the information of prior vaccination such as H zoster, pneumococcus or BCG for tuberculosis, these information of other institutions can't be collected, so the possibility of data collecting is quite rare. Fifth, as a hospital-based database, patient history for patients can be limited which prevents capturing a history of malignancy. This may result in capturing prevalent outcomes in the observation period as opposed to incident outcomes and thus overestimating the incidence. However, this limitation is likely to be non-differential when comparing Infliximab-Pfizer Biosimilar to Remicade. Sixth, MDV primarily captures data from acute-care hospitals diagnoses of malignancy may be limited (immortal time bias). This is likely to result in an underestimate in the absolute incidence, but it is likely to be non-differential when comparing Infliximab-Pfizer Biosimilar to Remicade. Seventh, while cancer and death registries exist, capabilities to link with anonymized MDV data is not possible limiting the ability to identify all cancer cases. Eighth, the methods listed to define outcomes may not be the most specific including non-validated outcomes and non-adjudicated outcomes; therefore, the results could be an overestimate of the true risks. Finally, although this study was initially planned to be conducted with 300 patients for serious infection and 1000 patients for the other outcomes at the conclusion of follow-up who have received Infliximab-Pfizer Biosimilar, following a CCI [redacted] on 11-July-2023 that included status of expected number of patients, the plan was revised. In the update plan comparative analyses will be conducted regardless of accumulation of the number of patients with an understanding that, if the study size is smaller than in the initial plan, the statistical precision of estimation will be reduced. In such a case, the interpretation of the results will be made carefully.

10.9. 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. 171 of December 20, 2004) and the MHLW Ordinance in the section 8. RATIONALE AND BACKGROUND 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

At the time of submission of regular report: once a year from approval to the submission of the final report, due to evaluate safety information and report to PMDA.

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

Review the risk management plan (RMP), including the following matters, will be reviewed at the time of each milestone.

- Whether or not to change the contents of the implementation plan, including whether there are additional elements to the Safety Specifications.
- Whether or not to formulate risk minimization measures for new elements of the Safety Specifications

16. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

Regarding the organizational system in the study, refer to the APPENDIX.

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

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

18. REFERENCES

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

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

19. LIST OF TABLES

20. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

APPENDIX. ORGANIZATIONAL SYSTEM FOR POST-MARKETING SURVEILLANCE

Organizational structure chart

CCI

List of relevant departments

CCI

ATTACHMENT 1. OUTCOME DEFINITIONS

1. Serious infections

Those to which the Additional Condition 1 applies in addition to the following Basic Conditions are defined serious infections.

The onset date of outcome is the date of hospitalization described in the Basic Conditions.

Table A1-1. Basic Conditions and Additional Conditions of Outcome Definition of Serious Infection to be Used In this Study

Condition	Description
Basic Condition	Patients with a date of hospitalization due to infection and definitive diagnosis[a]
Additional Condition 1	Patients to whom immune/infection test and other related tests (category code D) have been performed between 1 month before hospitalization[b] and during hospitalization

[a] ICD-10 codes of infections are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

2. Tuberculosis

Those to which the Additional Condition 1 applies in addition to the following Basic Conditions are defined tuberculosis.

The onset date of outcome is the date of drug prescription described in the Additional Condition 1.

Table A1-2. Basic Conditions and Additional Conditions of Outcome Definition of Tuberculosis to be Used in this Study

Condition	Description
Basic Condition	Patients with a definitive diagnosis[a] of tuberculosis
Additional Condition 1	Patients prescribed an anti-tuberculosis agent (drugs in Therapeutic Category Code 616 or 622) in the month of hospital visit for tuberculosis or the following month of the date of hospitalization[b]

[a] ICD-10 codes of tuberculosis are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

3. Serious blood disorder

Serious blood disorders are defined as diseases that are relevant to pancytopenia, granulocytopenia, thrombocytopenia, or anemia.

In addition to the following Basic Condition, diseases that are relevant to any of the Additional Conditions (1, 2, 3, 4, 5, or 6) are defined pancytopenia.

The onset date of outcome is the date of hospitalization described in the Basic Conditions.

Table A1-3-1. Basic Conditions and Additional Conditions for Blood Disorder (Pancytopenia) to be Used in this Study

Condition	Description
Basic Condition	Patients with a date of hospitalization due to pancytopenia and a definitive diagnosis[a]
Additional Condition 1	Patients receiving blood transfusion (Category Code 920) within the following month of the date of hospitalization for pancytopenia[b]
Additional Condition 2	Patients prescribed antibiotics or antifungals (ATC code J01 or J02) within the following month of the date of hospitalization for pancytopenia[b]
Additional Condition 3	Patients prescribed granulocyte colony-stimulating factors (National Health Insurance drug price list [first 7 digits]: 3399405, 3399406, 3399407, 3399408, 3399409, 3999410 or 3999411) within the following month of the date of hospitalization for pancytopenia[b]
Additional Condition 4	Patients prescribed antithymocyte globulin (National Health Insurance drug price list [first 7 digits]: 6399423) or ciclosporin (National Health Insurance drug price list [first 7 digits]: 3999004 or 3999406) for immunosuppressive therapy within the following month of the date of hospitalization for pancytopenia[b]
Additional Condition 5	Patients prescribed anabolic hormones (drugs in Therapeutic Category code 244) within the following month of the date of hospitalization for pancytopenia[b]
Additional Condition 6	Patients prescribed thrombopoietin receptor agonists (National Health Insurance drug price list [first 7 digits]: 3999028 or 3999430) within the following month of the date of hospitalization for pancytopenia[b]

[a] ICD-10 codes of pancytopenia are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

In addition to the following Basic Condition, diseases that are relevant to any of the Additional Conditions (1, 2, or 3) are defined granulocytopenia.

The onset date of outcome is the date of hospitalization described in the Basic Conditions.

Table A1-3-2. Basic Conditions and Additional Conditions for Blood Disorder (Granulocytopenia) to be Used in this Study

Condition	Description
Basic Condition	Patients with a date of hospitalization due to granulocytopenia and a definitive diagnosis[a]
Additional Condition 1	Patients prescribed antibiotics or antifungals (ATC code J01 or J02) within the following month of the date of hospitalization for granulocytopenia[b]

Table A1-3-2. Basic Conditions and Additional Conditions for Blood Disorder (Granulocytopenia) to be Used in this Study

Condition	Description
Additional Condition 2	Patients prescribed granulocyte colony-stimulating factors (National Health Insurance drug price list [first 7 digits]: 3399405, 3399406, 3399407, 3399408, 3399409, 3999410 or 3999411) within the following month of the date of hospitalization for granulocytopenia[b]
Additional Condition 3	Patients for whom the immunological test (Category Code D012) or the microbiological test (Category Code D017-D023) has been calculated within the following month of the date of hospitalization for granulocytopenia[b]

[a] ICD-10 codes of granulocytopenia are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

In addition to the following Basic Condition, diseases that are relevant to any of the Additional Conditions (1, 2, 3 or 4) are defined thrombocytopenia.

The onset date of outcome is the date of hospitalization described in the Basic Conditions.

Table A1-3-3. Basic Conditions and Additional Conditions for Blood Disorder (Thrombocytopenia) to be Used in this Study

Condition	Description
Basic Condition	Patients with a date of hospitalization due to thrombocytopenia and a definitive diagnosis[a]
Additional Condition 1	Patients receiving blood transfusion (Category Code 920) within the following month of the date of hospitalization for thrombocytopenia[b]
Additional Condition 2	Patients prescribed adrenocorticosteroids (drugs in Therapeutic Category Code 245) within the following month of the date of hospitalization for thrombocytopenia[b]
Additional Condition 3	Patients prescribed immunoglobulin (ATC code J06B) within the following month of the date of hospitalization for thrombocytopenia[b]
Additional Condition 4	Patients for whom anti-platelet antibody test (Receipt Computerized Code: 160039710) is performed within the following month of the date of hospitalization for thrombocytopenia[b]

[a] ICD-10 codes of thrombocytopenia are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

In addition to the following Basic Condition, diseases that are relevant to any of the Additional Conditions (1, 2, 3, 4, 5, 6, or 7) are defined anemia.

The onset date of outcome is the date of hospitalization described in the Basic Conditions.

Table A1-3-4. Basic Conditions and Additional Conditions for Blood Disorder (Anemia) to be Used in this Study

Condition	Description
Basic Condition	Patients with a date of hospitalization due to anemia and a definitive diagnosis[a]
Additional Condition 1	Patients receiving blood transfusion (Category Code 920) within the following month of the date of hospitalization for anemia[b]
Additional Condition 2	Patients prescribed erythropoiesis factors or hypoxia inducible factor prolyl hydoxylase (HIF-PH) inhibitors (ATC code B03XA) within the following month of the date of hospitalization for anemia[b]
Additional Condition 3	Patients prescribed glucocorticoid (ATC code H02AB) within the following month of the date of hospitalization for anemia[b]
Additional Condition 4	Patients prescribed immunoglobulin (ATC code J06B) within the following month of the date of hospitalization for anemia[b]
Additional Condition 5	Patients prescribed methylthioninium (Receipt Computerized Code: 622402701) is performed within the following month of the date of hospitalization for anemia[b]
Additional Condition 6	Patients prescribed ascorbic acid (drugs in Therapeutic Category Code 314) within the following month of the date of hospitalization for anemia[b]
Additional condition 7	Patients receiving plasma exchange therapy (Category Code J039) within the following month of the date of hospitalization for anemia[b]

[a] ICD-10 codes of anemia are listed in the disease code list (Attachment)
[b] Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

4. Interstitial pneumonia

Those to which the following Basic Condition, Additional Condition 1 and Additional Condition 2 as well as Additional Condition 3 or Additional Condition 4 apply are defined as interstitial pneumonia.

The onset date of outcome is the date of test conduct described in the additional condition 1.

Table A1-4. Basic conditions and additional conditions of outcome definition of interstitial pneumonia to be used in this study

Condition	Description
Basic Condition	Patients with a definitive diagnosis[a] of interstitial pneumonia
Additional Condition 1	Patients who have undergone imaging/imaging test (Category Code E) in the month of hospital visit or the month of the date of hospitalization for interstitial pneumonia[b]
Additional Condition 2	Patients who have undergone interstitial pneumonia marker test (Category Code D007) or drug lymphocyte stimulation test (Category Code D016) in the month of hospital visit or the following month of the date of hospitalization for interstitial pneumonia[b]

Table A1-4. Basic conditions and additional conditions of outcome definition of interstitial pneumonia to be used in this study

Condition	Description
Additional Condition 3	Patients prescribed adrenocortical steroids (drugs in Therapeutic Category Code 245) or antifibrotic agents (Receipt Computerized Code: 620008559, 622439201 or 622439301) in the month of hospital visit or the following month of the date of hospitalization for interstitial pneumonia[b]
Additional Condition 4	Patients who have undergone tests to differentiate from infection (Category Code D012, D017,D018,D019,D020,D021,D022,D023) or tests related to transbronchial lung biopsy (Category Code D302 or D415) within the month of hospital visit or the following month of the date of hospitalization for interstitial pneumonia[b]

[a] ICD-10 codes of interstitial pneumonia are listed in the disease code list (Attachment)
[b]Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

5. Malignancy

Those to which the Additional Condition 1 applies in addition to the following Basic Conditions are defined malignancy.

The time point of the onset of outcome is the month of hospital visit when the definitive diagnosis described in the Basic Condition is made.

Table A1-5. Basic Conditions and Additional Conditions of Outcome Definition of Malignancy to be Used in this Study

Condition	Description
Basic Condition	Patients with a definitive diagnosis[a] of malignancy
Additional Condition 1	Patients who have undergone imaging/imaging test (Category Code E) in the month of hospital visit or within 1 month before or after the date of hospitalization for malignancy[b]

[a] ICD-10 codes of malignancy are listed in the disease code list (Attachment)
[b]Including the day of hospitalization
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

ATTACHMENT 2. DISEASE CODE LIST

Table A2-1. Disease Code List for Infection

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Intestinal infectious diseases	A00-A09	A00.1, A01.2, A01.3, A02.8, A03.2, A03.8, A06.6, A07.0, A07.3
Tuberculosis	A15-A19	A15.3, A15.5, A15.7-A15.9, A16.0, A16.1, A17.1, A17.9, A19.0. A19.1, A19.8
Certain zoonotic bacterial diseases	A20-A28	A20.0-A20.3, A20.7, A20.8, A21.1, A21.7, A21.8, A22.2, A22.8, A23.0-A23.3, A23.8, A24.2-A24.4, A25.0, A26.8, A26.9, A28.9
Other bacterial diseases	A30-A49	A30.0, A30.1, A30.3, A30.8, A32.0, A34, A36.1, A36.2, A37.0, A37.1, A37.8, A39.3, A40.8, A43.8, A44.1, A44.8
Infections with a predominantly sexual mode of transmission	A50-A64	A56.2, A56.8, A60.9, A63.8
Other spirochetal diseases	A65-A69	A66.0, A66.3-A66.9, A67, A68.0, A69.8
Other diseases caused by chlamydiae	A70-A74	A71.0
Rickettsioses	A75-A79	A75.0, A75.1, A77.0, A77.3, A77.9, A79.0
Viral infections of the CNS	A80-A89	A80.0-A80.2, A80.4, A81.9, A82.1, A83.1-A83.3, A83.5, A83.6, A83.8, A83.9, A84, A87.8, A88.8, A89
Arthropod-borne viral fevers & viral hemorrhagic fevers	A90-A99	A92.1-A92.4, A93.0-A93.2, A95, A96, A98.0-A98.4, A98.8
Viral infections characterized by skin & mucous membrane lesions	B00-B09	B04, B05.3, B05.4, B08.8
Viral hepatitis	B15-B19	B16.0, B16.1, B17.0, B18.0, B18.8, B19.0
HIV disease	B20-B24	B20.1, B20.5, B20.7-B20.9, B21.3, B21.7-B21.9, B22.7, B23.1, B23.2
Other viral diseases	B25-B34	B27.8, B33.4
Mycoses	B35-B49	B35, B36.2, B36.3, B38.3, B38.4, B38.7, B38.8, B39.0, B39.3-B39.5, B40.7-B40.9, B41, B42.0, B43.1, B43.8, B45.8, B46.2, B46.8, B48.1, B48.2
Protozoal diseases	B50-B64	B50.8, B51.0, B51.8, B52.0, B52.8, B53.1, B53.8, B55.0, B55.9, B56, B57.0, B57.1, B57.3-B57.5, B60.0, B64
Helminthiases	B65-B83	B65.0, B66.2, B67.1-B67.3, B67.6, B69.0, B69.1, B69.8, B70.1, B71.0, B71.8, B72, B73, B74.1-B74.4, B76.1, B76.8, B77.0, B81.3, B81.8, B83.3, B83.4, B83.9
Pediculosis, acariasis & other infestations	B85-B89	B87.1-B87.3, B87.8, B87.9, B88.2, B88.8

Table A2-1. Disease Code List for Infection

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Sequelae of infectious & parasitic diseases	B90-B94	B92, B94.2, B94.8, B94.9
Other infectious diseases	B99	-
Hemophagocytic syndrome, infection- associated	D76.2	-
Other histiocytosis syndromes	D76.3	-
Immunodeficiency following hereditary defective response to Epstein-Barr virus	D82.3	-
Thyroiditis	E06.0, E06.1, E06.9	-
Inflammatory diseases of the CNS	G00-G06	G01, G02, G03.8, G04.1, G05
Demyelinating diseases of the CNS	G36.0, G37.0, G37.4	-
Geniculate ganglionitis	G51.1	-
Mononeuritis multiplex	G58.7	-
Hereditary and idiopathic neuropathy, unspecified	G60.9	-
Polyneuropathy, unspecified	G62.9	-
Disorders of eyelid, lacrimal system and orbit	H00-H06	H00.1, H01.1, H01.8, H01.9, H02, H03, H04.1, H04.2, H04.5, H04.6, H04.8, H04.9, H05.2-H05.5, H05.8, H05.9, H06
Disorders of conjunctiva	H10.0, H10.2, H10.4	-
Corneal ulcer	H16.0	-
Other keratitis	H16.8	-
Unspecified keratitis	H16.9	-
Other iridocyclitis	H20.8	-
Chorioretinal inflammation, unspecified	H30.9	-
Other specified retinal disorders	H35.8	-
Purulent endophthalmitis	H44.0	-
Unspecified disorder of globe	H44.9	-
Optic neuritis	H46	-
Diseases of external ear	H60-H61	H60.4, H60.5, H60.8, H61.1-H61.3, H61.8, H61.9
Diseases of middle ear and mastoid	H65-H73	H67, H68.1, H69, H70.8, H71, H72, H73.9
Vestibular neuronitis	H81.2	-
Labyrinthitis	H83.0	-
Disorders of acoustic nerve	H93.3	-
Acute rheumatic fever	I00-I01	I01.1, I01.8, I01.9

Table A2-1. Disease Code List for Infection

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Other forms of heart disease	I30, I31, I33, I38, I40, I51.4, I51.8,	I31.2, I31.3
Diseases of arteries, arterioles and capillaries	I71.2, I71.4, I72.9, I74.0, I77.6	-
Diseases of veins, lymphatic vessels & lymph nodes, NOC	I80.9, I88, I89.1	I88.8
Acute upper respiratory infections	J00-J06	J01.8
Influenza and pneumonia	J09-J18	J10.0, J10.8, J16.8, J17, J18.2
Other acute lower respiratory infections	J20-J22	J20.7, J21.8
Other diseases of upper respiratory tract	J30-J39	J30, J32.8, J33, J34.1-J34.3, J35.3, J35.9, J38.0-J38.6, J39.3, J39.9
Chronic lower respiratory diseases	J40-J44	J41.8, J43, J44.0, J44.1, J44.9
Suppurative & necrotic conditions of lower respiratory tract	J85-J86	-
Pleural effusion, NOC	J90	-
Diseases of mediastinum, NOC	J98.5	-
Disorders of diaphragm	J98.6	-
Diseases of oral cavity, salivary glands and jaws	K05.0-K05.3, K05.5, K06.8, K07.6, K10.2, K10.3, K11.2, K11.3, K12.0-K12.3, K13.0, K14.0, K14.2	-
Diseases of oesophagus, stomach & duodenum	K20, K22.1, K29.1, K29.7-K29.9, K31.8	-
Diseases of appendix	K35.3, K35.8, K36, K37	-
Noninfective gastroenteritis & colitis, unspecified	K52.9	-
Other diseases of the intestines	K57.1, K57.3, K57.9, K61, K62.6, K62.8	-
Peritonitis	K65.0, K65.8, K65.9	-

Table A2-1. Disease Code List for Infection

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Other inflammatory liver diseases	K75.0, K75.1, K75.9	-
Disorders of gallbladder, biliary tract & pancreas	K81.0, K81.1, K81.9, K83.0, K85.0, K85.9	-
Other postprocedural disorders of digestive system, NOC	K91.8	-
Infections of the skin and subcutaneous tissue	L00-L08	L00, L01.1, L04.1-L04.3, L04.8, L05, L08.1, L08.8
Other dermatitis	L30.3, L30.9	-
Pustulosis palmaris et plantaris	L40.3	-
Cicatricial alopecia [scarring hair loss]	L66.3, L66.4	-
Other follicular disorders	L73.1, L73.2, L73.9	-
Other eccrine sweat disorders	L74.8	-
Other disorders of the skin and subcutaneous tissue	L89.9, L98.0	-
Pyogenic arthritis	M00	M00.8
Spondylopathies	M46.2, M46.3, M46.5, M46.9, M47.2	-
Infective myositis	M60.0	-
Other soft tissue disorders	M71.1, M72.6, M72.8	-
Osteomyelitis	M86	M86.4
Glomerular diseases	N00.9, N01.7, N01.9, N05.9	-
Renal tubulo-interstitial diseases	N10, N12, N15.1, N15.9	-
Other specified disorders of kidney and ureter	N28.8	-
Other diseases of urinary system	N30.2, N30.3, N30.8, N30.9, N32.3, N34.0-N34.2, N36.1, N39.0	-
Diseases of male genital organs	N41.0-N41.2, N41.9, N45.0, N45.9, N48.1, N48.2, N49.1, N49.2, N50.0	-

Table A2-1. Disease Code List for Infection

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Inflammatory disorders of breast	N61	-
Inflammatory diseases of female pelvic organs	N70-N77	N73.6, N73.8, N73.9, N74, N75.0, N75.9, N76.8
Infections of genitourinary tract in pregnancy	O23	O23.3
Maternal care for (suspected) damage to fetus from viral disease in mother	O35.3	-
Infection of amniotic sac and membranes	O41.1	-
Complications predominantly related to the puerperium	O85, O86, O91	O86.8
Other obstetric conditions, NOC	O98.3, O99.5	-
Gangrene, NOC	R02	-
Pleurisy	R09.1	-
Post-traumatic wound infection, NOC	T79.3	-
Complications of surgical and medical care, NOC	T81.4, T82.6, T82.7, T83.5, T84.5, T84.6, T84.7, T85.7	-

Nishikawa A, Yoshinaga E, Nakamura M, et al. Validation Study of Algorithms to Identify Malignant Tumors and Serious Infections in a Japanese Administrative Healthcare Database. Annals of Clinical Epidemiology 2022;4(1):20–31. Cited from SUPPLEMENTARY INFORMATION in https://doi.org/10.37737/ace.22004. (Accessed: June 11, 2024)

Table A2-2. Disease Code List for Tuberculosis

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Respiratory tuberculosis, bacteriologically and histologically confirmed	A15	-
Respiratory tuberculosis, not confirmed bacteriologically or histologically	A16	-
Tuberculosis of nervous system	A17	-
Tuberculosis of other organs	A18	-
Miliary tuberculosis	A19	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-3-1. Disease Code List for Serious Blood Disorder (Pancytopenia)

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Other aplastic anemias	D61	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-3-2. Disease Code List for Serious Blood Disorder (Granulocytopenia)

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Agranulocytosis	D70	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-3-3. Disease Code List for Serious Blood Disorder (Thrombocytopenia)

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Purpura and other haemorrhagic conditions	D69	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-3-4. Disease Code List for Serious Blood Disorder (Anemia)

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Anemia due to enzyme disorders	D55	-
Acquired hemolytic anaemia	D59	-
Other anemias	D64	-
Methemoglobinemia	D74	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-4. Disease Code List for Interstitial Pneumonia

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Acute drug-induced interstitial lung disorders	J70.2	-
Chronic drug-induced interstitial lung disorders	J70.3	-
Drug-induced interstitial lung disorders, unspecified	J70.4	-
Acute respiratory distress syndrome	J80	-
Pulmonary edema	J81	-
Pulmonary eosinophilia, not elsewhere classified	J82	-
Other interstitial pulmonary diseases	J84	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-5. Disease Code List for Malignancy

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
HIV disease resulting in Kaposi sarcoma	B21.0	-
HIV disease resulting in Burkitt lymphoma	B21.1	-
HIV disease resulting in other types of non-Hodgkin lymphoma	B21.2	-
Malignant neoplasms of lip, oral cavity and pharynx	C00-C14	C00.5, C02.3, C02.4, C02.8, C04.8, C05.8, C06.8, C08.8, C09.8, C10.8, C11.8, C13.8, C14.2, C14.8
Malignant neoplasms of digestive organs	C15-C26	C16.8, C17.3, C17.8, C18.8, C21.2, C21.8, C24.8, C26.0, C26.8
Malignant neoplasms of respiratory and intrathoracic organs	C30-C39	C31.8, C32.8, C38.8, C39
Malignant neoplasms of bone and articular cartilage	C40-C41	C40.8, C40.9, C41.8
Melanoma and other malignant neoplasms of skin	C43-C44	C44.8
Malignant neoplasms of mesothelial and soft tissue	C45-C49	C45.7, C46.0-C46.8, C47.8, C48.8, C49.8
Malignant neoplasm of breast	C50	-
Malignant neoplasms of female genital organs	C51-C58	C51.8, C54.8, C57.1-C57.8
Malignant neoplasms of male genital organs	C60-C63	C60.8, C63.8
Malignant neoplasms of urinary tract	C64-C68	C67.8, C68.1, C68.8, C68.9
Malignant neoplasms of eye, brain and other parts of CNS	C69-C72	C69.5, C69.8, C69.9, C71.8, C72.2, C72.8
Malignant neoplasms of thyroid and other endocrine glands	C73-C75	C75.8, C75.9
Malignant neoplasms of ill-defined, secondary and unspecified sites	C76-C80	C76.7, C76.8

Table A2-5. Disease Code List for Malignancy

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue	C81-C96	C82.5, C84.9, C85.7, C86.4, C88.7, C88.9, C92.6, C92.8, C93.7, C95.7, C96.7, C96.9
In situ neoplasms	D00-D09	D01.5, D01.7, D02.4, D03.2, D03.4, D03.5, D04.8, D05.7, D06.7, D07.6, D09.1, D09.3, D09.7
Neoplasms of uncertain or unknown behaviour	D37-D48	D38.6, D39.9, D40.9, D41.7, D41.9, D43.7, D43.9, D44.2, D44.6, D46.0, D46.7, D47.9
Other histiocytosis syndromes	D76.3	-
Other chronic pain	R52.2	-
Poisoning by antineoplastic and immunosuppressive drugs	T45.1	-

Nishikawa A, Yoshinaga E, Nakamura M, et al. Validation Study of Algorithms to Identify Malignant Tumors and Serious Infections in a Japanese Administrative Healthcare Database. Annals of Clinical Epidemiology 2022;4(1):20–31. Cited from SUPPLEMENTARY INFORMATION in https://doi.org/10.37737/ace.22004. (Accessed: June 11, 2024)

Table A2-6. Disease Code List for Indicated disease

Disease/procedure	ICD-10 code(s) version 2013	Exceptions
Rheumatoid arthritis	M05, M06	-
Ulcerative colitis	K51	-
Crohn's disease	K50	-
Psoriasis (Psoriasis vulgaris, Psoriasis arthropica, Pustular psoriasis and Psoriatic erythroderma)	L40	-

Source: "Statistical Classification of Disease, Injuries and Causes of Death" Ministry of Health, Labour and Welfare (mhlw.go.jp)

Table A2-7. Disease Code List for Comorbidity disease (Covariate)

Disease/procedure	ICD-10 code(s)	Exceptions
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x	-
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	-
Diabetes	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6,	-

	E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2– E13.5, E13.7, E14.2–E14.5, E14.7	
Liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4 I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	-
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2– N05.7, N18.x, N19.x, N25.0, Z49.0– Z49.2, Z94.0, Z99.2	
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1	-

Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130-9.

ATTACHMENT 3. DRUG LIST

Table A3-1. List of DMARDS

GENERAL NAME
Actarit
Auranofin
Bucillamine
Iguratimod
Leflunomide
Methotrexate
Mizoribine
Penicillamine
Salazosulfapyridine
Sodium Aurothiomalate
Tacrolimus Hydrate

Table A3-2. List of Amino salicylate

GENERAL NAME
Mesalazine
Salazosulfapyridine

Table A3-3. List of Immunosuppressant (Steroid)

GENERAL NAME
Betamethasone
Betamethasone Acetate/Betamethasone Sodium Phosphate
Betamethasone Sodium Phosphate
Cortisone Acetate
Dexamethasone
Dexamethasone Palmitate
Dexamethasone Sodium Phosphate
Hydrocortisone
Hydrocortisone Sodium Succinate
Methylprednisolone
Methylprednisolone Acetate
Prednisolone
Prednisolone Sodium Succinate
Triamcinolone
Triamcinolone Acetonide

Table A3-4. List of Immunosuppressant (non-steroid)

GENERAL NAME
Apremilast
Azathioprine
Carotegrast methyl
Ciclosporin
Mercaptopurine Hydrate
Tacrolimus Hydrate

Table A3-5. List of Biologics

GENERAL NAME
Abatacept(Genetical Recombination)
Adalimumab(Genetical Recombination)
Bimekizumab(Genetical Recombination)
Brodalumab(Genetical Recombination)
Certolizumab Pegol(Genetical Recombination)
Etanercept(Genetical Recombination)
Golimumab(Genetical Recombination)
Guselkumab(Genetical Recombination)
Ixekizumab(Genetical Recombination)
Ozoralizumab(Genetical Recombination)
Risankizumab(Genetical Recombination)
Sarilumab(Genetical Recombination)
Secukinumab(Genetical Recombination)
Tildrakizumab(Genetical Recombination)
Tocilizumab(Genetical Recombination)
Ustekinumab(Genetical Recombination)
Vedolizumab(Genetical Recombination)

Table A3-6. List of Janus kinase inhibitor

GENERAL NAME
Baricitinib
Filgotinib Maleate
Peficitinib Hydrobromide
Tofacitinib Citrate
Upadacitinib Hydrate

Table A3-7. List of Anti-tuberculosis

GENERAL NAME
Aluminoparaaminosalicylate Calcium Hydrate
Bedaquiline Fumarate
Calcium Paraaminosalicylate Hydrate
Cycloserine
Delamanid
Enviomycin Sulfate
Ethambutol Hydrochloride
Ethionamide
Isoniazid
Isoniazid Sodium Methanesulfonate Hydrate
Kanamycin Sulfate
Pyrazinamide
Rifabutin
Rifampicin
Streptomycin Sulfate