NON-INTERVENTIONAL STUDY PROTOCOL

A3921194

XELJANZ TABLETS 5 MG SPECIAL INVESTIGATION

-ALL-CASE SURVILLANCE-

STATISTICAL ANALYSIS PLAN

(THIS DOCUMENT IS ENGLISH TRANSLATION OF THE ORIGINAL JAPANESE VERSION)

Version: 10.0

Author: PPD (Clinical Statistics, PPD)

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1. REVISION FROM THE PREVIOUS VERSION

Version	Date	Author(s)	Summary of Changes/Comments
1.0	30/APR/2014	PPD	Initial version
2.0	20/MAR/2015	PPD	3. Interim and Final Analyses Modified the results of interim analysis. 5.1. Safety Analysis Set ・Changed descriptions according to the "Guidance on Selection Criteria of Analysis Sets and Data Handling." 5.2. Efficacy Analysis Set ・Changed descriptions according to the above guidance. Added the detailed definitions of control group. 6.1. Safety Endpoints ・"Procedural Manual" was changed to "Procedural Manual for Extracting Key Survey Items in Xeljanz Tablets 5 mg Special Investigation (All-Case)." 8.1.3. Analysis of Binary Data ・Added statistical methods to compare proportions among treatment groups and subgroups. 8.1.5. Analysis of Malignant Tumors, Serious Infections, and Death ・Added definitions of "difference in incidence rates between treatment groups and its 95% confidence interval," "ratio of incidence proportions between treatment groups and its 95% confidence interval," "difference in pooled incidence rates between treatment groups and its 95% confidence interval," and "ratio of pooled incidenc proportions between treatment groups and its 95% confidence interval." ・Changed the calculating method for "Standardized Incidence Ratio (SIR) and its 95% confidence interval." 8.2.2. Analysis of Patient Background and Treatment History ・Added the description "Similarly, the numbers and the proportions of patients will be calculated by methotrexate (MTX), biological agents, DMARDs and immunosuppressive agents other than MTX, oral steroids and other drugs" to "• Frequency distribution of concomitant drugs" and • Frequency distribution of prior medications." ・Added overall administration period in "• Status of administration."

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.1. Analysis of malignant tumors ・Added the calculated difference in incidence rates and its 95% confidence interval in "• Incidence rate of malignant tumors." ・Added the calculated ratio of incidence proportions and its 95% confidence interval in "• Incidence proportion of malignant tumors." 8.2.3.2. Analysis of serious infections ・Added the calculated difference in incidence rates and its 95% confidence interval in "• Incidence rate of serious infections." ・Added the calculated ratio of incidence proportions and its 95% confidence interval in "• Incidence proportion of serious infections." 8.2.3.3. Analsis of deaths ・Added the calculated difference in incidence rates and its 95% confidence interval in "• Mortality rate." ・Added the calculated ratio of incidence proportions and its 95% confidence interval in "• Incidence proportion of deaths." 8.2.3.4. Safety analysis in the Xeljanz group ・Changed the priority of outcome in "Table 9: Tabulation items concerning the details of adverse drug reactions by event" to "last event" in "• Details of adverse drug reactions by event." ・Changes were made so that "• Subgroup analysis" will be conducted if at least one adverse drug reaction of key survey items (neutrophil count decreased and neutropenia, lymphocyte count decreased and lymphopenia, hemoglobin decreased and anemia, lipid increased and hyperlipidemia, gastrointestinal perforation, cardiovascular adverse events, hepatic dysfunction, and interstitial pneumonia) is observed. ・Added tabulation of adverse events in "• Key survey iterms." CCI [redacted] 9. Listings ・Added "List of surgical therapies for rheumatoid arthritis"and "List of patients excluded from analysis (patients aged 16 years or younger, patients receiving Xeljanz for conditions other than rheumatoid arthritis)."

Version	Date	Author(s)	Summary of Changes/Comments
3.0	04/SEP/2015	PPD	10. References ・Added literatures. 11.1.2. Patient Background ・Changed specific disease names of past history and complications. 11.1.3. Patient Background Considered for Safety ・The section title “11.1.3 Patient background considered for safety/efficacy” was changed to reflect patient backgrounds corresponding to respective events. ・Added the reference population based on which risk ratios and their 95% confidence intervals are calculated. 11.1.4. Patient Background Considered for Efficacy ・Made addition associated with the change of section title” 11.1.3 Patient background considered for safety/efficacy.” 11.1.5. Numbers of subgroup patients in reference population and those with malignant tumors (2010) ・Added items. ・Inserted “Table 6: Number of subgroup patients in reference population and those with malignant tumors” in this section, and updated the table with 2010 data. 11.2. Interim Analysis ・Modified the details of interim analysis. Corrected errors in writing including typos and omissions. 5.1. Safety Analysis Set, and all the sections thereafter Changed the name "Subpopulation that meets the guideline" to " Subpopulation that meets the MTX criteria". 8.1.5. Analysis of Malignant Tumors, Serious Infections, and Death ・Divided the section into “8.1.5. Analysis of Incidence per Exposure and Incidence Proportion of Specified Events” and “8.1.6. Group Comparison of Incidence per Exposure and Incidence Proportion of Specified Events.”

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.2. Analysis of Patient Background and Treatment History ・Added “A biological therapeutic or immunosuppressant terminated on the same day as the first dose of Xeljanz or started on the same day as the last dose of Xeljanz will not be considered as a concomitant drug.” to “・Concomitant drugs.” Added “These calculations will be performed for all concomitant drugs and for only those initiated by 6 months after the start of Xeljanz.” to compare with post-marketing surveys on other medications. ・Added “These calculations will be performed for all non-drug therapies and for only those initiated by 6 months after the start of Xeljanz.” to “・Non-drug therapies ” to compare with post-marketing surveys on other medications. ・Added “A biological therapeutic or immunosuppressant terminated on the same day as the first dose of Xeljanz will be considered as a prior medication.” to “・Prior medications.” ・Added definitions of initial daily dose, total dose, average daily dose, and average actual daily dose to “・Status of administration.” 8.2.3.4. Safety analysis in the Xeljanz group ・Added “Adverse drug reactions and adverse events will be analyzed for all those reactions or events that developed during the survey period, and those that developed by 6 months after the start of Xeljanz.” to compare with post-marketing surveys on other medications. ・Added Serious infections (including herpes zoster and tuberculosis) and Malignant tumors (including lymphoma) to “・Subgroup analysis.” ・Added a description of the incidences of key survey items, and incidences in patients with or without past histories and complications to “・Key survey items.”

Version	Date	Author(s)	Summary of Changes/Comments
			11.1.2. Patient Background ・Added factors Age 4, Smoking history 2, History of MTX use (Dose just prior to the start of survey 1), History of MTX use (Dose just prior to the start of survey 2), History of MTX use (Duration), History of oral steroid use (Dose just prior to the start of survey), History of oral steroid use (Duration), History of tacrolimus use (Duration), Prior medication (biological agents), Initial daily dose of Xeljanz, White blood cell count, Lymphocyte count, β-D-glucan, and Organization that established the hospital. ・Changed the variable “Duration of disease” so as to be treated as a continuous data, as well. ・Added categories SDAI, CDAI, and DAS28. 11.1.3. Patient Background Considered for Safety ・Added nominal scales Body weight, Prior medication (biological agents) (Within 3 months), White blood cell count, Lymphocyte count, β-D-glucan, and Organization that established the hospital; and ordinal scales Age 3, Age 4, History of MTX use (Dose just prior to the start of survey 1), History of MTX use (Dose just prior to the start of survey 2), History of MTX use (Duration), History of oral steroid use (Dose just prior to the start of survey), History of oral steroid use (Duration), History of tacrolimus use (Duration), and Initial daily dose. ・Added categories SDAI, CDAI, and DAS28. 11.1.4. Patient Background Considered for Efficacy ・Added ordinal scales Age 3, Age 4, and Initial daily dose. ・Added categories SDAI, CDAI, and DAS28. Corrected errors in writing including typos and omissions.
4.0	26/MAY/2016	PPD	3. Interim and Final Analyses ・Changed the objective and timing of, and patients to be included in the interim analysis. ・Changed the sentence, " At interim analyses, only the analyses of necessary items among statistical analyses specified in this plan will be performed (Refer to Appendix 11.2 for details)" to " At interim analyses, only the analyses of necessary items among statistical analyses specified in this plan will be performed Such items will be selected for each analysis to be performed, and specified separately". 5.1. Safety Analysis Set ・Added "Subpopulation that does not meet the MTX criteria" .

Version	Date	Author(s)	Summary of Changes/Comments
			6.3. Covariates ・Revised covariates concerning development of malignant tumor and serious infection. ・Added "Covariates with a high proportion of missing data will not be included in the model analysis". ・Deleted "Subjects will be segmented to 3 age categories, <50 years, ≥50 and <65 years, and ≥65 years, if age will be handled as a categorical data". 7. Handling of Missing Data ・Added a method for the complementation of efficacy endpoints, the start date of event, and the date of final dose (observation) was added. 8.1.3. Analysis of Binary Data ・Added "Unknown, unspecified, and missing data will be excluded from the analysis set when an analysis test is performed. 8.1.5. Analysis of Incidence per Exposure and Incidence Proportion of Specified Events ・Changed the calculation method for the incidence and its 95% confidence interval. 8.2.2. Analysis of Patient Background and Treatment History ・Changed "・Status of the Implementation of Tests Before the Initiation of Administration of Xeljanz " to "・Status of the Implementation of Tests ", and added the data on the status of the implementation of tests after initiation of the administration. ・Added the data on each assessment timepoint in the control group in "・Status of administration ". ・Added " Tabulation and analysis by subgroup ", and accordingly, added the data in Xeljanz group for subsets sorted by the initial daily dosage, and in Subpopulation that meets the MTX criteria and Subpopulation that does not meet the MTX criteria. 8.2.3.1. Analysis of malignant tumors ・Added onset during the treatment period (+28 days) as a criterion for the definition of patients with malignant tumor. ・Specified the period during which the number of patients and the incidence would be calculated for "・Incidence rate of malignant tumor". ・Added a list showing the duration of event, and time to data cutoff in "・Analysis to time to malignant tumor".

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.2. Analysis of serious infections ・Added onset during the treatment period (+28 days) as a criterion for the definition of patients with serious infections. Changed the primary evaluation to onset during treatment period (+28 days). ・Added a method of tabulation and analysis specific to the Xeljanz group. ・Specified the period during which the number of patients and the incidence would be calculated for "・Incidence rate of serious infections ".・Added a list showing the duration of event, and time to data cutoff in "・Analysis to time to serious infections ". ・Added a list showing the duration of event, and time to data cutoff in "・Analysis to time to deaths ". 8.2.3.4. Safety analysis in the Xeljanz group ・Added a tabulation on patient background among patients with all-causality serious infection and herpes zoster in Xeljanz group in "・Key survey items". ・Added "・Key survey item for Subpopulation that meets the MTX criteria and Subpopulation that does not meet the MTX criteria". CCI [redacted] 8.2.4.1. SDAI，CDAI ・Added an analysis with LOCF. 8.2.4.2. DAS28 ・Added an analysis with LOCF. 9. Listings ・Added "List of time to onset of malignant tumor, serious infection, and death, and time to data cutoff", "List of patients with herpes zoster", and "List of concomitant medications used in patients with herpes zoster". 11.1.2. Patient Background ・Added or omitted some items and categories. 11.1.3. Patient Background Considered for Safety ・Added or omitted some items and categories. 11.1.4. Patient Background Considered for Efficacy ・Added or omitted some categories.

Version	Date	Author(s)	Summary of Changes/Comments
			11.2. Interim Analysis ・Omitted parameters to be analyzed since the data will now be recorded in a separate document. Refined typos were corrected, and presentation and wording.
5.0	08/SEP/2016	PPD	5.1 “Safety analysis set” ・Added the definition of “Subpopulation of newly entered patients” 8.1.5 “Incidence rateper exposure amount and the 95% confidence interval” ・Changed the method for confidence interval 8.2.1 Table 2 “Categories of Tabulation Items for Discontinuation and Dropout”, 8.2.2 Table 4 “Categories of Tabulation Items for Administration Status”, 8.2.3.4 Table 8 ”Tabulation Items Concerning the Details of Adverse Drug Reactions by Even” ・Changed the category of time periods 8.2.2 “Analysis of Patient Background and Treatment History” ・Added “unknown” from the daily number of administrations 8.2.3.1 “Development of malignant tumors” ・Delete “squamous cell carninoma” from the type of cancer. 8.2.3.1 “ Standardized incidence rate (SIR) for the development of malignant tumors” Appendix 11.1.5. “Numbers of patients with malignant tumors in reference population” ・Updated reference data from 2010 to 2012 8.2.3.4 “Key suvey items” ・Added Analyses for incidence rate by time period 8.2.3.4 “Subgroup analysis” ・Added any adverse drug reaction CCI [redacted]

Version	Date	Author(s)	Summary of Changes/Comments
			9 “Listings” ・Added a list of patients with serious infection, a list of patients with neutrophil count decreased and neutropenia, a list of patients with lymphocyte count decreased and lymphopenia, a list of patients with lipid increased and hyperlipidemi, a list of patients with malignant tumors (including lymphoma), a list of patients with gastrointestinal perforation, a list of patients with cardiovascular adverse events, a list of patients with hepatic dysfunction, a list of patients with interstitial pneumon, a list of patients with opportunistic infection, a list of patients with tuberculosis, a list of patients with pneumocystis pneumonia, a list of deaths Appendix 11.1.4 “11.1.4. Patient Background Considered for Efficacy” ・Added Status of MTX use Refined typos were corrected, and presentation and wording.
6.0	27/OCT/2016	PPD	5.4. Subgroups ・Added average actual daily dose. 8.2.2. Analysis of Patient Background and Treatment History ・Added some categories in "・Status of administration ". 8.2.3.2. Analysis of serious infections ・Added the analyses for serious infections excluding serious herpes zoster and for serious herpes zoster in “・Incidence rate of serious infections” and “・Incidence proportion of serious infections” . 8.2.3.4. Safety analysis in the Xeljanz group ・Added summary for patients’ background of patients with and without all-causality pneumocystis jirovecii pneumonia in Xeljanz group in "・Key survey items". 8.2.4. Efficacy Analysis ・Added subgroup analyses by average actual daily dose. 11.1.2. Patient Background ・Added BMI, History of oral steroid use (Duration) and History of tacrolimus use (Duration). 11.1.3. Patient Background Considered for Safety ・Added BMI. Refined typos were corrected, and presentation and wording.
7.0	15/SEP/2017	PPD	2.1. Study Design ・Modified because of the protocol amendmrnt. ・Added definition of death.

Version	Date	Author(s)	Summary of Changes/Comments
			6.3. Covariates ・Added candidate covariates related to the development of malignant tumors and serious infections and created a table of the candidate covariates. 7. Handling of Missing Data ・Added a handling method of missing data about candidate covariates related to the development of malignant tumors and serious infections. 8.1.6. Group Comparison of Incidence Rate and Incidence Proportion of Specified Events ・Changed definition of variance in “Difference in pooled incidence proportion between the treatment groups and the 95% confidence interval”. ・Specified a calculation method in “Propensity scores”. 8.2.2. Analysis of Patient Background and Treatment History ・Deleted an analysis for only concomitant drugs initiated by 6 months after the start of Xeljanz in “Concomitant drugs”. ・Deleted an analysis for only non-drug therapies initiated by 6 months after the start of Xeljanz in “Non-drug therapies”. 8.2.3.1. Analysis of malignant tumors ・Specified a calculation method in “Adjusted hazard ratio for the development of malignant tumors”. 8.2.3.2. Analysis of serious infections ・Specified a calculation method in “Adjusted hazard ratio for the development of serious infections”. 8.2.3.4. Safety analysis in the Xeljanz group ・Deleted some analyses in “Subgroup analysis”. ・Deleted some analyses in “Key survey items”. 8.2.4. Efficacy Analysis ・Deleted percent changes. 8.2.4.3. Subgroup analysis ・Changed definition of efficacy to SDAI remission after 6 months of administration 10. References ・Added some references. 11.1.2. Patient Background ・Added some items and categories. 11.1.3. Patient Background Considered for Safety ・Added some items and categories. 11.1.4. Patient Background Considered for Efficacy ・Added some items and categories. Refined typos were corrected, and presentation and wording.

Version	Date	Author(s)	Summary of Changes/Comments
8.0	19/SEP/2018	PPD	2.1. Study Design ・Moved the definition of serious infection to section 6.1.1. 5.1. Safety Analysis Set ・Divided into section 5.1.1 and 5.1.2. ・Adjusted the definition of the analysis set. 5.2. Efficacy Analysis Set ・Adjusted the definition of the analysis set. 5.4. Subgroups ・Added sex and age class. 6.1.1. Comparison of Xeljanz group and control group ・Adjusted the definition of malignant tumor and death. ・Added two evaluations about adverse events. 6.1.2. Safety analysis of the Xeljanz group ・Added that the evaluation of adverse events should be carried out using only the company evaluation. 6.3. Covariates ・Added BMI, complications (hepatic dysfunction), complications (renal dysfunction), MTX criteria, initial daily dose, neutrophil count, lymphocyte count, DAS28. 7. HANDLING OF MISSING DATA ・Adjusted current descriptions. 8.1.6. Group Comparison of Incidence Rate and Incidence Proportion of Specified Events ・Added definition of multiple imputation method. 8.2.1. Summary of Patients ・Adjusted current descriptions. 8.2.2. Analysis of Patient Background and Treatment History ・Adjusted current descriptions. 8.2.3.1. Comparison of Xeljanz group and control group ・Divided into section 8.2.3.1.1, 8.2.3.1.2 and 8.2.3.1.3. 8.2.3.1.1. Analysis of malignant tumors ・Adjusted current descriptions. 8.2.3.1.2. Analysis of serious infections ・Adjusted current descriptions. 8.2.3.1.3. Analsis of deaths ・Adjusted current descriptions. 8.2.3.2. Safety analysis in the Xeljanz group ・Adjusted current descriptions. ・Moved sensitivity analysis in comparison of the Xeljanz group and the control group to section 8.2.3.1.4.

Version	Date	Author(s)	Summary of Changes/Comments
			CCI [redacted] 8.2.4. Efficacy Analysis ・Adjusted current descriptions. 9. Listings ・Added definition of death. 10. References ・Added some references. 11.1.2. Patient Background ・Added neutrophil count and hemoglobin. ・Added category of lymphocyte count. 11.1.3. Patient Background Considered for Safety ・Added lymphocyte count. 11.1.5. Numbers of patients with malignant tumors in reference population (2013) ・Changed reference data from 2012 to 2013. Refined typos were corrected, and presentation and wording.
9.0	27/NOV/2020	PPD	5.1.1. Safety analysis of the Xeljanz group ・Modified the description of the transfer patients. 5.2. Efficacy Analysis Set ・Adjusted current descriptions. 5.4. Subgroups ・Added definition of contraindicated patients. 7. HANDLING OF MISSING DATA ・Deleted some descriptions about multivariate analysis. 8.1.6. Group Comparison of Incidence Rate and Incidence Proportion of Specified Events ・Adjusted current descriptions. 8.2.1. Summary of Patients ・Adjusted current descriptions. 8.2.3.1.1. Analysis of malignant tumors ・Added large intestine, pancreas, bladder, kidney / urinary tract (excluding bladder) to cancer types. ・Added to apply Weibull distribution. ・Added distributions of propensity acore and covariates before and after adjustment. ・Added calendar year for SIR. 8.2.3.1.2. Analysis of serious infections ・Added to apply Weibull distribution. ・Added distributions of propensity acore and covariates before and after adjustment.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.1.3. Analsis of deaths ・Added SMR CCI [redacted] 8.2.3.2. Safety analysis in the Xeljanz group ・Added some diseases for current analyses. CCI [redacted] 9. Listings ・Added list of contraindicated patients with adverse drug reactions. 10. References ・Added some references. 11.1.3. Patient Background Considered for Safety ・Deleted organization that established the hospital. 11.1.5. Numbers of patients with malignant tumors in reference population (2013) ・Deleted this section. Refined typos were corrected, and presentation and wording.
10.0	06/DEC/2021	PPD	After the database was released, it was found that the handling of the death cases was not appropriate, so the following sections were corrected. 6.1.1. Comparison of Xeljanz group and control group ・Changed the handling of death cases. 7. Handling of Missing data ・When comparing the xeljanz group and the control group, the conditions to include as death cases were added.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the special investigation of Xeljanz Tablets 5 mg (A3921194). In this plan, texts cited from the protocol are shown in italics.

2.1. Study Design

This survey is a non-interventional study that includes patients who received Xeljanz Tablets (hereinafter referred to as Xeljanz) (Xeljanz group) and patients who started medications for rheumatoid arthritis other than Xeljanz (hereinafter referred to as control drugs) (control group) among patients with uncontrolled rheumatoid arthritis despite the continued use of methotrexate (hereinafter referred to as MTX) at a dose exceeding 8 mg/week for at least 3 months in the cohort.

The control group will include Xeljanz-naive patients, and clinical trial participants are not allowed to be registered in the control group.

<Scheduled number of patients to be investigated>

Target sample size: Subjects who meet the conditions in "2. Subjects" for each group and the sample size is shown below.

1) Xeljanz group: 4000 subjects for safety analysis

The target sample size is set to be 4000 subjects by adding a certain sample size a) b) exceeding 3000 subjects beginning from the start of registration (3-year observation) to the subsequent number of subjects (6-month observation period). See "6.5 observation period" for more information. However, even if Xeljanz is administered to subjects who do not meet the conditions described in "2. Subjects" for inevitable reason(s), while such subjects will not be included in the above sample size, the request to enroll subjects and complete survey forms will be made for subjects in the Xeljanz group for the sake of all-cases survey.

2) Control group: A certain sample size [a) b)] exceeding 2000 subjects for safety analysis

[Remarks]

a) The sample size in both groups will be set to be the number of subjects for whom the degree of statistical accuracy described in [Rationale for sample size] is maintainable. See the Appendix for more information.

b) The registration period until a certain sample size is reached will be the same period for both groups.

<Rationale for the scheduled number of patients to be investigated>

The incidence of malignant tumors after administration of Xeljanz in a Japanese long-term study (Study No. A3921041) is 1.16 (/100 patient-years). Since the dropout rate in clinical studies is 31% in subjects who proceeded to the Japanese long-term study (Study No. A3921041) from a Japanese phase II study (Study No. A3921039) (duration of treatment, 3 years) and 14% in subjects who proceeded from a Japanese phase II study (Study No. A3921040) (duration of treatment, 1.4 years), the dropout rate at the completion of 3-year observation under the actual use conditions in routine practice is assumed to be about 50%.

If the number of patients in the Xeljanz group is set at 4000, events can be confirmed in 104 patients based on the incidence of malignant tumors in Japanese patients of 1.16 (/100 patient-years).

Meanwhile, if the number of patients in the Xeljanz group is set at 4000 and the incidence of malignant tumors in the control group is assumed to be comparable to that in the Xeljanz group, at least 2000 patients will be required to allow a statistically valid comparison between the groups. Therefore, the number of patients in the control group was set at 2000.

Depending on the progress of registration, if the registered number of patients in either group significantly exceeds the above number earlier than the other group, a sample size with 3-year observation period can be changed to the combination of a sample size for whom the degree of statistical accuracy is maintainable if it is compared with 4000 patients in the Xeljanz group and 2000 patients in the control group (see the Appended Table). Also, the registration period for patients in the inter-group comparison needs to be the same.

<Scheduled period of the survey>

Duration of surveillance: From the date marketing of Xeljanz begins to the completion of assessment by regulatory authorities

Enrollment period: From marketing commencement for Xeljanz to clearing of approval conditions for all-cases survey

Completion of survey forms for the Xeljanz group will no longer be mandated upon registration of 4000 subjects [c)] in the Xeljanz group, which is the target sample size, after the approval from regulatory authorities is obtained. Meanwhile, registration will be continued until the final assessment is made by regulatory authorities.

For the control group, both completion of survey forms and registration will no longer be mandated after the target sample size is reached and the approval from regulatory authorities is obtained.

**The results of collecting and analyzing 6 months' worth of data on the 4000 subjects in the Xeljanz group will be submitted to the regulatory authorities together with the results of collection and analysis of 6 months' worth of data on the subjects in the Xeljanz group who do not meet the conditions described in "2. Subjects" and the control group.*

c) Subjects who meet the conditions described in "2. Subjects".

Observation period

[1] Xeljanz group:

(1) Registered subjects up to a certain sample size exceeding 3000 subjects from the start of registration: 3 years (36 months) from the date of treatment commencement

(2) Registered subjects after the above (1): Only 6 months from the date of treatment commencement

[2] Control group: 3 years (36 months) from the date of treatment commencement

[3] Follow-up surveillance

For a period of 3 years from the date of treatment commencement, follow-up surveillance will be conducted for subjects in the Xeljanz group (1) and the control group on information related to the drug administration conditions and adverse events after discontinuation (serious infections (12 months), malignant tumors, adverse events leading to death).

2.2. Study Objectives

This survey will be performed in patients administered Xeljanz Tablets (hereinafter referred to as Xeljanz) to obtain information on the following under the actual use conditions after marketing:

1) Development of adverse drug reactions, factors that may affect safety, and efficacy

2) Safety (malignant tumors and serious infections in particular) and efficacy in long-term use

The development of malignant tumors and serious infections will be compared with the control group.

Since it has been suggested in Japanese clinical trials that Xeljanz may promote the manifestation of malignant tumors, the development of malignant tumors in the Xeljanze group will be compared with that in the control group by 3-year observation. The development of serious infections in the Xeljanze group will be compared with that in the control group by 1-year observation.

3. INTERIM AND FINAL ANALYSES

In this survey, interim analyses for periodic safety update reports will be performed. Interim analyses shown in Table 1 will be performed for purposes other than periodic safety update reports.

Table 1. Other Interim Analyses

	Objective	Timing of implementation	Target patients
1	Safety evaluation of Xeljanz during an early post-marketing period	The timing at which 6-month data of about 500 patients in Xeljanz group are fixed.	Xeljanz group: Patients for whom at lease Volume 1 is fixed at the specified timing.

Table 1. Other Interim Analyses

	Objective	Timing of implementation	Target patients
2	Safety evaluation of Xeljanz Safety evaluation of control group	The timing at which 6-month data of about 1000 patients in Xeljanz group are fixed.*	Xeljanz group: Patients for whom at lease Volume 1 is fixed at the specified timing. Control group: patients for whom at least Volume 1 is fixed at that timing.
3	Safety evaluation of Xeljanz Safety evaluation of control group	The timing at which 6-month data of about 2000 patients in Xeljanz group are fixed.*	Xeljanz group: Patients for whom at lease Volume 1 is fixed at the specified timing. Control group: patients for whom at least Volume 1 is fixed at that timing.
4	Safety evaluation of Xeljanz intended to discharge the all-cases survey.	The timing at which 6-month data in 4000 patients in the Xeljanz group are fixed.	Xeljanz group: Patients for whom at lease Volume 1 is fixed at the specified timing. Control group: patients for whom at least Volume 1 is fixed at that timing.
5	Comparison of serious infection with control group	The timing at which 1-year data in all patients in Xeljanz group and control group are fixed.	All cases of Xeljanz and Control groups
* The time of implementation will be decided based on the number of collected cases and duration.			

At interim analyses, only the analyses of necessary items among statistical analyses specified in this plan will be performed. Items necessary for the interim analysis will be specified separately. At the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESES AND DECISION RULES

Since this survey is not a confitmatory study, statistical tests will be exploratory. Unless otherwise specified, tests will be 2-sided and the significance level will be 5%. A 2-sided confidence interval will be used for interval estimation, and the confidence coefficient will be 95%.

5. ANALYSIS SETS

5.1. Safety Analysis Set

5.1.1. Safety analysis of the Xeljanz group

- Safety analysis set

Of the enrolled patients with a scheduled observation period of 3 years and 6 months, those who have been confirmed to have received Xeljanz at least once are included. However, the following patients will be excluded from the safety analysis set.

a. No CRF was collected (description in the report: “CRF not collected”);

b. There was a violation or flaw of the contract (description in the report: “Violation/flaw of contract”);

c. There was a violation in the enrollment process (description in the report: “Enrollment violation”);

d. No information on the administration of survey drug was reported (description in the report: “No administration information”);

e. No information on adverse events was reported (ie., existence or non-existence of adverse events is unidentifiable) - No visits after the initial prescription (description in the report: “No information on adverse events - No re-visits”);

f. No information on adverse events was reported - Visits conducted after the initial prescription,but no record (description in the report: “No information on adverse events - No record).

• MTX adherent safety analysis set

The MTX adherent safety analysis set is defined as the patients with rheumatoid arthritis who have been poorly controlled if methotrexate (MTX) at a dose of more than 8 mg/week is continuously used for 3 months or longer among the new patients of the safety analysis set, that is described in the "Guidelines for the use of tofacitinib for all patients post-marketing surveillance".

The new patient is defined as the patients in which administration of Xeljanz was started for the first time after the registration of this surveillance in the Xeljanz group. In addition, the target patients with rheumatoid arthritis are 16 years old or older, and patients under 16 years old are excluded.

5.1.2. Comparison of the Xeljanz group and the control group

•Comparative analysis set

Of the enrolled patients with a scheduled observation period of 3 years, those who were confirmed to treat Xeljanz in the Xeljanz group and a control drug (control drug is MTX, biological agents, DMARDs or immunosuppressive drug) at least once were included in the control group. The patients who apply to a to f in Section 5.1.1 are excluded.

The control group also excludes patients who do not meet the MTX criteria and patients who have been treated with Xeljanz.

•MTX adherent comparative analysis set

The MTX adherent comparative analysis set of the Xeljanz group is the patients who meets the MTX criteria among the new patients of the comparative analysis set.

As for the control group, since the comparative analysis set of the control group is limited to the patients who meet the MTX criteria, the same set is also used as the control group of MTX adherent comparative analysis set.

5.2. Efficacy Analysis Set

•Efficacy Analysis Set

The efficacy analysis set is defined as the safety analysis set excluding patients meeting at least one of the following criteria.

g. No results of efficacy evaluation were reported (description in the report: “No efficacy information”)
   Efficacy evaluation to be reported: Tender joint count (TJC), swollen joint count (SJC), patient VAS, physician VAS, ESR, and CRP

h. Diseases not investigated in the survey (description in the report: “Disease outside the survey scope”)
   Diseases not investigated in the survey: Patients aged 16 years or younger, patients receiving Xeljanz for conditions other than rheumatoid arthritis

Efficacy in the control group will not be investigated.

•MTX adherent efficacy analysis set

The MTX adherent efficacy analysis set is the patients who meets the MTX criteria among the efficacy analysis set.

The acceptance or rejection of the safety and efficacy analysis se will be examined after treating patients consulted at multiple centers as the same patients. Multi-center consultation patients are patients in which the investigation has been completed and it has been confirmed that multiple identifications have been assigned to the same patient by transfer of hospital or department. Patients in which the investigation is completed and it is confirmed that there is no transfer or department transfer are considered as single-center consultation paients.

5.3. Other Analysis Sets

None.

5.4. Subgroups

For the Xeljanz group, safety and efficacy will be analyzed for each of the following subgroups.

- Sex
- Age class (≥65 years, <65 years)
- Presence or absence of hepatic dysfunction (Presence of hepatic dysfunction is defined as the item “current hepatic dysfunction” in the medical history being checked.)
- Presence or absence of renal dysfunction (Presence of renal dysfunction is defined as the item “current renal dysfunction” in the medical history being checked.)
- Average actual daily dose (<7.5mg, ≧7.5 mg)

Patients that may be contraindicated in the package insert of Xeljanz (hereinafter referred to as contraindicated patients) are extracted based on the criteria specified separately, and a subpopulation analysis of safety is performed.

In addition, safety and efficacy will be analyzed for each of the patient background subgroups specified in Appendix 11.1.3 and 11.1.4.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

6.1.1. Comparison of Xeljanz group and control group

•Malignant tumors are tumors with definitive diagnosis among all-causality malignant tumors (including lymphoma).

•Time to occurrence of malignant tumor

•Serious infections are infections corresponding to the following among all-causality infections.

1. Results in death, or is life-threatning;

2. Results in disability, or may lead to disability;

3. Requires inpatient hospitalization or prolongation of hospitalization;

4. Are serious in accordance with the above.

•Time to occurrence of serious infection

•Death refers to the case where the death column is checked in the status of treatment of Xeljanz (continued or discontinued) or the status of follow-up (continued or discontinued) in the case report rorm (CRF).

The death was defined to exclude post-survey deaths for comparing fairly in the xeljanz and control groups, because post-survey deaths are likely to be collected only in the xeljanz group. However, it was found that there were death cases those were possiblly to have been confirmed at the end of the survey and had no reason for discontinuation of the treatment or the follow-up, when the final analysis for the reexamination application (cutoff data on 12/July/2021) was conducted. Since it was found that there were cases that were considered to be high, such cases were exceptionally regarded as cases where the investigation was discontinued due to patient death, and were included in the analysis as cases of death. Such cases were exceptionally regarded as death cases where the survey was discontinued due to death, and were included in the analysis as death cases. The handling of death cases is described in Section 7.

•Time to death

The causal relationship and seriousness of the adverse events (including malignant tumors, serious infections, and deaths) of the Xeljanz group in this survey were evaluated separately from the doctor's evaluation in the CRF and the corporate evaluation. In addition, after a patient in the Xeljanz group was transferred to a facility without a survey contract, the information obtained from the transfer destination is not described in the CRF, but there are adverse events entered in the database at the discretion of the company. Since this information is not collected in the control group, malignant tumors, serious infections, and deaths in the comparison between the Xeljanz group and the control group are investigated as adverse events including company evaluation and adverse events based only on the information described in the CRF.

6.1.2. Safety analysis of the Xeljanz group

- Adverse drug reactions (treatment-related adverse events).
- Adverse events (all-causality adverse events).

- Key survey items: The procedures to extract events to be handled as key survey items are specified in "Procedural Manual for Extracting Key Survey Items in Xeljanz Tablets 5 mg Special Investigation (All-Case)." Key survey items are shown below.

  - *Serious infections;*
  - *Neutrophil count decreased and neutropenia;*
  - *Lymphocyte count decreased and lymphopenia;*
  - *Hemoglobin decreased and anemia;*
  - *Lipid increased and hyperlipidemia;*
  - *Malignant tumors (including lymphoma);*
  - *Gastrointestinal perforation;*
  - *Cardiovascular adverse events;*
  - *Hepatic dysfunction;*
  - *Interstitial pneumonia.*

6.2. Efficacy Endpoints (Xeljanz Group)

- SDAI (Simplified Disease Activity Index)

$$\mathrm{SDAI} = \mathrm{TJC} + \mathrm{SJC} + \mathrm{PatinentVAS}\ [\mathrm{mm}]\ /10 + \mathrm{physician\ VAS}\ [\mathrm{mm}]\ /10 + \mathrm{CRP}\ [\mathrm{mg/dL}]$$

- CDAI (Clinical Disease Activity Index)

$$\mathrm{CDAI} = \mathrm{TJC} + \mathrm{SJC} + \mathrm{PatientVAS}\frac{[\mathrm{mm}]}{10} + \mathrm{physicianVAS}\ [\mathrm{mm}]\ /10$$

- DAS28 (4/ESR）[1]

$$\mathrm{DAS28(4/ESR)} = 0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.70\ \ln(\mathrm{ESR}\ [\mathrm{mm/hr}]\ ) + 0.014(\mathrm{Patient's\ VAS}\ [\mathrm{mm}]\ )$$

Unless otherwise specified, DAS28 (4/ESR) will be used as DAS28. If inconvenience occurs such as the case where there are many patients without the measurement of ESR and patient VAS, the use of DAS28 (3/ESR), DAS28 (4/CRP), or DAS28 (3/CRP) will be considered.

DAS28 (3/ESR)[1]

$$\mathrm{DAS28(3/ESR)} = \{0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.70\ln(\mathrm{ESR[mm/hr]})\} \times 1.08 + 0.16$$

- DAS28 (4/CRP)[1]

$$\mathrm{DAS28(4/CRP)} = 0.56\sqrt{\mathrm{TJC}} + 0.28\sqrt{\mathrm{SJC}} + 0.36\ln(10 \times \mathrm{CRP[mg/dL]} + 1) + 0.014(\mathrm{PatientVAS[mm]}) + 0.96$$

- DAS28 (3/CRP)[1]

$$DAS28(3/CRP) = \{0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.36\ln(10 \times CRP[mg/dL] + 1)\} \times 1.10 + 1.15$$

TJC: Tender Joint Count

SJC: Swollen Joint Count

- Patient VAS and physician VAS

6.3. Covariates

For both the Xeljanz and control groups, candidate covariats related to the development of malignant tumors and serious infections are shown below.

Covariats	Malignant tumor	Serious infection
Sex	○	○
Age	○	○
Weight	○	○
Stage of rheumatoid arthritis	○	○
Class of rheumatoid arthritis	○	○
Duration or disease	○	○
Past history (infection)	×	○
Past history (malignant tumor)	○	×
Past history (lung disorder)	×	○
Past history (interstitial pneumonia)	×	○
Complication (infection)	×	○
Complication (malignant tumor)	○	×
Complication (hepatitis B)	○	×
Complication (hepatitis C)	○	×
Complication (diabetes mellitus)	×	○
Smoking history	○	○
Family history of malignant tumors (including lymphoma)	○	○
History of MTX use (Within 3 months prior to the start of survey)	○	○
MTX criteria	○	○
History of oral steroid use (Within 3 months prior to the start of survey)	○	○
History of tacrolimus use (Within 3 months prior to the start of survey)	○	○
Past use of biological agents (Within 3 months prior to the start of survey)	○	○

Covariats	Malignant tumor	Serious infection
Initial dose of Xeljanz	○	○
Neutrophil count	○	○
Lymphocyte count	○	○
Prophylactic administration to prevent tuberculosis	×	○
Prophylactic administration to prevent pneumocystis jiroveci pneumonia	×	○
Prophylactic administration to prevent hepatitis B	×	○
DAS28	○	○
○：Applicable，×：Not applicable		

Covariates may be added or removed based on the results of the interim analyses of this survey and newly obtained findings. In that case, this plan will be revised.

7. HANDLING OF MISSING DATA

If there is no measurement within the acceptance range for the definition of visit timing for laboratory test values and efficacy endpoints (Appendix 11.1.1), data at the visit timing will be handled as missing.

If data on SDAI, CDAI, DAS28, TJC, SJC, patient VAS, physician VAS, ESR, or CRP is missing on Months 3 and 6, missing data will be imputed by LOCF using observed data after dosing for a sensitivity analysis on efficacy.

If the seriousness of, procedure for, and outcome of, adverse events are missing, they will be tabulated as “unknown.”

If the date of event or death is missing for the analysis in consideration of time to the onset of malignant tumor and serious infection, and death, such a date will be imputed by the date on which no event or death is confirmed from among all data collected. The earliest of such date to complement the data would be the date on which the administration of Xeljanz or control drug therapy is started.

If the final date of dose or observation is missing, such a date will be complemented by the date on which a dose or observation is confirmed from among all data collected. The earliest of such date to complement the data would be the date on which the administration of Xeljanz or control drug therapy is started.

If candidate covariates (6.3) are missing (including unknown), they are not complemented in the univariate analysis. They are is regarded as "unknown" and analyzed as one category in the multivariate analysis.

They are complemented by the multiple imputation method in the comparison of the Xeljanz group and the control group.

The death cases described in Section 6.1.1 define the cases in which treatment was not discontinued and continued until the end of the survey, or the cases in which no discontinuation was reported in the follow-up after discontinuation of treatment and death was reported within 3 years + 28 days from the start of treatment.

These are cases that meet the following two conditions and are regarded as cases in which the survey was discontinued due to death (the reason for discontinuation of the survey was death) in the comparison of deaths.

- Cases in which treatment has not been discontinued due to transfer or no return visit, and there is no reason for discontinuation of the survey.
- Cases in which death was reported as the reason for the seriousness of the serious adverse event and the outcome was within 3 years + 28 days from the start of the treatment, or an adverse event leading to death was reported and the death date was within 3 years + 28 days from the start of the treatment.

8. STATISTICAL METHODS AND ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of Continuous Data

Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) will be calculated.

8.1.2. Analysis of Categorical Data

The frequency of each classification and the proportion will be calculated.

8.1.3. Analysis of Binary Data

Frequency and the proportion will be calculated. If a confidence interval for proportion is calculated, a 2-sided 95% confidence interval will be calculated. At the tests, unknown, unspecified, and unmeasured data will be excluded from the analysis.

If a test is performed, Fisher's exact test will be performed for a relationship with nominal scale data and Cochran-Armitage test (exact method) will be performed for a relationship with ordinal scale data.

Ratios and differences of proportions and their 95% confidence intervals will be calculated to compare proportions among treatment groups.

Risk ratios and their 95% confidence intervals will be calculated to compare proportions among subgroups.

If a model analysis is performed, a logistic regression model will be used.

8.1.4. Analysis of Time-to-event

Summary statistics (median, 1st quartile, and 3rd quartile) by the Kaplan-Meier method will be calculated. In addition, a Kaplan-Meier plot will be prepared.

Time to each event and time to censoring will be separately specified for each item.

If a model analysis is performed, a Cox proportional hazard model will be used.

8.1.5. Analysis of Incidence Rate and Incidence Proportion of Specified Events

Incidence rate and incidence proportion will be calculated for specified events including initial malignancy, initial sereious infection, and death, according to the following formulae.

- **Duration of exposure [patient-year]**

Total of time to each event and time to censoring in each group [day]/365.25

- **Incidence rateamount and the 95% confidence interval**[2,10,11]

$$\text{Incidence rate amount [patient/100 patient-years]} = 100 \times \frac{a}{PT}$$

95% confidence interval for incidence per exposure amount [patient/100 patient − years].

$$= \begin{cases} \left[100 \times \dfrac{\chi^2(0.025, 2a)/2}{PT}, 100 \times \dfrac{\chi^2(0.975, 2(a+1))/2}{PT}\right] & (a \neq 0) \\ \left[0.00, 100 \times \dfrac{\chi^2(0.95, 2))/2}{PT}\right] & (a = 0) \end{cases}$$

a: Number of patients with the event [patient]

PT: Duration of exposure [patient-year]

$\chi^2(p, d)$: the lower p quantile for the chi − square distribution with d degrees of freedom

- **Incidence proportion and the 95% confidence interval**[2,12,13]

$$\text{Incidence proportion [\%]} = 100 \times \frac{a}{N}$$

95% confidence interval for incidence proportion [%]

$$= \left[100 \times \left(1 + \frac{N - a + 1}{aF(0.025, 2a, 2(N - a + 1))}\right)^{-1}, 100 \times \left(1 + \frac{N - a}{(a+1)F(0.975, 2(a+1), 2(N-a))}\right)^{-1}\right]$$

N: Number of patients included in the analysis [patient]

$F(p, m, n)$: the lower p quantile for the F distribution with m and n degrees of freedom

8.1.6. Group Comparison of Incidence Rate and Incidence Proportion of Specified Events

Specified events including initial malignancy, initial severe infection, and death will be compared between groups in terms of the following quantities:

- **Incidence ratio between the treatment groups and the 95% confidence interval**[2]

$$\text{Incidence ratio} = \frac{a/PT_1}{b/PT_0}$$

95% confidence interval for incidence ratio

$$= \exp\left[\left\{\ln\left(\frac{a/PT_1}{b/PT_0}\right) \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{1}{a} + \frac{1}{b}}\right\}\right]$$

Xeljanz group a: Number of patients with the event [patient], PT_1: Duration of exposure [patient-year]

Control group b: Number of patients with the event [patient], PT_0: Duration of exposure [patient-year]

- **Difference in incidence rates between treatment groups and its 95% confidence interval**[2]

$$\text{Difference in incidence rates } [\text{patient}/100 \text{ patient} - \text{years}] = 100 \times \left(a/PT_1 - b/PT_0\right)$$

95% confidence interval for difference in incidence rates [patient/100 patient − years]

$$= 100 \times \left\{ \left(\frac{a}{PT_1} - \frac{b}{PT_0} \right) \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{a}{PT_1^2} + \frac{b}{PT_0^2}} \right\}$$

- **Ratio of incidence proportions between treatment groups and its 95% confidence interval**[2]

$$\text{Ratio of Incidence proportions} = \frac{a/N_1}{b/N_0}$$

95% confidence interval for ratio of incidence proportions

$$= \exp\left[\left\{\ln\left(\frac{a/N_1}{b/N_0}\right) \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{1}{a} - \frac{1}{N_1} + \frac{1}{b} - \frac{1}{N_0}}\right\}\right]$$

Xeljanz group

N_1: Number of patients included in the analysis [patient]

Control group

N_0: Number of patients included in the analysis [patient]

- **Difference in incidence proportion between the treatment groups and the 95% confidence interval**[2]

$$\text{Difference in incidence proportion [\%]} = 100 \times \left(\frac{a}{N_1} - \frac{b}{N_0}\right)$$

95% confidence interval [%] for the difference in incidence proportion

$$= 100 \times \left\{\left(\frac{a}{N_1} - \frac{b}{N_0}\right) \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{a(N_1 - a)}{{N_1}^3} + \frac{b(N_0 - b)}{{N_0}^3}}\right\}$$

- **Pooled incidence ratio between the treatment groups and the 95% confidence interval**[2]

$$\text{Pooled incidence ratio} = \frac{\sum\left(\frac{a_i PT_{0i}}{T_i}\right)}{\sum\left(\frac{b_i PT_{1i}}{T_i}\right)}$$

95% confidence interval for pooled incidence

$$= \exp\left\{\ln\left[\frac{\sum\left(\frac{a_i PT_{0i}}{T_i}\right)}{\sum\left(\frac{b_i PT_{1i}}{T_i}\right)}\right] \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{\sum\left(\frac{M_{1i} PT_{1i} PT_{0i}}{T_i^2}\right)}{\left(\sum\frac{a_i PT_{0i}}{T_i}\right)\left(\sum\frac{b_i PT_{1i}}{T_i}\right)}}\right\}$$

Xeljanz group

a_i: Number of patients with the event in Stratum i [patient]

PT_{1i}: Duration of exposure in Stratum i [patient-year]

Control group

b_i: Number of patients with the event in Stratum i [patient]

PT_{0i}: Duration of exposure in Stratum i [patient-year],

$M_{1i}=a_{i+}b_i$

$T_i=PT_{1i}+PT_{0i}$

- **Difference in pooled incidence rates between treatment groups and its 95% confidence interval**[2]

$$\text{Difference in pooled incidence rates } [\text{patient/100 patient} - \text{years}] = 100 \times \left\{\frac{\sum\left(\frac{a_i PT_{0i} - b_i PT_{1i}}{T_i}\right)}{\sum\left(\frac{PT_{1i} PT_{0i}}{T_i}\right)}\right\}$$

95% confidence interval for difference in pooled incidence rates [patient/100 patient − years]

$$= 100 \times \left\{ \frac{\sum\left(\frac{a_i PT_{0i} - b_i PT_{1i}}{T_i}\right)}{\sum\left(\frac{PT_{1i} PT_{0i}}{T_i}\right)} \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{\sum\left(\frac{PT_{1i} PT_{0i}}{T_i}\right)^2 \left(\frac{a_i}{PT_{1i}^2} + \frac{b_i}{PT_{0i}^2}\right)}{\left(\sum \frac{PT_{1i} PT_{0i}}{T_i}\right)^2}} \right\}$$

- **Ratio of pooled incidence proportions between treatment groups and its 95% confidence interval**[2]

$$\text{Ratio of pooled incidence proportions} = \frac{\sum\left(\frac{a_i N_{0i}}{S_i}\right)}{\sum\left(\frac{b_i N_{1i}}{S_i}\right)}$$

95% confidence interval for ratio of pooled incidence proportions

$$= \exp\left\{ \ln\left[\frac{\sum\left(\frac{a_i N_{0i}}{S_i}\right)}{\sum\left(\frac{b_i N_{1i}}{S_i}\right)}\right] \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{\sum\left(\frac{M_{1i} N_{1i} N_{0i}}{S_i^2} - \frac{a_i b_i}{S_i}\right)}{\left(\sum \frac{a_i N_{0i}}{S_i}\right)\left(\sum \frac{b_i N_{1i}}{S_i}\right)}} \right\}$$

Xeljanz group

a_i: Number of patients with the event in Stratum i [patient]

N_{1i}: Number of patients in Stratum i [patient]

Control group

b_i: Number of patients with the event in Stratum i [patient]

N_{0i}: Number of patients in Stratum i [patient],

$M_{1i}=a_i+b_i$

$S_i=N_{1i}+N_i$

- **Difference in pooled incidence proportion between the treatment groups and the 95% confidence interval**[2]

$$\text{Difference in pooled incidence proportion [\%]} = 100 \times \frac{\sum\left(\frac{a_i N_{0i} - b_i N_{1i}}{S_i}\right)}{\sum\left(\frac{N_{1i} N_{0i}}{S_i}\right)}$$

95% confidence interval for the difference in pooled incidence proportion [%]

$$= 100 \times \left[\frac{\sum\left(\frac{a_i N_{0i} - b_i N_{1i}}{S_i}\right)}{\sum\left(\frac{N_{1i} N_{0i}}{S_i}\right)} \pm 97.5 \text{ percentile for standard normal distribution} \times \sqrt{\frac{\sum\left(\frac{a_i N_{0i} - b_i N_{1i}}{S_i}\right)}{\sum\left(\frac{N_{1i} N_{0i}}{S_i}\right)} \sum U_i + \sum V_i} \Big/ \left(\sum \frac{N_{1i} N_{0i}}{S_i}\right)^2 \right]$$

$$U_i = \frac{N_{1i}^2 b_i - N_{0i}^2 a_i + N_{1i} N_{0i} (N_{0i} - N_{1i})/2}{S_i^2}$$

$$V_i = \frac{a_i (N_{0i} - b_i) + b_i (N_{1i} - a_i)}{2 S_i}$$

- **Adjusted hazard ratio and the 95% confidence interval**

The hazard ratio adjusted for covariates and the 95% confidence interval will be estimated using a Cox proportional hazard model.

In addition, the proportional hazard assumption will be confirmed using the log-log plots of Kaplan-Meier estimates.

- **Propensity scores**[4,5]

Propensity scores will be calculated by a logistic regression analysis and random forests[15] using treatment groups as an objective variable and covariates described in "6.3 Covariates" as an explanatory variable. If candidate covariates (6.3) are missing (including unknown), they will be complemented by multiple imputation. The number of the datasets will be determined depending on a situation of the missing.[16] This analysis is conducted by each dataset and the estimate is obtained by the integrated results

- **Analysis by multiple imputation method**

Missing data (including unknown) of covariates are complemented from variables with a small number of missing data by random forests using a fully conditional specification (FCS) algorithm as a multiple imputation method. The number of data sets to be complemented and created by the multiple imputation method is determined according to the rate of missing data. After complementation, analysis is performed for each created data set. The average value of the analysis results obtained for each data set is used as the point estimation value by the multiple imputation method. The point estimate and variance are calculated as follows.

Point estimate $\bar{\theta}_M = \frac{1}{M}\sum_{m=1}^{M}\tilde{\theta}_m$

Variance $T_M = \bar{W}_M + \left(1+\frac{1}{M}\right)\bar{B}_M$

$$\bar{W}_M = \frac{1}{M}\sum_{m=1}^{M}\mathrm{var}(\tilde{\theta}_m),\ \bar{B}_M = \frac{1}{M-1}\sum_{m=1}^{M}(\tilde{\theta}_m - \bar{\theta}_M)^2$$

- **Standardized incidence ratio (SIR) and the 95% confidence interval**

$$\mathrm{SIR}\ [\%] = \frac{\sum_{ij} d_{ij}}{\sum_{ij} py_{ij}\lambda_{ij}} = \frac{D}{E}$$

Sex and age class	Reference population			Control population	
	Population	Number of patients	Incidence Rate	Duration of exposure	Number of patients
ij	N_{ij}	n_{ij}	λ_{ij} $(=n_{ij}/N_{ij})$	py_{ij}	d_{ij}

$$SIR(SMR) = \frac{\sum_{ijk} d_{ijk}}{\sum_{ijk} py_{ijk}\lambda_{ijk}} = \frac{D}{E}$$

Sex, age class and calendar year	Reference population			Control population	
	Population	Number of patients	Incidence Rate	Duration of exposure	Number of patients (deaths)
ijk	N_{ijk}	n_{ijk}	λ_{ijk} (=n_{ijk}/N_{ijk})	py_{ijk}	d_{ijk}

$$\text{Lower limit of 95\% confidence interval of standardized incidence ratio} = \frac{\chi^2_{2D,0.025}}{2E}$$

$$\text{Upper limit of 95\% confidence interval of standardized incidence ratio} = \frac{\chi^2_{2(D+1),0.975}}{2E}$$

$\chi^2_{v,\alpha}$: Alpha percent point in chi-square distribution with *v* degrees of freedom

8.2. Statistical Analysis

8.2.1. Summary of Patients

- **Composition of patients**

In registered patients, the number of registered patients, patients for whom the CRF is collected, patients included in the safety analysis, and patients included in the efficacy analysis will be calculated. In addition, the number of patients for whom the CRF is not collected, patients excluded from the safety analysis, and patients excluded from the efficacy analysis, and the number of patients by reason for exclusion will be calculated.

In patients included in the safety analysis in the Xeljanz group, the number of patients who meet the MTX criteria will be calculated. In addition, the number of patients who do not meet the MTX criteria and the number of patients by reason for exclusion will be calculated.

- **Status of discontinuation and dropout**

In the safety and efficacy analysis sets, the number and proportion of patients who discontinued administration of Xeljanz and follow-up in the Xeljanz group and the number of patients by reason for discontinuation will be calculated for each of the number of days to discontinuation shown in Table 2.

The number and proportion of patients who discontinued the survey and follow-up in the control group and the number of patients by reason for discontinuation will be calculated.

Time to discontinuation of administration of Xeljanz in the Xeljanz group and time to discontinuation of the survey in the control group will be summarized in accordance with Section 8.1.4. The censoring period in patients without discontinuation will be the newest date of completion of administration.

Table 2. Categories of Tabulation Items for Discontinuation and Dropout

Item	Category
Reason for discontinuation	Remission (Xeljanz group only), inadequate clinical effect (Xeljanz group only), adverse events (Xeljanz group only), death of patient, no revisits, transfer to other hospitals and departments, administration of Xeljanz Tablets (surveythe control group only), others
Number of days to discontinuation	Start of treatment - 1 month (Day 1 to Day 31), 1 month< - 3 months (Day 32 to Day 92), 3 months< - 6 months (Day 93 to Day 184), 6 months< - 9 months (Day 185 to Day 275), 9 months< - 12 months (Day 276 to Day 366), 12 months< - 18 months (Day 367 to Day 549), 18 months< - 24 months (Day 550 to Day 731), 24 months< -30 months (Day 732 to Day 914), 30 months< -36 months (Day 914 to Day 1096), >36 months (Day 1097-)

- **Lists of excluded patients**

Patients excluded from the safety analysis set, patients excluded from the subpopulation that meets the MTX criteria, patients excluded from the efficacy analysis set, and reasons for exclusion will be listed.

8.2.2. Analysis of Patient Background and Treatment History

- **Distribution and summary statistics of patient background**

In the safety and efficacy analysis sets, the frequency of patient background will be calculated. Summary statistics will be calculated for continuous data.

In each of the safety and efficacy analysis sets, the calculation will also be made for new patients whose treatment started from this survey, patients who participated in clinical trials, and patients transferring from other hospital. Furthermore, in new patients, the calculation will also be made for the subpopulations that do and do not meet the MTX criteria in the Xeljanz group.

Items for which the calculation will be made are shown in “Appendix 11.1.2 Patient Background.”

- **Status of the implementation of tests**

In the safety analysis set in the Xeljanz group, the number and proportion of patients with tests before the initiation of administration of Xeljanz shown in Table 3 will be calculated for each test timing.

The number and proportion of patients with no test prior to the start of study treatment, and with a test performed after the start of study treatment (Day 2 onward) will be calculated.

Table 3. Categories of Tabulation Items for the Status of the Implementation of Tests

Item	Category
Test	Test (implemented if at least one is met), chest X-ray or chest CT (chest X-ray, chest CT), interferon γ or tuberculin reaction (interferon γ, tuberculin reaction), hepatitis B and C virus test (HBs antigen, HBs antibody, HBc antibody, HBV-DNA test, HCV antibody)
Test timing	after the initiation of administration of Xeljanz (Day 2-), before the initiation of administration of Xeljanz ≤3 months (Day -30 to Day 0), before the initiation of administration of Xeljanz >3 months (-Day 31), before the initiation of administration of Xeljanz >3 months to ≤6 months (Day -183 to Day -31), before the initiation of administration of Xeljanz >6 months to ≤12 months (Day -364 to Day -182), before the initiation of administration of Xeljanz >12 months to ≤24 months (Day -729 to Day -365), before the initiation of administration of Xeljanz >24 months (-Day -730)

- **Past medical histories**

In the safety analysis set, the number and proportion of patients with past medical histories will be calculated for each system organ class (SOC) and preferred term (PT).

- **Complications**

In the safety analysis set, the number and proportion of patients with complications (current medical history) will be calculated for each SOC and PT.

- **Concomitant drugs**

In the safety and efficacy analysis sets in the Xeljanz group, the number and proportion of patients who used concomitant drugs will be calculated. A biological therapeutic or immunosuppressant terminated on the same day as the first dose of Xeljanz or started on the same day as the last dose of Xeljanz will not be considered as a concomitant drug.

Similarly, the number and the proportion of patients will be calculated by methotrexate (MTX), biological agents, DMARDs and immunosuppressive agents other than MTX, oral steroids and other drugs.

- **Non-drug therapies**

In the safety and efficacy analysis sets in the Xeljanz group, the number and proportion of patients who underwent surgical therapies for rheumatoid arthritis (surgery scheduled before the initiation of this survey) will be calculated.

- **Prior medications**

In the safety and efficacy analysis sets, the number and proportion of patients who used each prior medication will be calculated. A biological therapeutic or immunosuppressant terminated on the same day as the first dose of Xeljanz will be considered as a prior medication.

Similarly, the number and the proportion of patients will be calculated by methotrexate (MTX), biological agents, DMARDs and immunosuppressive agents other than MTX, oral steroids and other drugs.

- **Status of administration**

The following variables will be calculated for the safety analysis set of Xeljanz group: Daily number of administrations at the first time, initial daily dose, duration of administration, overall administration period, duration of each administration, duration of actual administration, total number of administrations, total dose, average daily number of administrations, average daily dose, average daily number of actual administrations, and average actual daily dose.

Daily number of administrations at the first time [time] = daily number of administrations recorded in the administration status for the oldest initiation date

Initial daily dose［mg］ = 5*Daily number of administrations at the first timeDuration of administration [day] = newest completion date - oldest initiation date + 1

Overall administration period [patient-year] = Administration period including drug cessation periods / 365.25

Duration of each administration [day] = completion date - initiation date + 1

Duration of actual administration [day] = sum of the duration of each administration (not including drug cessation periods)

Total number of administrations [time] = product of each daily number of administrations and the duration of each administration

Total dose［mg］ = 5*Total number of administrations

Average daily number of administrations [time/day] = total number of administrations/duration of administration

Average daily dose［mg］ = 5*Average daily number of administrations

Average daily number of actual administrations [time/day] = total number of administrations/duration of actual administration

Average actual daily dose［mg］ = 5*Average daily number of actual administrations

Continuous data will be summarized in accordance with Section 8.1.1. Categorical data shown in Table 4 will be summarized in accordance with Section 8.1.2.

In addition, as a method to allow more detailed understanding of the daily number of administrations, the distribution ratio of the daily number of administrations (once, twice, ≥3 times, unknown) during the duration of actual administration in each patient will be calculated in percentage (%) (eg; once, 10%; twice, 85%; and ≥3 times, 5%). For the distribution ratio of each daily number of administrations, frequency and the proportion will be calculated by category (≤20%, >20% to ≤40%, >40% to ≤60%, >60% to ≤80%, and >80% to ≤100%).

The initial drug used for treatment will be tabulated for the safety analysis set of the control group. Also, the number and proportion of patients in each assessment period who are receiving the same drug as the initial drug will be calculated.

For each assessment timepoint, comply with the target dates specified in "Appendix 11.1.1 Definition of Visit Timing".

Table 4. Categories of Tabulation Items for Administration Status

Item	Category	Note
Daily number of administrations at the first time [time]	Once, twice, ≥3 times	Xeljanz group only
Initial daily dose［mg］	5 mg, 10 mg, >10 mg, other	Xeljanz group only
Duration of administration [day]	Start of treatment - 1 month (Day 1 to Day 31), 1 month< - 3 months (Day 32 to Day 92), 3 months< - 6 months (Day 93 to Day 184), 6 months< - 9 months (Day 185 to Day 275), 9 months< - 12 months (Day 276 to Day 366), 12 months< - 18 months (Day 367 to Day 549), 18 months< - 24 months (Day 550 to Day 731), 24 months< -30 months (Day 732 to Day 914), 30 months< -36 months (Day 914 to Day 1096), >36 months (Day 1097-)	Continuous data
Overall administration period [patient-year]	Start of treatment - 1 month (Day 1 to Day 31), 1 month< - 3 months (Day 32 to Day 92), 3 months< - 6 months (Day 93 to Day 184), 6 months< - 9 months (Day 185 to Day 275), 9 months< - 12 months (Day 276 to Day 366), 12 months< - 18 months (Day 367 to Day 549), 18 months< - 24 months (Day 550 to Day 731), 24 months< -30 months (Day 732 to Day 914), 30 months< -36 months (Day 914 to Day 1096), >36 months (Day 1097-)	A cumulative value is calculated for each category.
Duration of actual administration [day]	No category	Continuous data Xeljanz group only
Total number of administrations [time]	No category	Continuous data Xeljanz group only

Table 4. Categories of Tabulation Items for Administration Status

Item	Category	Note
Total dose［mg］	No category	Continuous data Xeljanz group only
Average daily number of administrations [time/day]	≤once, >once to ≤twice, >twice to ≤3 times, >3 times	Xeljanz group only
Average daily dose［mg］	≤5mg, >5 mg to ≤10 mg, >10 mg	Xeljanz group only
	<7.5mg, ≧7.5mg	
Average daily number of actual administrations [time/day]	≤once, >once to ≤twice, >twice to ≤3 times, >3 times	Xeljanz group only
Average actual daily dose［mg］	≤5mg, >5 mg to ≤10 mg, >10 mg	Xeljanz group only
	<7.5mg, ≧7.5mg	
Drugs initially administered	MTX, biological products, DMARDs or immunosuppressants, MTX + biological products, MTX + DMARDs or immunosuppressants, biological products + DMARDs or immunosuppressants, MTX + biological products + DMARDs or immunosuppressants	Control group only Drugs which are written in "Status of drug administration" within 7 days from the oldest date of commencement

- Tabulation and analysis of each subset

Patient characteristics will be tabulated for each subgroup sorted by the initial daily dose in Xeljanz group (5 or 10 mg). Also, for each subgroup sorted by the initial daily dose, patient characteristics will be further tabulated for new patients started in this surveillance, patients who took part in clinical study, patients transferring from other hospital, subpopulation that meets the MTX criteria, and subpopulation that does not meet the MTX criteria.

Items for which the calculation will be made are shown in "Appendix 11.1.2 Patient Background".

8.2.3. Safety Analysis

8.2.3.1. Comparison of Xeljanz group and control group

A comparison of the Xeljanz group and the control group is performed for each of the MTX adherent comparative analysis set and the comparative analysis set. The main analysis set is the MTX adherent comparative analysis set.

The adverse events including corporate evaluation is used for the main analysis, and as a secondary analysis, the analysis of adverse events based only on the doctor's evaluation is also used.

8.2.3.1.1. Analysis of malignant tumors

There are the following 3 definitions for patients with malignant tumors, and the analysis will be performed for each of them. As the primary evaluation, patients with malignant tumors during overall observation period will be used. For other definitions, the incidence of malignant tumor will be calculated, and other relevant analyses will be performed if such result is remarkably different from the data on overall observation period.

- Patients with malignant tumors during overall observation period: Patients with malignant tumors during overall observation period are patients in whom malignant tumors developed from the date of the initiation of treatment to the date of the completion or discontinuation of follow-up.

- Patients with malignant tumors during treatment period: Patients with malignant tumors during treatment period are patients in whom malignant tumors developed from the date of the initiation of treatment to the date of the completion of treatment.

- Patients with malignant tumors during treatment period+28 days: Treatment period will cover 28 days following the completion of treatment; that is, patients to be included in the analysis will be those with malignant tumors developed from the date of the initiation of treatment + 28 days (or not longer than 3 years if the treatment period + 28 days exceeds 3 years).

Other definitions used in the comparison of malignant tumors are shown in Table 5.

Table 5. Definitions in the Comparison of Malignant Tumors

Term	Definition
Patients without malignant tumors	Patients who do not correspond to the each definition of patients with malignant tumors
Time to malignant tumor during overall observation period	Date of the development of malignant tumor - date of the initiation of treatment + 1
Censoring period for patients without malignant tumors during overall observation period	Date of completion or discontinuation of follow-up - date of the initiation of treatment + 1
Time to malignant tumor during treatment period	Date of the development of malignant tumor - date of the initiation of treatment + 1
Censoring period for patients without malignant tumors (treatment period)	Date of the completion of treatment - date of the initiation of treatment+ 1
Time to malignant tumor during the treatment period (+28 days)	Date of the development of malignant tumor - date of the initiation of treatment + 1
Censoring period for patients without malignant tumors during the treatment period (+28 days)	Date of the completion of treatment + 28- date of the initiation of treatment + 1

- **Development of malignant tumors**

The number of malignant tumors in each group and the proportion of occurrence are calculated for each SOC and PT. Furthermore, it is calculated for each cancer type (stomach, lung, breast, cervix, uterine body, ovary, malignant lymphoma, large intestine, pancreas, bladder, kidney / urinary tract (excluding bladder), other). Females are targeted for malignant tumors of the breast, cervix, uterine body and ovaries.

- **Incidence rate of malignant tumors**

The number of patients with malignant tumors in each group, incidence rate, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the incidence ratio between treatment groups and the 95% confidence interval and the difference in incidence rate between treatment groups and the 95% confidence interval will be calculated.

For covariates concerning malignant tumors (Section 6.3), incidence by single factor will be calculated, and the pooled incidence ratio and the 95% confidence interval and the pooled difference in incidence rate and the 95% confidence interval will be calculated.

- **Incidence proportion of malignant tumors**

The number of patients with malignant tumors in each group, the incidence proportion, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the ratio of incidence proportion and the 95% confidence interval and the difference in incidence proportion and the 95% confidence interval will be calculated.

For covariates concerning malignant tumors (Section 6.3), the incidence proportion by single factor will be calculated, and the ratio of the pooled incidence proportion and the 95% confidence interval and the difference in the pooled incidence proportion and the 95% confidence interval will be calculated. Age will be handled as categorical data.

- **Analysis of time to malignant tumor**

Time to malignant tumor in each group will be summarized in accordance with Section 8.1.4. As for the censoring period in patients without malignant tumors, Table 5 will be followed. In addition, a graph showing the transition of the incidence rate estimated using the calculated parameters by applying the Weibull distribution together with the Kaplan-Meier plot, and a graph of the transition of the hazard function are created.

- **Adjusted hazard ratio for the development of malignant tumors**

As for time to malignant tumor, the adjusted hazard ratio of the Xeljanz group to the control group for the development of malignant tumors and the 95% confidence interval will be calculated in accordance with Section 8.1.5. Covariates used for adjustment are shown in Section 6.3.

As for the development of malignant tumors in the Xeljanz group compared to the control group, the propensity score-weighted (inverse probability of treatment weighting, IPTW) hazard ratio and the 95% confidence interval will be calculated. The weight is obtained from $Z_i + \frac{\hat{e}_i(1-Z_i)}{1-\hat{e}_i}$ ($\hat{e}_i$: the estimated propensity score, Z_i: 1 (if xeljanz group) or 0 (if control group)).[17] The other propensity score-weighted hazard ratio and the 95% confidence interval also will be calculated from setting an upper limit on the weight, because it is possible that some weights are too high if $\hat{e}_i$ is nearly equarl 1. The upper limit is determined depending on a situation of the estimation accuracy.[18]

In addition to the propensity score-weighted, further adjustment using a model with covariates of large effect will be conducted. The covariates which show large change in adjusted hazard ratio from the non-adjusted hazard ratio in the univariate model, will be included in this model in order to control the number of cobvariates in the model.

- **Distribution of propensity score and covariates before and after adjustment for hazard ratio of malignant tumor**

The distribution of propensity scores before and after adjustment by weighting of propensity scores is estimated using kernel density estimation and shown by violin plot. In the control group, a boxplot of weights is created.

In addition, the proportion of each category of patient background used for the covariate and the difference between the standardized groups are calculated before and after adjustment. The standardized difference is treated as a continuous amount in the patient background of 3 or more categories, and calculated by the difference / standard deviation of the average value of each group. In the patient background of the binary data, it is calculated by the difference / standard deviation of the ratio of each group. In addition, parameters are calculated in logistic regression model.

- **Standardized incidence rate (SIR) for the development of malignant tumors**

Using the number of malignant tumors in each group, the SIR and its 95% confidence interval with the Japanese as the reference population are calculated according to Section 8.1.6. The expected number of patients is calculated using the population and morbidity by gender and age in 2013.

In addition, the SIR and its 95% confidence interval calculated by using the population and the number of morbidity by gender, age, and calendar year as the expected number of patients are calculated according to Section 8.1.6. If there is no reference population and prevalence in the applicable calendar year, use the reference population and prevalence by gender and age in the latest year.

In addition, SIR is calculated for each cancer type (stomach, lung, breast, cervix, uterine body, ovary, malignant lymphoma, large intestine, pancreas, bladder, kidney / urinary tract (excluding bladder)). Females are targeted for malignant tumors of the breast, cervix, uterine body and ovaries.

Similarly, it is calculated for non MTX adherent safety analysis set.

The Cancer Information of the National Cancer Center Service is used as Japanese popuration data, and the expected number of patients is calculated using the population and the number of morbidity in the statistical data on cancer.

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8.2.3.1.2. Analysis of serious infections

There are the following 3 definitions for patients with serious infections, and the analysis will be performed for each of them. As the primary evaluation, patients with serious infections during treatment period + 28 days will be used. For other definitions, the incidence of serious infections will be calculated, and other relevant analyses will be performed if such result is remarkably different from the data on treatment period + 28 days.

- Patients with serious infections during treatment period+28 days: Patients with onset of serious infections during the treatment period (+28 days): Treatment period will cover 28 days following the completion of treatment; that is, patients to be included in the analysis will be those with onset of serious infections developed from the date of the initiation of during the period of treatment + 28 days.

- Patients with serious infections druing treatment period: patients with serious infections during treatment period are patients in whom serious infections developed from the date of the initiation of treatment to 1-year later (Day 366) or the date of the completion of treatment, whichever comes first.

- Patients with serious infections during overall observation period (up to 1 year): patients with serious infections during overall observation period (up to 1 year) are patients in whom serious infections developed from the date of the initiation of treatment to the date of the completion or discontinuation of follow-up.

Other definitions used in the comparison of serious infections are shown in Table 6.

Table 6. Definitions in the Comparison of Serious Infections

Term	Definition
Patients without serious infections	Patients who do not correspond to the each definition of patients with serious infections
Time to serious infections during the treatment period (+28 days)	Date of the development of serious infections- date of the initiation of treatment + 1 Both treatment groups will be analyzed for the duration of treatment + 28 days (up to not longer than 1 years).
Censoring period for patients without serious infections during the treatment period (+28 days) 投	Date of the completion of treatment + 28- date of the initiation of treatment + 1 Both treatment groups will be analyzed for the duration of treatment + 28 days (up to not longer than 1 years).
Time to serious infection dring treatment period	Date of the development of serious infection - date of the initiation of treatment + 1 The upper limit is 1 year (366)
Censoring period for patients without serious infections during treatment period	Date of the completion of treatment - date of the initiation of treatment + 1 The upper limit is 1 year (366)
Time to serious infection during overall observation period	Date of the development of serious infection - date of the initiation of treatment + 1 The upper limit is 1 year (366)
Censoring period for patients without serious infection s during overall observation period	Date of completion or discontinuation of follow-up - date of the initiation of treatment + 1 The upper limit is 1 year (366)

- **Development of serious infections**

The number of m serious infections in each group and the proportion of occurrence are calculated for each SOC and PT. Furthermore, it is calculated for each infection type.

- **Incidence rate of serious infections**

The number of patients with serious infections in each group, incidence rate, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the incidence ratio between treatment groups and the 95% confidence interval and the difference in incidence rate between treatment groups and the 95% confidence interval will be calculated.

The above analyses will be also conducted for serious infections excluding serious herpes zoster and for serious herpes zoster, respectively.

For covariates concerning serious infections (Section 6.3), incidence by single factor will be calculated, and the pooled incidence ratio and the 95% confidence interval and the pooled difference in incidence rate and the 95% confidence interval will be calculated.

Incidence ratio with its 95% CI will be calculated for events of herpes zoster, opportunistic infection, and tuberculosis as well as “serious infections” .

- **Incidence proportion of serious infections**

The number of patients with serious infections in each group, the incidence proportion, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the ratio of incidence proportion and the 95% confidence interval and the difference in incidence proportion and the 95% confidence interval will be calculated.

The above analyses will be also conducted for serious infections excluding serious herpes zoster and for serious herpes zoster, respectively.

For covariates concerning serious infections (Section 6.3), the incidence proportion by single factor will be calculated, and the ratio of the pooled incidence proportion and the 95% confidence interval and the difference in the pooled incidence proportion and the 95% confidence interval will be calculated. Age will be handled as categorical data.

Incidence proportion with its 95% CI will be calculated for events of herpes zoster, opportunistic infection, and tuberculosis as well as “serious infections” .

- **Analysis of time to serious infection**

- Time to serious infection in each group will be summarized in accordance with Section 8.1.4. As for the censoring period in patients without serious infection, Table 5 will be followed. In addition, a graph showing the transition of the incidence rate estimated using the calculated parameters by applying the Weibull distribution together with the Kaplan-Meier plot, and a graph of the transition of the hazard function are created.**Adjusted hazard ratio for the development of serious infections**

As for time to serious infection, the adjusted hazard ratio of the Xeljanz group to the control group for the development of serious infections and the 95% confidence interval will be calculated in accordance with Section 8.1.5 Covariates used for adjustment are shown in Section 6.3.

As for the development of serious infections in the Xeljanz group compared to the control group, the propensity score- weighted (inverse probability of treatment weighting, IPTW) hazard ratio and the 95% confidence interval will be calculated. The weight will be similarly obtained in Section 8.2.3.1.

In addition to the propensity score-weighted, further adjustment using a model with covariates of large effect will be conducted. The covariate which show large change in adjusted hazard ratio from the non-adjusted hazard ratio in the univariate model, will be included in this model in order to control the number of covariates in the model.

- **Distribution of propensity score and covariates before and after adjustment for hazard ratio of serious infections**

The distribution of propensity scores before and after adjustment by weighting of propensity scores is estimated using kernel density estimation and shown by violin plot. In the control group, a boxplot of weights is created.

In addition, the proportion of each category of patient background used for the covariate and the difference between the standardized groups are calculated before and after adjustment. The standardized difference is treated as a continuous amount in the patient background of 3 or more categories, and calculated by the difference / standard deviation of the average value of each group. In the patient background of the binary data, it is calculated by the difference / standard deviation of the ratio of each group. In addition, parameters are calculated in logistic regression model.

8.2.3.1.3. Analsis of deaths

There are the following 2 definitions for deaths, and the analysis will be performed for each of them. As the primary evaluation, deaths (overall observation period) will be used.

- Deaths (overall observation period): Deaths (overall observation period) are patients who die from the date of the initiation of treatment to the date of the completion or discontinuation of follow-up.

- Deaths (treatment period): Deaths (treatment period) are patients in whom deaths developed from the date of the initiation of treatment to the date of the completion of treatment.

Other definitions used in the comparison of deaths are shown in Table 7.

Table 7. Definitions in the Comparison of Deaths

Term	Definition
Survivors	Patients who do not correspond to the each definition of deaths
Time to death (overall observation period)	Date of the death - date of the initiation of treatment + 1
Censoring period for survivors (overall observation period)	Xeljanz group: Date of completion or discontinuation of follow-up - date of the initiation of treatment + 1
Time to death (treatment period)	Xeljanz group: Date of the death - date of the initiation of treatment + 1
Censoring period for survivors (treatment period)	Date of the completion of treatment - date of the initiation of treatment + 1

- **Mortarity rate**

The number of patients with deaths in each group, incidence, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the incidence ratio and the 95% confidence interval and the difference in incidence rate and the 95% confidence interval will be calculated.

- **Incidence proportion of deaths**

The number of patients with deaths in each group, the incidence proportion, and the 95% confidence interval will be calculated in accordance with Section 8.1.5.

In addition, the ratio of incidence proportion and the 95% confidence interval and the difference in incidence proportion and the 95% confidence interval will be calculated.

- **Analysis of time to death**

Time to death in each group will be summarized in accordance with Section 8.1.4. As for the censoring period insurvivors, Table 7 will be followed.

- **SMR**

Using the number of deaths in each group, the SMR and its 95% confidence interval with the Japanese as the reference population are calculated according to Section 8.1.6. The expected number of deaths is calculated using the population and deaths by gender, age and calendar year. If there is no reference population and death in the applicable calendar year, use the reference population and death by gender and age in the latest year.

Similarly, it is calculated for non MTX adherent safety analysis set.

For Japanese data, refer to the general counter of e-Stat official statistics, and calculate the expected number of deaths using the population and the number of deaths in the Vital Statistics Survey.

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8.2.3.2. Safety analysis in the Xeljanz group

Statistical analyses in this section will be performed in the safety analysis set in the Xeljanz group. Adverse drug reactions and adverse events will be analyzed for all those reactions or events that developed during the survey period, and those that developed by 6 months after the start of Xeljanz.

- **Development of adverse drug reactions**

The number of patients with adverse drug reactions and the incidence proportion will be calculated for each SOC and PT.

The number of patients with adverse drug reactions and the incidence proportion will also be calculated for each SOC and PT for new patients in whom treatment started from this survey, patients who participated in clinical trials, and patients administered Xeljanz at other institutions. Furthermore, the calculation will also be performed for the subpopulations that do and do not meet the MTX criteria in the Xeljanz group.

- **Development of serious adverse drug reactions**

The number of patients with serious adverse drug reactions and the incidence proportion will be calculated for each SOC and PT.

The number of patients with serious adverse drug reactions and the incidence proportion will also be calculated for each SOC and PT for new patients in whom treatment started from this survey, patients who participated in clinical trials, and patients administered Xeljanz at other institutions. Furthermore, the calculation will also be performed for the subpopulations that do and do not meet the MTX criteria in the Xeljanz group.

- **Development of serious adverse events**

The number of patients with serious adverse events and the incidence proportion will be calculated for each SOC and PT.

- **Development of adverse events**

The number of patients with adverse events and the incidence proportion will be calculated for each SOC and PT.

- **Development of adverse drug reactions in patients included in and excluded from the safety analysis set**

The number of patients with adverse drug reactions among patients for whom the CRF is collected and who are included in and excluded from the safety analysis set and the incidence proportion will be calculated for each SOC and PT.

- **Details of adverse drug reactions by event**

The number of patients with adverse drug reactions and the incidence proportion will be calculated for each SOC and PT for each category in Table 8.

If an adverse drug reaction with the same PT occurs multiple times in the same patient, the order of precedence in Table 8 will be applied.

Table 8. Tabulation Items Concerning the Details of Adverse Drug Reactions by Event

Item	Category	Order of precedence
Seriousness	Serious, non-serious	Serious → non-serious
Known/unknown	Known, unknown	Unknown → known
Outcome	Resolved/recovered, recovering, recovered with sequel, not recovered, unknown	An event that last developed
Number of days to onset	Start of treatment - 1 month (Day 1 to Day 31), 1 month< - 3 months (Day 32 to Day 92), 3 months< - 6 months (Day 93 to Day 184), 6 months< - 9 months (Day 185 to Day 275), 9 months< - 12 months (Day 276 to Day 366), 12 months< - 18 months (Day 367 to Day 549), 18 months< - 24 months (Day 550 to Day 731), 24 months< -30 months (Day 732 to Day 914), 30 months< -36 months (Day 914 to Day 1096), >36 months (Day 1097-)	An event that first developed
Change in administration of Xeljanz	No change, dose reduction, temporary suspension, discontinuation	Discontinuation → temporary suspension → dose reduction → no change

- **Subgroup analysis**

The number and proportion of patients with at least 1 following each adverse drug reaction will be tabulated for each factor specified in Section 5.4 in accordance with Section 8.1.3. Tests will be performed between the levels of each background factor.

- Serious infections;
- Neutrophil count decreased and neutropenia;
- Lymphocyte count decreased and lymphopenia;
- Hemoglobin decreased and anemia;
- Lipid increased and hyperlipidemia;
- Malignant tumors (including lymphoma);
- Gastrointestinal perforation;
- Cardiovascular adverse events;
- Hepatic dysfunction;
- Interstitial pneumonia;
- Helpes Zoster.

The following tabulation and analysis will be performed for sex, age class and each subgroup in patients with and without hepatic dysfunction and patients with and without renal dysfunction:

- Development of adverse drug reactions;
- Development of serious adverse drug reactions;
- Development of serious adverse events.

A list of adverse reactions for contraindicated patients are created. Furthermore, if necessary, the number of patient with adverse reactions and their proportions are calculated for each SOC and PT.

- **Key survey items**

Number, incidence proportion, and its 95% confidence interval (CI), and its 95% CI will be calculated according to the formulae presented in Section 8.1.5 for patients who developed an adverse drug reaction or event corresponding to each of the key survey items listed in Section 6.1. The following events will be also evaluated.of herpes zoster, opportunistic infection, and tuberculosis will be evaluated as a single category “serious infections” and also individually as herpes zoster, opportunistic infection, or tuberculosis.

However, in the case of events with 10 or less patients of expression, it is considered that the number of patients is not sufficient for evaluation of the incidence proportion and the incidence rate, so the calculation is not performed.

- Opportunistic infection;
- Herpes zoster;
- Tuberculosis;
- Pneumocystis pneumonia;
- Venous thromboembolism;
- Renal dysfunction.

In addition, incidence rate with the 95% CI will be calculated by time period of onset (Table 9) and overall period for adverse drug reactions and adverse envents of followitngs. However, the statistics by the time period will not be calculated if the number of patients with the events are less than 10 due to the insufficient number for evaluation by time period.

- Malignant tumor;
- Opportunistic infection;
- Herpes zoster;
- Tuberculosis;
- Pneumocystis pneumonia;
- Interstitial pneumonia;
- Lymphocyte count decreased and lymphopenia;
- Cardiovascular adverse events;
- Hepatic dysfunction;
- Interstitial pneumonia;
- Helpes Zoster.

Events during treatment period +28 days (from the date of the initiation of administration of Xeljanz to 28days after the date of the completion of administration of Xeljanz) will be counted for calculating the incidence rate. The dehinitions of exposure period and consoring are following Section 8.2.3.1.1_Ref461114447 “Patients with malignant tumors during treatment period+28 days” replacing malignant tumor with the interested event.

For malignancy tumor, incidence rate by the time period will be calculated for events based on Section 8.2.3.1.1 “Patients with malignant tumors during overall observation period”.

Table 9. Catedories of time period for analysis by time period in key survey intems

Item	Category	Order of precedence
Number of days to onset	Start of treatment - 1 month (Day 1 to Day 31), 1 month< - 3 months (Day 32 to Day 92), 3 months< - 6 months (Day 93 to Day 184), 6 months< - 9 months (Day 185 to Day 275), 9 months< - 12 months (Day 276 to Day 366), 12 months< - 18 months (Day 367 to Day 549), 18 months< - 24 months (Day 550 to Day 731), 24 months< -30 months (Day 732 to Day 914), 30 months< -36 months (Day 914 to Day 1096), >36 months (Day 1097-)	An event that first developed
Number of days to onset (cumulative)	Start of treatment - 1 month (Day 1 to Day 31), Start of treatment - 3 months (Day 1 to Day 92), Start of treatment - 6 months (Day 1 to Day 184), Start of treatment - 9 months (Day 1 to Day 275), Start of treatment - 12 months (Day 1 to Day 366), Start of treatment - 18 months (Day 1 to Day 549), Start of treatment - 24 months (Day 1 to Day 731), Start of treatment -30 months (Day 1 to Day 914), Start of treatment -36 months (Day 1 to Day 1096), Overall period	An event that first developed

- **Key survey items for MTX adherent safety analysis set and non MTX adherent safety analysis set.**

For MTX adherent safety analysis set and non MTX adherent safety analysis set , adverse drug reactions and adverse events applicable to key survey item (Section 6.1) will be tabulated, in accordance with Section 8.1.5, for the number of patients, the frequency and its 95% confidence interval, duration of exposure, and the incidence and its 95% confidence interval. Also, herpes zoster, opportunistic infection, and tuberculosis will be calculated as an individual event.

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8.2.4. Efficacy Analysis

Analysis is performed for each of the MTX adherent efficacy analysis set and the efficacy analysis set. The main analysis target set is the MTX adherent efficacy analysis set.

8.2.4.1. SDAI and CDAI

- **Changes in SDAI and CDAI**

Summary statistics for the measurement of SDAI at each time point and the change from the initiation of administration of Xeljanz will be calculated. For the change, 95% confidence intervals will be calculated.

As for each time point, "Appendix 11.1.1 Definition of Visit Timing" will be followed.

The calculation will be performed for CDAI in the same manner.

Furthermore, summary statistics of measurements, the change will be calculated at each time point up to Month 6 will be calculated with imputation by LOCF (Section 7) for missin data (ie, no data within the acceptable window for a visit in Appendix 11.1.1).

The subgroup analyses by the dose below will be calculated for the aboube analyses.

- Average actual daily dose (<7.5mg, ≧7.5 mg)

- **Disease activity of SDAI and CDAI**

The proportion of remission and disease activity at each time point for SDAI and the 95% confidence interval for the proportion of remission will be calculated.

As for each time point, "Appendix 11.1.1 Definition of Visit Timing" will be followed.

The calculation will be performed for CDAI in the same manner.

Also, the values with LOCF for "changes in SDAI and CDAI" as described above will be used to calculate the remission at each time point up to Month 6, as well as the proportion of patients in remission and disease activity, as well as a 95% confidence interval for the proportion of patients in remission.

The subgroup analyses by the average actual daily dose will be calculated for the aboube analyses.

Criteria for the assessment of the remission and disease activity of SDAI and CDAI will be based on Table 10.

Table 10. Criteria for the Assessment of the Disease Activity of SDAI and CDAI

Evaluation index	Remission	Low disease activity	Moderate disease activity	High disease activity
SDAI	≤3.3	>3.3 to ≤11	>11 to ≤26	>26
CDAI	≤2.8	>2.8 to ≤10	>10 to ≤22	>22

8.2.4.2. DAS28

- **Changes in DAS28**

Summary statistics for the measurement of DAS28(4/ESR) at each time point and the change from the initiation of administration of Xeljanz will be calculated. For the change, 95% confidence intervals will be calculated.

As for each time point, “Appendix 11.1.1 Definition of Visit Timing” will be followed.

Furthermore, summary statistics of measurements, the change will be calculated at each time point up to Month 6 will be calculated with imputation by LOCF (Section 7) for missin data (ie, no data within the acceptable window for a visit in Appendix 11.1.1)

The subgroup analyses by the average actual daily dose will be calculated for the aboube analyses.

- **Disease activity of DAS28**

The proportion of remission and disease activity at each time point for DAS28(4/ESR) and the 95% confidence interval for the proportion of remission will be calculated.

As for each time point, “Appendix 11.1.1 Definition of Visit Timing” will be followed.

Also, the values with LOCF for "changes in DAS28" as described above should be used to calculate the remission at each assessment timepoint up to Month 6 of treatment, as well as the proportion of patients in remission and disease activity, as well as a 95% confidence interval for the proportion of patients in remission.

The subgroup analyses by the average actual daily dose will be calculated for the aboube analyses.

Criteria for the assessment of the remission and disease activity of DAS28(4/ESR) will be based on Table 11.

Table 11. Criteria for the Assessment of the Disease Activity of DAS28

Evaluation index	Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28	<2.6	≥2.6 to <3.2	≥3.2 to ≤5.1	>5.1

- **EULAR response of DAS28**

The proportion of EULAR response at each time point for DAS28 will be calculated.

As for each time point, “Appendix 11.1.1 Definition of Visit Timing” will be followed.

Also, the values with LOCF for "changes in DAS28" as described above should be used to calculate the remission at each assessment timepoint up to Month 6 of treatment, as well as the proportion of patients in remission and disease activity, as well as a 95% confidence interval for the proportion of patients in remission.

The subgroup analyses by the average actual daily dose will be calculated for the aboube analyses.

Criteria for the assessment of the response of DAS28 will be based on Table 12.

Table 12. Criteria for the assessment of the response of DAS28[1]

<table>
<tr><th rowspan="2">Baseline DAS28</th><th colspan="3">Response of DAS28</th></tr>
<tr><th>Response>1.2</th><th>0.6＜Response≤1.2</th><th>Response≤0.6</th></tr>
<tr><td>DAS28≤3.2
Low disease activity</td><td>Good
Response</td><td rowspan="2"></td><td rowspan="3"></td></tr>
<tr><td>3.2＜DAS28≤5.1
Moderate disease activity</td><td rowspan="2"></td><td rowspan="2">Moderate
Response</td></tr>
<tr><td>DAS28>5.1
High disease activity</td><td rowspan="2"></td><td colspan="2" rowspan="2">No response</td></tr>
</table>

- **Changes in TJC, SJC, patient VAS, physician VAS, CRP, and ESR**

Summary statistics will be calculated for the measurements of TJC, SJC, patient VAS, physician VAS, CRP, and ESR, which are used for the calculation of efficacy endpoints, at each time point, and the change from the initiation of administration of Xeljanz. For the change, 95% confidence intervals will be calculated.

As for each time point, “Appendix 11.1.1 Definition of Visit Timing” will be followed.

Furthermore, summary statistics of measurements, the change will be calculated at each time point up to Month 6 will be calculated with imputation by LOCF (Section 7) for missin data (ie, no data within the acceptable window for a visit in 11.1.1)

The subgroup analyses by the average actual daily dose will be calculated for the aboube analyses.

8.2.4.3. Subgroup analysis

For the following endpoint, an analysis will be performed for each of the subgroups specified in Section 5.4.

- Number and proportion of patients achieving SDAI remission after 6 months from initiated xeljanz administration

In addition, statistical tests will be performed between the levels of factors in accordance with Section 8.1.3. At the tests, unknown, unspecified, and unmeasured data will be excluded from the analysis.

CCI

[redacted]

[redacted]

9. LISTINGS

- List of patients
- List of patients with adverse drug reactions
- List of patients with serious adverse drug reactions
- List of patients with serious adverse events
- List of patients with adverse events
- List of time to malignant tumor, serious infection and death, and censoring period
- List of patients with adverse drug reactions among patients excluded from the safety analysis
- List of patients with adverse drug reactions among patients with hepatic dysfunction
- List of patients with adverse drug reactions among patients with renal dysfunction
- List of patients with adverse drug reactions among the elderly
- List of patients with adverse drug reactions among pregnant and parturient women
- List of efficacy endpoints
- List of surgical therapies for rheumatoid arthritis
- List of patients excluded from analysis (patients aged 16 years or younger, patients receiving Xeljanz for conditions other than rheumatoid arthritis)
- List of patients with serious infection

- List of patients with neutrophil count decreased and neutropenia
- List of patients with lymphocyte count decreased and lymphopenia
- List of patients with lipid increased and hyperlipidemia
- List of patients with malignant tumors (including lymphoma)
- List of patients with gastrointestinal perforation
- List of patients with cardiovascular adverse events
- List of patients with hepatic dysfunction
- List of patients with interstitial pneumon
- List of patients with opportunistic infection
- List of patients with herpes zoster
- List of patients with tuberculosis
- List of patients with pneumocystis pneumonia
- List of concomitant medications used in patients with herpes zoster
- List of deaths (Patients in which death was selected as the reason for discontinuation of treatment or investigation, patients in which death was selected in the seriousness of adverse events, and patients in which adverse events leading to death occurred.)
- List of contraindicated patients with adverse drug reactions

In addition, the following tables corresponding to Appendix Forms of periodic safety update reports will be prepared:

- Appendix Form 3 (list of the summary of included patients)
- Appendix Form 2 (list of the development of adverse drug reactions and infections)
- Appendix Form 10 (Appendix Form 2-2) (list of the development of serious adverse events)

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11. APPENDICES

11.1. Appendix 1: Details of Data Extraction

11.1.1. Definition of Visit Timing

Day 1: In the Xeljanz group, the oldest initiation date in the status of administration of Xeljanz.
In the control group, the oldest initiation date in the status of drug administration.

Visit timing	Evaluation item	Definition [acceptance range]
Before the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' - 'Date Day 1' + 1 = [-30 - 1] Target date = 1
1 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' - 'Date Day 1' + 1 = [2 - 62] Target date = 31
3 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［63- 138］ Target date=92
6 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［139- 230］ Target date=184
9 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［231- 321］ Target date=275
12 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［322- 412］ Target date=366
15 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［413- 503］ Target date=457
18 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［504-595］ Target date=549

Visit timing	Evaluation item	Definition [acceptance range]
21 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［596- 686］ Target date=640
24 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［687- 777］ Target date=731
27 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［778- 868］ Target date=822
30 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［869- 960］ Target date=914
33 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［961- 1051］ Target date=1005
36 month after the initiation of administration	Laboratory test Blood pressure Efficacy observation items	= 'Date of assessment' – 'Date Day 1' + 1 = ［1052-1142］ Target date=1096

If there are multiple data corresponding to 1 visit label, priority will be given to the date closest to the target date. If there are multiple closest dates, priority will be given to the date before the target date.

11.1.2. Patient Background

Item	Category	Note
Sex	Male, Female	
Age 1	<65 years, ≥65 years	Continuous data
Age 2	<50 years, ≥50 years to <65 years, ≥65 years	
Age 3	<40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years	

Item	Category	Note
Age 4	<50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years	
Height	<140 cm, ≥140 cm to <150 cm, ≥150 cm to <160 cm, ≥160 cm to <170 cm, ≥170 cm to <180 cm, ≥180 cm, Not measured	Continuous data
Body weight 1	<40 kg, ≥40 kg to <50 kg, ≥50 kg to <60 kg, ≥60 kg to <70 kg, ≥70 kg to <80 kg, ≥80 kg, Not measured	Continuous data
Body weight 2	<50 kg, ≥50 kg to <60 kg, ≥60 kg to <70 kg, ≥70 kg, Not measured	
BMI	<18.5, ≥18.5 to <25, ≥25	Continuous data
Inpatient/outpatient	Inpatient, Outpatient	
Disease to be investigated	Rheumatoid arthritis, Others	
Stage of rheumatoid arthritis	I, II, III, IV	
	I,-II, III, IV	
Class of rheumatoid arthritis	1, 2, 3, 4	
	1- 2, 3, 4	
Duration of disease 1	<6 months, ≥6 months to <2 years, ≥2 years to <5 years, ≥5 years to <10 years, ≥10 years to <20 years, ≥20 years, Unknown	Continuous data
Duration of disease 2	<2 years, ≥2 years to <5 years, ≥5 years to <10 years, ≥10 years to <20 years, ≥20 years, Unknown	
Past history	Absent, Present	
Past history (infection)	Absent, Present	
Past history (herpes zoster)	Absent, Present	
Past history (tuberculosis-related disease)	Absent, Present	
Past history (malignant tumor)	Absent, Present	
Past history (autoimmune disease)	Absent, Present	
Past history (Sjogren's syndrome)	Absent, Present	

Item	Category	Note
Past history (cardiovascular disease)	Absent, Present	
Past history (hypertension)	Absent, Present	
Past history (angina pectoris)	Absent, Present	
Past history (myocardial infarction)	Absent, Present	
Past history (heart failure)	Absent, Present	
Past history (arrhythmia)	Absent, Present	
Past history (pulmonary disorder)	Absent, Present	
Past history (interstitial pneumonia)	Absent, Present	
Past history (gastrointestinal disorder)	Absent, Present	
Past history (diverticulum)	Absent, Present	
Past history (gastrointestinal perforation)	Absent, Present	
Past history (hepatic dysfunction)	Absent, Present	
Past history (hepatitis B)	Absent, Present	
Past history (hepatitis C)	Absent, Present	
Past history (other hepatitis)	Absent, Present	
Past history (hepatitis B virus carrier)	Absent, Present	
Past history (hepatitis C virus carrier)	Absent, Present	
Past history (other hepatitis virus carrier)	Absent, Present	
Past history (renal dysfunction)	Absent, Present	
Past history (metabolic abnormality)	Absent, Present	
Past history (diabetes mellitus)	Absent, Present	

Item	Category	Note
Past history (lipid abnormality)	Absent, Present	
Past history (anemia)	Absent, Present	
Past history (others)	Absent, Present	
Complication	Absent, Present	
Complication (infection)	Absent, Present	
Complication (herpes zoster)	Absent, Present	
Complication (tuberculosis-related disease)	Absent, Present	
Complication (malignant tumor)	Absent, Present	
Complication (autoimmune disease)	Absent, Present	
Complication (Sjogren's syndrome)	Absent, Present	
Complication (cardiovascular disease)	Absent, Present	
Complication (hypertension)	Absent, Present	
Complication (angina pectoris)	Absent, Present	
Complication (myocardial infarction)	Absent, Present	
Complication (heart failure)	Absent, Present	
Complication (arrhythmia)	Absent, Present	
Complication (pulmonary disorder)	Absent, Present	
Complication (interstitial pneumonia)	Absent, Present	
Complication (gastrointestinal disorder)	Absent, Present	
Complication (diverticulum)	Absent, Present	
Complication (gastrointestinal perforation)	Absent, Present	

Item	Category	Note
Complication (hepatic dysfunction)	Absent, Present	
Complication (hepatitis B)	Absent, Present	
Complication (hepatitis C)	Absent, Present	
Complication (other hepatitis)	Absent, Present	
Complication (hepatitis B virus carrier)	Absent, Present	
Complication (hepatitis C virus carrier)	Absent, Present	
Complication (other hepatitis virus carrier)	Absent, Present	
Complication (renal dysfunction)	Absent, Present	
Complication (metabolic abnormality)	Absent, Present	
Complication (diabetes mellitus)	Absent, Present	
Complication (lipid abnormality)	Absent, Present	
Complication (anemia)	Absent, Present	
Complication (others)	Absent, Present	
Smoking history 1	Absent, Present, Unknown	
Smoking history 2	Past history absent, Past history present, Present, Unknown	
Family history of malignant tumors (including lymphoma)	Absent, Present, Unknown	
History of MTX use (Within 3 months prior to the start of survey)	Absent, Present, (History) Unknown	
History of MTX use (Dose just prior to the start of survey 1)	Absent, >0 mg to ≤8 mg/week, >8 mg/week	Continuous data

Item	Category	Note
History of MTX use (Dose just prior to the start of survey 2)	Absent, >0 mg to ≤2 mg/week, >2 mg to ≤4 mg/week, >4 mg to ≤6 mg/week, >6 mg to ≤8 mg/week, >8 mg to ≤10 mg/week, >10 mg to ≤12 mg/week, >12 mg to ≤14 mg/week, >14 mg to ≤16 mg/week, >16mg/week	
History of MTX use (Duration)	Absent, <6 months, ≥6 months to <3 years, ≥3 years to <5 years, ≥5 years, (Duration) Unknown，(History) Unknown	
Status of MTX use (Dose prior to the start date of survey 1)	Absent, >0 mg to ≤8 mg/week, >8 mg/week	Continuous data A weekly dose specified for the period including the day on which administration of Xeljanz starts Summary statistics should be calculated also under an assumption that patients with absence of data are excluded.
Status of MTX use (Dose prior to the start date of survey 2)	Absent, >0 mg to ≤2 mg/week, >2 mg to ≤4 mg/week, >4 mg to ≤6 mg/week, >6 mg to ≤8 mg/week, >8 mg to ≤10 mg/week, >10 mg to ≤12 mg/week, >12 mg to ≤14 mg/week, >14 mg to ≤16 mg/week, >16mg/week	
History of oral steroid use (Within 3 months prior to the start of survey)	Absent, Present	The presence/absence of oral steroid use within 90 days prior to the start of administration of Xeljanz (including the date of the initiation of administration) will be calculated.
History of oral steroid use (Dose just prior to the start of survey 1)	Absent , >0 mg/day to <2.5 mg/day, ≥2.5 mg/day to <5 mg/day, ≥5 mg/day	Daily dose that is prior to the start of survey, is within the dosing period of steroid, and includes the day closest to the

Item	Category	Note
History of oral steroid use (Dose just prior to the start of survey 2)	Absent , >0 mg/day to <5 mg/day, ≥5 mg/day	survey start. Summarize based on prednisolone equivalent dose (= 5×Dose/Pharmacologically equivalent strength) Pharmacologically equivalent strengths: hydrocortisone=20, cortisone=25, prednisone=5, prednisolone=5, methylprednisolone=4, triamcinolone=4, paramethasone=2, dexamethasone=0.75，betamethasone =0.6[8]
History of oral steroid use (Duration)	Absent, <6 months, ≥6 months to <3 years, ≥3 years, (Duration) Unknown， (History) Unknown	
Status of oral steroid use (Dose prior to the start date of survey 1)	Absent , >0 mg/day to <2.5 mg/day, ≥2.5 mg/day to <5 mg/day, ≥5 mg/day	Daily dose that is prior to the start of survey, is within the dosing period of steroid, and includes the day closest to the survey start. Summarize based on prednisolone equivalent dose (= 5×Dose/Pharmacologically equivalent strength) Pharmacologically equivalent strengths: hydrocortisone=20, cortisone=25, prednisone=5, prednisolone=5, methylprednisolone=4, triamcinolone=4, paramethasone=2, dexamethasone=0.75，betamethasone =0.6[8]
Status of oral steroid use (Dose prior to the start date of survey 2)	Absent , >0 mg/day to <5 mg/day, ≥5 mg/day	
History of tacrolimus use	Absent, Present	
History of tacrolimus use (Duration)	Absent, <6 months, ≥6 months to <3 years, ≥3 years, (Duration) Unknown， (History) Unknown	

Item	Category	Note
Past use of biological agents (Within 3 months prior to the start of survey)	Absent, Present	
Initial daily dose of Xeljanz［mg］	5 mg, 10 mg, >10 mg	Xeljanz group only
White blood cell count [/mm^3]［/mm^3］	<4000, ≥ 4000	Data that is prior to the start of survey, and the day closest to the survey start.
Neutrophil count [/mm^3]	<500, ≥500 to <1000, ≥1000	Data that is prior to the start of survey, and the day closest to the survey start.
	<4000, ≥ 4000	
Lymphocyte count [/mm^3]	<500, ≥500 to <1000, ≥1000	Data that is prior to the start of survey, and the day closest to the survey start.
	<1500, ≥1500	
Hemoglobin [g/dL]	<8, ≥8 to <9, ≥10	Data that is prior to the start of survey, and the day closest to the survey start.
β-D-glucan	Positive, Negative	Data that is prior to the start of survey, and the day closest to the survey start.
Chest X-ray or chest CT	Performed, Not performed	Xeljanz group only
Tuberculosis test	Performed, Not performed	Xeljanz group only Any of the above chest X-ray or chest CT, interferon γ, and tuberculin reaction will be performed.
Interferon γ	QuantiFERON, T-spot, TB Positive, assessment pending, or Negative for each	Xeljanz group only
Tuberculin reaction	-, 1+, 2+, 3+	Xeljanz group only
Systolic blood pressure	<120 mmHg, ≥120 mmHg to <140 mmHg, ≥140 mmHg to <160 mmHg, ≥160 mmHg to <180 mmHg, ≥180 mmHg	Continuous data Xeljanz group only
Diastolic blood pressure	<60 mmHg, ≥60 mmHg to <80 mmHg, ≥80 mmHg to <100 mmHg, ≥100 mmHg to <120 mmHg, ≥120 mmHg to <140 mmHg, ≥140 mmHg	Continuous data Xeljanz group only
HBs antigen	No data, Positive, Negative	Xeljanz group only
HBs antibody	No data, Positive, Negative	Xeljanz group only
HBc antibody	No data, Positive, Negative	Xeljanz group only
HBV-DNA test [log copy/mL]	No data, <2.6, ≥2.6	Xeljanz group only
HCV antibody	No data, Positive, Negative	Xeljanz group only

Item	Category	Note
Hepatitis B and C virus test	Performed, Not performed	Xeljanz group only Any of the above HBs antigen, HBs antibody, HBc antibody, HBV-DNA test, and HCV antibody will be performed.
Prophylactic administration to prevent tuberculosis	Performed, Not performed	
Prophylactic administration to prevent pneumocystis jiroveci pneumonia	Performed, Not performed	
Prophylactic administration to prevent hepatitis B	Performed, Not performed	
SDAI	≤3.3, >3.3 to ≤11, >11 to ≤26, >26	Continuous data Xeljanz group only
	≤11, >11 to ≤26, >26	
CDAI	≤2.8, >2.8 to ≤10, >10 to ≤22, >22	Continuous data Xeljanz group only
	≤10, >10 to ≤22, >22	
DAS28	<2.6, ≥2.6 to <3.2, ≥3.2 to ≤5.1, >5.1	Continuous data Xeljanz group only
	<3.2, ≥3.2 to ≤5.1, >5.1	
Organization that established the hospital	University hospitals, National hospitals established by the Ministry of Health, Labour and Welfare, Prefectural and municipal hospitals, Public institutions, Hospitals other than the above 4 hospitals established by companies and individuals, General practitioners and clinics	

11.1.3. Patient Background Considered for Safety

Nominal Scale

Item	Category	Note
Sex	Male, Female	Reference: Male
Age 1	<65 years, ≥65 years	Reference: <65 years
Past history (infection)	Absent, Present	Reference: Absent
Past history (herpes zoster)	Absent, Present	Reference: Absent

Nominal Scale

Item	Category	Note
Past history (tuberculosis-related disease)	Absent, Present	Reference: Absent
Past history (malignant tumor)	Absent, Present	Reference: Absent
Past history (autoimmune disease)	Absent, Present	Reference: Absent
Past history (Sjogren's syndrome)	Absent, Present	Reference: Absent
Past history (cardiovascular disease)	Absent, Present	Reference: Absent
Past history (hypertension)	Absent, Present	Reference: Absent
Past history (angina pectoris)	Absent, Present	Reference: Absent
Past history (myocardial infarction)	Absent, Present	Reference: Absent
Past history (heart failure)	Absent, Present	Reference: Absent
Past history (arrhythmia)	Absent, Present	Reference: Absent
Past history (pulmonary disorder)	Absent, Present	Reference: Absent
Past history (interstitial pneumonia)	Absent, Present	Reference: Absent
Past history (gastrointestinal disorder)	Absent, Present	Reference: Absent
Past history (diverticulum)	Absent, Present	Reference: Absent
Past history (gastrointestinal perforation)	Absent, Present	Reference: Absent
Past history (hepatic dysfunction)	Absent, Present	Reference: Absent
Past history (hepatitis B)	Absent, Present	Reference: Absent
Past history (hepatitis C)	Absent, Present	Reference: Absent
Past history (other hepatitis)	Absent, Present	Reference: Absent
Past history (hepatitis B virus carrier)	Absent, Present	Reference: Absent
Past history (hepatitis C virus carrier)	Absent, Present	Reference: Absent
Past history (other hepatitis virus carrier)	Absent, Present	Reference: Absent
Past history (renal dysfunction)	Absent, Present	Reference: Absent
Past history (metabolic abnormality)	Absent, Present	Reference: Absent
Past history (diabetes mellitus)	Absent, Present	Reference: Absent
Past history (lipid abnormality)	Absent, Present	Reference: Absent
Past history (anemia)	Absent, Present	Reference: Absent
Complication (infection)	Absent, Present	Reference: Absent
Past history (herpes zoster)	Absent, Present	Reference: Absent

Nominal Scale

Item	Category	Note
Past history (tuberculosis-related disease)	Absent, Present	Reference: Absent
Complication (malignant tumor)	Absent, Present	Reference: Absent
Complication (autoimmune disease)	Absent, Present	Reference: Absent
Complication (Sjogren's syndrome)	Absent, Present	Reference: Absent
Complication (cardiovascular disease)	Absent, Present	Reference: Absent
Complication (hypertension)	Absent, Present	Reference: Absent
Complication (angina pectoris)	Absent, Present	Reference: Absent
Complication (myocardial infarction)	Absent, Present	Reference: Absent
Complication (heart failure)	Absent, Present	Reference: Absent
Complication (arrhythmia)	Absent, Present	Reference: Absent
Complication (pulmonary disorder)	Absent, Present	Reference: Absent
Complication (interstitial pneumonia)	Absent, Present	Reference: Absent
Complication (gastrointestinal disorder)	Absent, Present	Reference: Absent
Complication (diverticulum)	Absent, Present	Reference: Absent
Complication (gastrointestinal perforation)	Absent, Present	Reference: Absent
Complication (hepatic dysfunction)	Absent, Present	Reference: Absent
Complication (hepatitis B)	Absent, Present	Reference: Absent
Complication (hepatitis C)	Absent, Present	Reference: Absent
Complication (other hepatitis)	Absent, Present	Reference: Absent
Complication (hepatitis B virus carrier)	Absent, Present	Reference: Absent
Complication (hepatitis C virus carrier)	Absent, Present	Reference: Absent
Complication (other hepatitis virus carrier)	Absent, Present	Reference: Absent
Complication (renal dysfunction)	Absent, Present	Reference: Absent
Complication (metabolic abnormality)	Absent, Present	Reference: Absent
Complication (diabetes mellitus)	Absent, Present	Reference: Absent
Complication (lipid abnormality)	Absent, Present	Reference: Absent
Complication (anemia)	Absent, Present	Reference: Absent
Smoking history 1	Absent, Present	Reference: Absent

Nominal Scale

Item	Category	Note
Smoking history 2	Past smoking history (absent), Past smoking history (Present), Present	
Family history of malignant tumors (including lymphoma)	Absent, Present	Reference: Absent
History of MTX use (Within 3 months prior to the start of survey)	Absent, Present	Reference: Absent
History of oral steroid use (Within 3 months prior to the start of survey)	Absent, Present	Reference: Absent
History of tacrolimus use (Within 3 months prior to the start of survey)	Absent, Present	Reference: Absent
Past use of biological agents (Within 3 months prior to the start of survey)	Absent, Present	Reference: Absent
White blood cell count [/mm^3]	<4000, ≥4000	Reference: <4000
Neutrophil count [/mm^3]	<2000, ≥2000	Reference: <2000
Lymphocyte count	<1000, ≥1000	Reference: <1000
β-D-glucan	Positive, Negative	Reference: Negative
HBs antigen	Positive, Negative	Reference: Negative
HBs antibody	Positive, Negative	Reference: Negative
HBc antibody	Positive, Negative	Reference: Negative
HBV-DNA test [log copy/mL]	<2.6, ≥2.6	Reference: <2.6
HCV antibody	Positive, Negative	Reference: Negative
Prophylactic administration to prevent tuberculosis	Performed, Not performed	Reference: Not performed
Prophylactic administration to prevent pneumocystis jiroveci pneumonia	Performed, Not performed	Reference: Not performed
Prophylactic administration to prevent hepatitis B	Performed, Not performed	Reference: Not performed

Ordinal Scale

Item	Category	Note
Age 2	<50 years, ≥50 years to <65 years, ≥65 years	Reference: <50 years

Ordinal Scale

Item	Category	Note
Age 3	<40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years	Reference: <40 years
Age 4	<50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years	Reference: <50 years
Body weight 2	<50 kg, ≥50 kg to <60 kg, ≥60 kg to <70 kg, ≥70 kg	Reference: <50 kg
BMI	<18.5, ≥18.5 to <25, ≥25	Reference: <18.5
Stage of rheumatoid arthritis	I, II, III, IV	Reference: I
	I- II, III, IV	Reference: I- II
Class of rheumatoid arthritis	1, 2, 3, 4	Reference: 1
	1-2, 3, 4	Reference: 1-2
Duration of disease 2	<2 years, ≥2 years to <5 years, ≥5 years to <10 years, ≥10 years to <20 years, ≥20 years	Reference: <2 years
History of MTX use (Dose just prior to the start of survey 1)	Absent, >0 mg to ≤8 mg/week, >8 mg/week	Reference: Absent
History of MTX use (Dose just prior to the start of survey 2)	Absent, >0 mg to ≤2 mg/week, >2 mg to ≤4 mg/week, >4 mg to ≤6 mg/week, >6 mg to ≤8 mg/week, >8 mg to ≤10 mg/week, >10 mg to ≤12 mg/week, >12 mg to ≤14 mg/week, >14 mg to ≤16 mg/week, >16 mg/week	Reference: Absent
History of MTX use (Duration)	Absent, <6 months, ≥6 months to <3 years, ≥3 years to <5 years, ≥5 years	Reference: Absent
Status of MTX use (Dose prior to the start date of survey 1)	Absent, >0 mg to ≤8 mg/week, >8 mg/week	Reference: Absent
Status of MTX use (Dose prior to the start date of survey 2)	Absent, >0 mg to ≤2 mg/week, >2 mg to ≤4 mg/week, >4 mg to ≤6 mg/week, >6 mg to ≤8 mg/week, >8 mg to ≤10 mg/week, >10 mg to ≤12 mg/week, >12 mg to ≤14 mg/week, >14 mg to ≤16 mg/week, >16 mg/week	Reference: Absent
History of oral steroid use (Dose just prior to the start of survey 1)	Absent , >0 mg/day to <2.5 mg/day, ≥2.5 mg/day to <5 mg/day, ≥5 mg/day	Reference: Absent
History of oral steroid use (Dose just prior to the start of survey 2)	Absent , >0 mg/day to <5 mg/day, ≥5 mg/day	Reference: Absent
Status of oral steroid use (Dose prior to the start date of survey 1)	Absent , >0 mg/day to <2.5 mg/day, ≥2.5 mg/day to <5 mg/day, ≥5 mg/day	Reference: Absent
Status of oral steroid use (Dose prior to the start date of survey 2)	Absent , >0 mg/day to <5 mg/day, ≥5 mg/day	Reference: Absent
Initial daily dose of Xeljanz［mg］	5 mg, 10 mg, >10 mg	Reference: 5mg

Ordinal Scale

Item	Category	Note
SDAI	≤3.3, >3.3 to ≤11, >11 to ≤26, >26	Reference: ≤3.3
	≤11, >11 to ≤26, >26	Reference: ≤11
CDAI	≤2.8, >2.8 to ≤10, >10 to ≤22, >22	Reference: ≤2.8
	≤10, >10 to ≤22, >22	Reference: ≤10
DAS28	<2.6, ≥2.6 to <3.2, ≥3.2 to ≤5.1, >5.1	Reference: <2.6
	<3.2, ≥3.2 to ≤5.1, >5.1	Reference: <3.2

11.1.4. Patient Background Considered for Efficacy

Nominal Scale

Item	Category	Note
Sex	Male, Female	Reference: Male
Age 1	<65 years, ≥65 years	Reference: <65 years
Past history (hepatic dysfunction)	Absent, Present	Reference: Absent
Past history (renal dysfunction)	Absent, Present	Reference: Absent
Past use of biological agents (Within 3 months prior to the start of survey)	Absent, Present	Reference: Absent

Ordinal Scale

Item	Category	Note
Age 2	<50 years, ≥50 years to <65 years, ≥65 years	Reference: <50 years
Age 3	<40 years, ≥40 years to <50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years to <80 years, ≥80 years	Reference: <40 years
Age 4	<50 years, ≥50 years to <60 years, ≥60 years to <70 years, ≥70 years	Reference: <50 years
Body weight 2	<50 kg, ≥50 kg to <60 kg, ≥60 kg to <70 kg, ≥70 kg	Reference: <50 kg
BMI	<18.5, ≥18.5 to <25, ≥25	Reference: <18.5
Stage of rheumatoid arthritis	I, II, III, IV	Reference: I
	I- II, III, IV	Reference: I- II
Class of rheumatoid arthritis	1, 2, 3, 4	Reference: 1
	1-2, 3, 4	Reference: 1-2
Duration of disease 2	<2 years, ≥2 years to <5 years, ≥5 years to <10 years, ≥10 years to <20 years, ≥20 years	Reference: <2 years

Ordinal Scale

Item	Category	Note
Initial daily dose of Xeljanz［mg］	5 mg, 10 mg, >10 mg	Reference: 5mg
Lymphocyte count [/mm^3]	<500, ≥500 to <1000, ≥1000	Reference: <500
Status of MTX use (Dose prior to the start date of survey 1)	Absent, >0 mg to ≤8 mg/week, >8 mg/week	Reference: absent
Status of MTX use (Dose prior to the start date of survey 2)	Absent, >0 mg to ≤2 mg/week, >2 mg to ≤4 mg/week, >4 mg to ≤6 mg/week, >6 mg to ≤8 mg/week, >8 mg to ≤10 mg/week, >10 mg to ≤12 mg/week, >12 mg to ≤14 mg/week, >14 mg to ≤16 mg/week, >16mg/week	Reference: absent
SDAI	≤3.3, >3.3 to ≤11, >11 to ≤26, >26	Reference: ≤3.3
	≤11, >11 to ≤26, >26	Reference: ≤11
CDAI	≤2.8, >2.8 to ≤10, >10 to ≤22, >22	Reference: ≤2.8
	≤10, >10 to ≤22, >22	Reference: ≤10
DAS28	<2.6, ≥2.6 to <3.2, ≥3.2 to ≤5.1, >5.1	Reference: <2.6
	<3.2, ≥3.2 to ≤5.1, >5.1	Reference: <3.2