Non-Interventional Study Protocol
A3921248

XELJANZ Tablets 5mg
SPECIAL INVESTIGATION
(A Long-Term Use Study in Patients with Ulcerative Colitis)

STATISTICAL ANALYSIS PLAN

Version: 4.0

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1. REVISION HISTORY

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0 29-NOV-2018 PPD	First edition
2.0 06-NOV-2020 PPD	2.1. Study Design ● Updated the safety specification to include venous thromboembolism.
	5.2. Effectiveness Analysis Set ● Added faecal calprotectin as an effectiveness evaluation. ● Specifically stated the target disease in this study instead of listing out-of-scope diseases.
	5.4.1. Subgroups by dose level ● Added subgroups by mean daily dose and the group of patients who were treated for a long term.
	5.4.2. Subgroups regarding patient characteristics ● Made modifications in the subgroups and categories.
	6.1. Safety Endpoints ● Updated the safety specification to include venous thromboembolism. ● Made a change from “Cardiovascular events” to “Cardiovascular events (including lipids increased and hyperlipidaemia)”. ● Made a change from “Times to onset of a serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection) and malignancy” to “Time to onset of each element in the safety specification”.
	6.2. Efficacy Endpoints ● Added faecal calprotectin.
	6.4. Covariates ● Specified a reference value for each covariate. ● Added candidate covariates for the development of herpes zoster. ● Made modifications in the subgroups.
	7. HANDLING OF MISSING DATA ● Made a change from “Times to onset of a serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection) and malignancy” to “Time to onset of each element in the safety specification”. ● Deleted a part of the description for multivariate analyses.
	8.2.1. Patient description ● Added descriptions for subgroups by mean daily dose and patients treated for a long term in the subsections “Constitution of patients” and “Completion of treatment or reason for discontinuation”.

Version/ Date/ Author(s)	Summary of Changes/Comments
	8.2.2. Patient characteristics and medical history ● Added descriptions for subgroups by mean daily dose and patients treated for a long term in the subsections “Patient characteristics” and “Dosing status of Xeljanz tablets”. ● Made some additions to and modifications in the factors and categories in the subsection “Patient characteristics”. ● Added the note “summary statistics” to and made modifications in the categories of mean daily dose by duration of treatment (mg) in the subsection “Dosing status of Xeljanz tablets”.
	8.2.3. Safety analyses ● Modified the events that will be included in summarization, from those that developed by the last observed administration of Xeljanz tablets to those that developed by the end of the observation period.
	8.2.3.1. Adverse reactions ● Added new categories for the factor time to onset in the subsection “Details of adverse reactions”. ● Updated the subsection “Safety specification” to include hepatitis B virus reactivation and venous thromboembolism. Also, made a change from “Cardiovascular events” to “Cardiovascular events (including lipids increased and hyperlipidaemia)”. ● Modified the method of analysis for “Timing of onset of elements in the safety specification”. ● Updated the lists of biologics/immunosuppressants and CYP3A4 inhibitors/CYP2C19 inhibitors in the subsection “Relationship between concomitant drugs and adverse reactions” to include some new drugs.
	8.2.3.2. Adverse events ● Updated the subsection “Safety specification” to include hepatitis B virus reactivation and venous thromboembolism. Also, made a modification from “Cardiovascular events” to “Cardiovascular events (including lipids increased and hyperlipidaemia)”. ● Modified the method of analysis for “Timing of onset of elements in the safety specification”. ● Updated the lists of biologics/immunosuppressants and CYP3A4 inhibitors/CYP2C19 inhibitors in the subsection “Relationship between concomitant drugs and adverse events” to include some new drugs.
	8.2.3.3. Subgroup analyses ● Added a subsection “Analyses by dosage subgroup”
	8.2.4.4. Changes in faecal calprotectin ● Added as a new item.
	10.1. Appendix 1: Details of Data Handling ● Updated the second set of endpoints to include faecal calprotectin.
	Made other corrections for typographical errors.

Version/ Date/ Author(s)	Summary of Changes/Comments
3.0 29-NOV-2021 PPD	2.1. Study Design ● Reclassified malignancy and cardiovascular events as important identified risks in accordance with the revision of the Risk Management Plan. ● Added descriptions for “Observation period” and “Dosage and administration of Xeljanz tablets”.
	5.4.1. Subgroups by dose level ● Added a phrase to explain the purpose of the subgroups. ● Amended the denominator for the mean daily dose to include non-dosing days during the treatment period.
	6.1. Safety Endpoints ● Added a condition for an event to be assessed as a safety endpoint. ● Updated the elements of serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infections) and herpes zoster in the safety specification to include some new events.
	7. HANDLING OF MISSING DATA ● Clarified the observation period for event-free patients.
	8.1.4. Analyses based on the person-year method ● Modified the definition of event-experiencing patients and exposure duration so that they are defined separately for events of malignancy and the others.
	8.1.5. Analyses of time-to-event data ● Added as a new item.
	8.2.2. Patient characteristics and medical history ● Modified the categorization of the duration of treatment in the subsection “Dosing status of Xeljanz tablets”.
	8.2.3. Safety analyses ● Added a description for the event-collection period for adverse reactions and AEs.
	8.2.3.1. Adverse reactions ● Modified the categorization of onset timing in the subsections “Details of adverse reactions” and “Timing of onset of elements in the safety specification”. Also, added a definition of the denominators for the calculation of proportion and of incidence. ● Modified the definition of the concomitant drugs included in the analysis of the “Relationship Between Concomitant Drugs and Adverse Reactions”.
	8.2.3.2. Adverse Events ● Modified the categorization of onset timing in the subsection “Timing of Onset of Elements in the Safety Specification”. Also, added a definition of the denominator for the calculation of proportion and of incidence. ● Modified the definition of the concomitant drugs included in the analysis of the “Relationship between concomitant drugs and adverse reactions”.

Version/ Date/ Author(s)	Summary of Changes/Comments
	8.2.3.3. Subgroup analyses ● Made editorial revisions regarding the content of "Analyses by dosage subgroup".
	9. LISTINGS ● Added "AEs considered as out of collection-period" as a listing item.
	Made other typographical corrections.
4.0 30-MAY-2022 PPD	6.1. Safety Endpoints ● Added descriptions that events that should be handled as an element of the safety specification should follow the definitions presented in the Appendix of Tofacitinib Periodic Safety Update Report (PSUR), and that the definition of an event that is not defined in the PSUR is presented in this SAP.
	7. HANDLING OF MISSING DATA ● Added a description how to impute the date of the end of treatment when it is missing. ● Added a description how to impute the end date for concomitant therapies (drug and non-drug) when it is missing.
	8.2.2. Patient characteristics and medical history ● Described what kinds of past history and complication will be considered. ● Described what kinds of concomitant drug, non-drug therapy, and prior treatment will be considered.

2. INTRODUCTION

This document describes the statistical analysis plan (SAP) for the Special Investigation of Xeljanz Tablets 5mg (hereinafter referred to as "this drug"). In this SAP, citations from the corresponding protocol are indicated in *italics*.

2.1. Study Design

This is a multicenter cohort investigation to be conducted in patients with ulcerative colitis treated with XELJANZ in clinical settings.

● Registration criteria

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

•Patients with ulcerative colitis treated with XELJANZ

•Patients naive to XELJANZ in the treatment of ulcerative colitis

● Sample size

470 to be collected in the safety analysis set (495 to be registered)*

● Rationale

Based on the results of clinical studies conducted up to approval, the incidence of herpes zoster in Japanese patients with ulcerative colitis chronically treated with XELJANZ was higher than that in the overall population of the studies. Therefore, on the assumption that the true incidence of herpes zoster in Japanese patients with ulcerative colitis is 8/100 person-years, the sample size will be 470 when the probability of the lower limit of 95% confidence interval for the incidence of herpes zoster not falling below 4/100 person-years (results for the overall population of the studies) is 80%.

**: If it is assumed that 5% of the registered patients are unevaluable for the safety due to failure to show up or other reasons, 495 patients need to be registered to ensure that 470 patients are included in the safety analysis set.*

● Safety specification

Important Identified Risks

• *Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection)*

• *Herpes zoster*

• *Neutropenia, lymphopenia, oligochromemia*

• *Hepatic impairment*

• *Reactivation of hepatitis B virus*

• *Gastrointestinal perforation*

• *Interstitial lung disease*

• *Venous thrombosis*

• Malignant tumor

• Cardiovascular event

Important Potential Risks

• *Rhabdomyolysis, myopathy*

Important Missing Information

Not applicable.

● Observation period

Each patient will be observed for 60 weeks from the start day of the treatment with this drug. Patients treated with this drug for more than 60 weeks will, however, be observed to the end of this study (June 2021). For patients who discontinued the treatment with this drug, data will be collected until the discontinuation.

All adverse events (AEs) occurring from the start of treatment to the end of the observation period will be collected for patients whose observation period is 60 weeks or less. For patients whose observation period exceeds 60 weeks, all AEs will be collected until 60 weeks and thereafter only malignancies and AEs leading to discontinuation of treatment will be collected.

● Analysis for safety evaluation

In the safety analysis set, the onset of major adverse reactions (AEs considered by the physician to be related to this drug)*, incidence of adverse reactions (number/percentage of patients with adverse reactions), and incidence of adverse events per duration of exposure (100 × number of patients with adverse reactions / total duration of exposure / 100 person-years) will be set as primary analysis items. In addition, factors that may affect the onset of adverse reactions will also be examined by conducting subgroup analyses based on patient background and other factors.*

● Analysis for effectiveness evaluation

In the effectiveness analysis set, the rate of remission based on partial Mayo score will be set as primary analysis items.

● Dosage and administration of this drug

For induction, the recommended dose of this drug is 10 mg administered twice daily (10 mg BID [bis in die]) for 8 weeks. If the response is inadequate after the 8 weeks course of treatment, another 8 weeks course may be administered.

For maintenance, the recommended dose is 5 mg twice daily (5 mg BID). If the response decreases during the maintenance, the dose level may be increased to 10 mg BID. Intractable patients for whom prior drug therapies (e.g., a TNF inhibitor) were ineffective may be treated with 10 mg BID.

2.2. Study Objective

This investigation aims to examine the safety and effectiveness of XELJANZ in post-marketing clinical settings when it is administered chronically to patients with ulcerative colitis, based on the approval conditions below.

Approval conditions

Ulcerative colitis

Due to a very limited number of patients studied in clinical trials in Japan, a Drug Use Investigation in all patients should be conducted after launch until data are collected on a target number of patients to

understand the background of patients using XELJANZ and collect data on the safety and effectiveness of XELJANZ early in order to take necessary actions for the proper use of the drug.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses will be conducted on a regular basis for the purpose of periodic safety reporting. Among the analysis items defined in this SAP, only selected items necessary for periodic safety reporting will be analyzed in each interim analysis. A final analysis will be conducted to support application of reexamination. For the final analysis, the full items defined in this SAP will be analyzed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

CCI

Unless otherwise stated, all statistical tests will be performed as a two-sided test with a significance level of 5%.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SET

5.1. Safety Analysis Set

The safety analysis set (SAS) is a full analysis set (FAS) that is as closer as possible to all patients treated with this drug. Specifically, the SAS consists of all registered or reported patients except those who meet any of the following conditions:

a. No case report form (CRF) has been collected. (Indicated as “CRF not collected” in the study report.)

b. Any violation or deficiency was found regarding the study contract. (Indicated as “Contract violation/deficiency” in the study report.)

c. The registration does not meet all the requirements. (Indicated as “Invalid registration” in the study report.)

d. No administration of this drug has been reported. (Indicated as “No treatment information” in the study report.)

e. No information has been reported for adverse events. − No revisit after the first prescription (Indicated as “No AE information − No revisit” in the study report.)

f. No information has been reported for adverse events. − Revisit was done after the first prescription with no record (Indicated as “No AE information − No record” in the study report.)

Details of each criterion should follow the Guidance for Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Drug Use-Results Surveys.

5.2. Effectiveness Analysis Set

The effectiveness analysis set (EAS) consists of all patients in the SAS except those who meet any of the following conditions:

g. No effectiveness assessment has been reported (Indicated as “No effectiveness information” in the study report.)
The effectiveness assessments concerned include: Mayo stool frequency subscore, Mayo rectal bleeding subscore, Mayo findings of flexible sigmoidoscopy subscore, Mayo physician's global assessment of disease activity subscore, and faecal calprotectin.

h. The disease of the patient is out of scope for this study (Indicated as “Out-of-scope disease” in the study report.)
The disease investigated in this study: Ulcerative colitis

5.3. Other Analysis Sets

Not applicable.

5.4. Subgroups

5.4.1. Subgroups by dose level

The following subgroups will be defined depending on the mean daily dose to evaluate the safety of this drug and the dose response of the safety in patients treated mainly at 10 mg BID:

● Subgroups by mean daily dose (patients treated mainly at 10 mg BID, patients treated at a higher dose level, patients treated at a lower dose level)

Among the patients in the SAS, those who were treated at a mean daily dose of 17 mg or higher will be defined as patients treated mainly at 10 mg BID.

Among the patients in the SAS, those who were treated at a mean daily dose of 15 mg or higher will be defined as patients treated at a higher dose level; similarly, those who were treated at a mean daily dose of <15 mg will be defined as patients treated at a lower dose level.

The mean daily dose should be calculated as:

Mean daily dose = (Total dose administered during the treatment period) / (Total number of days in the treatment period including non-dosing days)

● Patients treated for a long term

Among the patients in the SAS, those with a duration of treatment of >16 weeks are defined as patients treated for a long term.

5.4.2. Subgroups regarding patient characteristics

Subgroup analyses of safety will be performed with respect to the patient characteristics defined in Section 8.2.2.

Subgroup analyses of safety will also be performed with respect to the following factors:

- Complication of hepatic function disorder [absent or present]
- Complication of renal impairment [absent or present]
- Pediatric (<15 years), adult (≥15 to <65 years), or elderly (≥65 years)
- Past history of hepatitis B virus carrier [absent or present]
- Complication of hepatitis B virus carrier [absent or present]
- Pregnancy (present)
- Prior treatment with a 5-aminosalicylic acid preparation [absent or present]
- Prior treatment with steroid [absent or present]
- Prior treatment with an immunomodulator (azathioprine or 6-mercaptopurine) [absent or present]
- Prior treatment with tacrolimus [absent or present]
- Prior treatment with a biologic agent [absent or present]

In addition, subgroup analyses of safety will be performed for contraindicated patients (patients to whom administration of this drug may be contraindicated according to the package insert of this drug) using separately-specified criteria to extract eligible patients.

Subgroup analyses of effectiveness will be performed with respect to the following patient characteristics:

- Complication of hepatic function disorder [absent or present]
- Complication of renal impairment [absent or present]
- Pediatric (<15 years), adult (≥15 to <65 years), or elderly (≥65 years)
- Prior treatment with steroid [absent or present]
- Absence or presence of refractory UC based on treatment responsiveness [absent, steroid-resistant, steroid-dependent, present but not steroid-dependent or steroid-resistant]
- Prior treatment with an immunomodulator (azathioprine or 6-mercaptopurine) [absent or present]
- Prior treatment with tacrolimus [absent or present]
- Prior treatment with a biologic agent [absent or present]
- Effectiveness of prior biologics (no prior use, 1st line ineffective, 2nd line ineffective, indeterminate)

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

The safety endpoints and their definition in this study are presented below. Events assessed as a safety endpoint will be those that developed from the start of treatment to the end of observation period or 60

weeks after the start of treatment, whichever came first, except for malignancies, for which all events occurring by the end of observation period will be assessed as a safety endpoint.

- Adverse reactions: Adverse events considered by the physician as treatment-related
- Adverse events (AEs): All-causality AEs
- Serious adverse events (SAEs) and serious adverse reactions: AEs and adverse reactions considered by the physician as serious
- Safety specification: The definition of the events considered as an element in the safety specification of this drug should follow the definition of the Important Identified Risks and Important Potential Risks presented in the Appendix of the latest Tofacitinib Periodic Safety Update Report (PSUR). Below is the definition at the time of the preparation of this SAP (3.0 version), except for hepatitis B virus reactivation, of which definition is given in this SAP below, because it is not defined in the PSUR.
  - Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection): Events that are serious and coded as MedDRA SOC Infections and Infestations; MedDRA HLT Tuberculous infections, Mycobacteria identification and serology; MedDRA PT Febrile neutropenia, Asymptomatic COVID-19, Coronavirus infection, Coronavirus test positive, Coronavirus test, COVID-19 immunisation, COVID-19 pneumonia, COVID-19 prophylaxis, COVID-19 treatment, COVID-19, Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 antibody test, SARS-CoV-2 antibody test positive, SARS-CoV-2 carrier, SARS-CoV-2 sepsis, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, SARS-CoV-2 test, SARS-CoV-2 viraemia, or Suspected COVID-19
  - Herpes zoster: Events coded as MedDRA PT Disseminated varicella zoster virus infection, Genital herpes zoster, Herpes zoster, Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Herpes zoster pharyngitis, or Ophthalmic herpes zoster
  - Neutrophils decreased, lymphocytes decreased, and haemoglobin decreased: Events retrieved by MedDRA SMQ Haematopoietic erythropenia (Broad and Narrow); or coded as MedDRA PT Agranulocytosis, Band neutrophil count decreased, Band neutrophil percentage decreased, Cyclic neutropenia, Febrile neutropenia, Granulocyte count decreased, Granulocytopenia, Idiopathic neutropenia, Neutropenia, Neutropenic infection, Neutropenic sepsis, Neutrophil count decreased, Neutrophil percentage decreased, B-lymphocyte count decreased, Lymphocyte count decreased, Lymphopenia, T-lymphocyte count decreased, or Lymphocyte percentage decreased
  - Hepatic function disorder: Events retrieved by MedDRA SMQ Drug related hepatic disorders - severe events only (Narrow); or coded as MedDRA PT Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic enzyme increased, or Transaminases increased
  - Hepatitis B virus reactivation: Events associated with hepatitis B that developed in patients with past history of hepatitis B virus carrier or with a complication of hepatitis B virus carrier

- Gastrointestinal perforation: Events retrieved by MedDRA SMQ Gastrointestinal perforation (Narrow); or coded as MedDRA PT Abscess bacterial, Abscess rupture, Appendicectomy, Appendicitis, Biliary abscess, Colitis, Diverticulitis, Diverticulum, Gallbladder abscess, Liver abscess, Pancreatic abscess, Pelvic abscess, Perihepatic abscess, Postoperative abscess, Pyloric abscess, Rectovaginal septum abscess, Splenic abscess, or Subdiaphragmatic abscess
- Interstitial lung disease: Events retrieved by MedDRA SMQ Interstitial lung disease (Broad and Narrow)
- Venous thromboembolism: Events retrieved by MedDRA SMQ Embolic and thrombotic events, venous (Narrow)
- Malignancy: Events retrieved by MedDRA SMQ Malignancy related conditions (Narrow), Malignancy related therapeutic and diagnostic procedures (Narrow), Malignant or unspecified tumours (Narrow), or Tumour markers (Narrow)
- Cardiovascular events (including lipids increased and hyperlipidaemia): Events retrieved by MedDRA SMQ Myocardial infarction (Narrow), Other ischaemic heart disease (Narrow), or Central nervous system vascular disorders (Narrow); or coded as MedDRA PT Cardiac failure congestive, Sudden cardiac death, Cardiac death, Pulmonary embolism, Acquired mixed hyperlipidaemia, Apolipoprotein B/Apolipoprotein A-1 ratio increased, Autoimmune hyperlipidaemia, Blood cholesterol abnormal, Blood cholesterol esterase increased, Blood cholesterol increased, Blood triglycerides abnormal, Blood triglycerides increased, Diabetic dyslipidaemia, Dyslipidaemia, Familial hypertriglyceridaemia, High density lipoprotein abnormal, High density lipoprotein decreased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Hypo HDL cholesterolaemia, Intermediate density lipoprotein increased, LDL/HDL ratio increased, Lipid metabolism disorder, Lipids abnormal, Lipids increased, Lipoprotein (a) abnormal, Lipoprotein (a) increased, Low density lipoprotein abnormal, Low density lipoprotein increased, Non-high-density lipoprotein cholesterol increased, Remnant hyperlipidaemia, Remnant-like lipoprotein particles increased, Total cholesterol/HDL ratio abnormal, Total cholesterol/HDL ratio increased, Type I hyperlipidaemia, Type II hyperlipidaemia, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type III hyperlipidaemia, Type IV hyperlipidaemia, Type V hyperlipidaemia, Very low density lipoprotein abnormal, or Very low density lipoprotein increased
- Cardiovascular events (excluding lipids increased and hyperlipidaemia): Events retrieved by MedDRA SMQ Myocardial infarction (Narrow), Other ischaemic heart disease (Narrow), or Central nervous system vascular disorders (Narrow); or coded as MedDRA PT Cardiac failure congestive, Sudden cardiac death, Cardiac death, or Pulmonary embolism
- Lipids increased and hyperlipidaemia: Events coded as MedDRA PT Acquired mixed hyperlipidaemia, Apolipoprotein B/Apolipoprotein A-1 ratio increased, Autoimmune hyperlipidaemia, Blood cholesterol abnormal, Blood cholesterol esterase increased, Blood cholesterol increased, Blood triglycerides abnormal, Blood triglycerides increased, Diabetic dyslipidaemia, Dyslipidaemia, Familial hypertriglyceridaemia, High density lipoprotein abnormal, High density lipoprotein decreased, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Hypo HDL cholesterolaemia, Intermediate density lipoprotein increased, LDL/HDL ratio increased, Lipid metabolism disorder, Lipids abnormal, Lipids increased, Lipoprotein (a) abnormal, Lipoprotein (a) increased, Low density lipoprotein abnormal, Low

density lipoprotein increased, Non-high-density lipoprotein cholesterol increased, Remnant hyperlipidaemia, Remnant-like lipoprotein particles increased, Total cholesterol/HDL ratio abnormal, Total cholesterol/HDL ratio increased, Type I hyperlipidaemia, Type II hyperlipidaemia, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type III hyperlipidaemia, Type IV hyperlipidaemia, Type V hyperlipidaemia, Very low density lipoprotein abnormal, or Very low density lipoprotein increased

- Rhabdomyolysis and myopathy: Events retrieved by MedDRA SMQ Rhabdomyolysis/Myopathy (Narrow); or coded as MedDRA PT Blood creatine phosphokinase increased

- Time to onset of each element in the safety specification

6.2. Efficacy Endpoints

Effectiveness will be evaluated using the Mayo score tool. The Mayo score depends on four subscores, each of which ranges from 0-3 with higher scores indicating severer disease activity. The four subscores indicate the disease activity assessed in terms of stool frequency (score range: 0-3), rectal bleeding (0-3), mucosal appearance at endoscopy (0-3), and physician's global assessment (0-3).

The Mayo score is the sum of the four subscores and ranges from 0-12. The partial Mayo score is defined as the sum of the three of the four subscores excluding the findings of flexible sigmoidoscopy subscore and ranges from 0-9.

In addition to Mayo scores, faecal calprotectin, which highly correlates with the degree of the inflammation of UC and can be determined noninvasively and more conveniently than colonoscopic measures, will also be used to assess the effectiveness of this drug.

In this study, the partial Mayo score will be used as the primary efficacy endpoint.

- Partial Mayo score: Stool frequency subscore + rectal bleeding subscore + physician's global assessment subscore

- Mayo score: Stool frequency subscore + rectal bleeding subscore + findings of flexible sigmoidoscopy subscore + physician's global assessment subscore

- Mayo subscores

  Stool frequency:

  0 point: Normal number of stools for the patient

  1 point: 1-2 stools more than normal

  2 points: 3-4 stools more than normal

  3 points: 5 or more stools more than normal

  Rectal bleeding:

0 point: None blood seen

1 point: Slight of blood with stool less than half the time

2 points: Obvious blood with stool most of the time

3 points: Blood alone passed

Findings of flexible sigmoidoscopy:

0 point: Normal or inactive disease

1 point: Mild disease (erythema, decreased vascular pattern, mild friability)

2 points: Moderate disease (marked erythema, absent vascular pattern, any friability, erosion)

3 points: Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment:

0 point: Normal

1 point: Mild disease

2 points: Moderate disease

3 points: Severe disease

- Faecal calprotectin

6.3. Other Endpoints

Not applicable.

6.4. Covariates

Candidate covariates for the development of Serious infections (including Tuberculosis, Pneumonia, Pneumocystis pneumonia, Sepsis, and Opportunistic infection), Herpes zoster, and Malignancy considered in this study are shown below.

Covariate	Serious infections	Herpes zoster	Malignancy
Gender [reference: male]	○	○	○
Age [reference: <50 years]	○	○	○
Body weight [reference: <50 kg]	○	○	○
BMI [reference: <18.5 kg]	○	○	○
Duration of UC [reference: <2 years]	○	○	○

Covariate	Serious infections	Herpes zoster	Malignancy
Severity of UC [reference: moderate]	○	○	○
Past history (Infections) [reference: absent]	○	○	×
Past history (Malignancy) [reference: absent]	×	×	○
Past history (Lung disorder) [reference: absent]	○	×	×
Complications (Infections) [reference: absent]	○	○	×
Complications (Malignancy) [reference: absent]	×	×	○
Complications (Hepatic function disorder) [reference: absent]	○	○	○
Complications (Hepatitis B) [reference: absent]	×	×	○
Complications (Hepatitis C) [reference: absent]	×	×	○
Complications (Renal impairment) [reference: absent]	○	○	○
Complications (Diabetes mellitus) [reference: absent]	○	○	○
Smoking [reference: absent]	○	○	○
Family history of malignancy (including lymphoma) [reference: absent]	×	×	○
Prior treatment with a 5-aminosalicylic acid preparation [reference: absent]	○	○	○
Prior treatment with steroid [reference: absent]	○	○	○
Prior treatment with an immunomodulator (azathioprine, 6-mercaptopurine) [reference: absent]	○	○	○
Prior treatment with tacrolimus [reference: absent]	○	○	○
Prior treatment with a biologic agent [reference: absent]	○	○	○
Baseline neutrophil count [reference: <2000/μL]	○	○	○
Baseline lymphocyte count [reference: <1000/μL]	○	○	○
Prior vaccination with a herpes zoster vaccine [reference: absent]	○	○	×
Prior vaccination with a pneumococcal vaccine [reference: absent]	○	×	×
Prior vaccination with a tuberculosis vaccine [reference: absent]	○	×	×
Prior vaccination with a pneumocystis jirovecii pneumonia vaccine [reference: absent]	○	×	×
Prior vaccination with a hepatitis B vaccine [reference: absent]	○	×	×

○: Applied, ×: Not applied

Additional covariates may be included or some deleted after consideration based on an interim analysis of this study or emerging knowledge. If this will occur, this SAP will be revised.

7. HANDLING OF MISSING DATA

If the date of the end of the treatment with this drug is missing, the date of the last observation recorded in the CRF entry “Status of the treatment with Xeljanz” will be used instead. Treatment completers whose end-of-treatment date has not been recorded will be handled in a way that the treatment continued until the last observation date.

Similarly, if the date of the end of a drug therapy or non-drug therapy is missing, the date of the last observation will be used instead.

If the severity, action taken, or outcome for an AE is missing, it will be treated as "unknown" when summarizing data.

If an efficacy endpoint was not measured within its visit window (Appendix 1), it will be treated as missing data and no imputation will be done. The partial Mayo score will be treated as missing data unless the stool frequency subscore, rectal bleeding subscore, and physician's global assessment subscore have all been measured. Similarly, the Mayo score will be treated as missing data unless the stool frequency subscore, rectal bleeding subscore, findings of flexible sigmoidoscopy subscore, and physician's global assessment subscore have all been measured.

Cleaning-uncompleted data will be in principle handled as follows:

- Items for which data are missing: For both purposes of summarization and listing, the corresponding data will be treated as missing data (or as "unknown" if they are a categorical variable).
- Items for which data are inconsistent: For both purposes of summarization and listing, the inconsistent data will be treated as missing data. A list of how each set of inconsistent data have been handled will be presented separately.
- No signature: For both purposes of summarization and listing, any record in a CRF with no signature of a contract physician (including when the CRF is signed only by individuals other than contract physicians) will be treated as missing data.

With regard to analyses that involve the time to onset of each element in the safety specification, if development of an event has been reported in a patient but its onset date is unknown, the onset date will be imputed with the last date on which the patient can be confirmed to be free from the event in view of all kinds of data collected; the shortest possible date imputed may be the start date of treatment. For patients in whom development has not been reported but the date of the end of observation is unknown, the end date will be imputed with the last date on which administration of this drug can be confirmed in view of all kinds of data collected; the shortest possible date imputed may be the start date of treatment.

Missing data (including the case of "unknown") for candidate covariates (Section 6.4) will not be imputed in univariate analyses. For multivariate analyses, missing data for candidate covariates will be treated as a subcategory of the category "unknown".

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous variables

For continuous variables, summary statistics (n, mean, standard deviation [SD], median, maximum, minimum) will be presented.

8.1.2. Categorical variables

For categorical variables, patients (or another kind of relevant elements) included in each category will be summarized in terms of n and proportion.

8.1.3. Binary variables

For binary variables, patients included in each binary category will be summarized in terms of n and proportion. The two-sided 95% confidence interval (CI) will be determined using an exact method if a CI should be determined for the proportion.

When comparisons of the proportion should be made between subgroups, their risk ratios (RRs) will be presented with corresponding 95% CIs. Each RR and its 95% CI will also be presented graphically (See Appendix 2).

8.1.4. Analyses based on the person-year method

The incidence of an event per exposure duration will, if it should be presented, be calculated using the following formula:

Incidence (patients/100 patient-year) = $100 \times y/PT$

y: Number of patients who experienced the event

PT: Total exposure duration (years),

Here the exposure duration for event-free patients will be given by the period from the start of treatment to the end of the observation period unless this exceeds 60 weeks; if this period exceeds 60 weeks, the exposure duration should be 60 weeks. The exposure duration for patients who experienced the event is, in principle, the period from the start of treatment to the day the event was first observed, but if the event occurred 60 weeks or later after the start of treatment, the patient will be handled as an event-free patient and their exposure duration should be 60 weeks. For malignancy, however, no such upper limit will be set; the exposure duration for malignancy-free patients will be the period from the start of treatment to the end of the observation period, while the exposure duration for patients in whom malignancy developed will be the period from the start of treatment to the day of the first observation of the event. The 95% CI will be calculated using the following formula:

$$\left[\frac{100}{PT}\times\frac{1}{2}\chi^2_{2y}(\alpha/2),\ \frac{100}{PT}\times\frac{1}{2}\chi^2_{2(y+1)}(1-\alpha/2)\right]$$

y: Number of observed events

$\chi^2_{2y}(\alpha/2)$: The $\alpha/2$-fractile point of the chi-square distribution with $2y$ degrees of freedom

8.1.5. Analyses of time-to-event data

Kaplan-Meier plots will be presented for time-to-event data. Event-free patients will be censored at the end of their observation period or 60 weeks after the start of treatment, whichever came first. If the time to event exceeds 60 weeks, the patient will be treated as event-free and censored at 60 weeks. For malignancy, however, no such upper limit will be set for the time to onset, and malignancy-free patients will be censored at the end of their observation period.

8.2. Statistical Analyses

8.2.1. Patient description

- **Summarization of Participating Sites and Patients by Type of Site**

Using data from CRF-collected patients, sites and patients will be summarized in terms of n and proportion by type of site, with possible types defined below:

- National, public, or private university hospital
- National hospital established by the Ministry of Health, Labour and Welfare (MHLW)
- Prefectural or municipal hospital
- Public institution
- Hospital other than the four types above that has been established by a corporation or individual
- Clinic or practice

In addition, the mean, minimum, and maximum number of patients per site will be presented.

- **Constitution of patients**

Using data from registered patients, the number of registered patients, observation-completed patients, patients included in the SAS (including the numbers by mean daily dose), patients treated for a long term (including subgroups by mean daily dose) and patients included in the EAS will be presented. In addition, the number of CRF-uncollected patients, patients excluded from the SAS, patients excluded from the SAS for each category of reason for exclusion, patients excluded from the EAS, and patients excluded from the EAS for each category of reason for exclusion will be presented.

- **Completion of treatment or reason for discontinuation**

Using the SAS (including the subgroups by mean daily dose), set of patients treated for a long term (including the subgroups by mean daily dose), and EAS, patients who discontinued the treatment with this

drug will be summarized in terms of n and proportion by time of discontinuation [≤8 weeks, >8 to ≤16 weeks, >16 to ≤26 weeks, >26 to ≤60 weeks, >60 weeks], and patients who completed the treatment with this drug will be summarized in terms of n and proportion. In addition, patients who discontinued the treatment will be summarized in terms of n and proportion by reason for discontinuation.

- **Listing of patients excluded from analyses**

Patients excluded from the SAS will be listed in tabular form with their reason for exclusion. Similarly, patients excluded from the EAS will be listed in tabular form with their reason for exclusion.

8.2.2. Patient characteristics and medical history

- **Patient characteristics**

Using the SAS (including subgroups by mean daily dose), set of patients treated for a long term (including subgroups by mean daily dose), and EAS, patients will be, according to the methods described in Section 8.1, summarized with respect to the following patient characteristics:

- Gender [male, female]
- Age (continuous)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Age [<50 years, ≥50 to <65 years, ≥65 years]
- Body weight (continuous)
- Body weight [<50 kg, ≥50 to <60 kg, ≥60 to <70 kg, ≥70 kg]
- BMI (continuous)
- BMI [<18.5, ≥18.5 to <25, ≥25]
- Diagnosis [ulcerative colitis, other]
- Duration of UC (continuous)
- Duration of UC [<2 years, ≥2 to <5 years, ≥5 to <10 years, ≥10 to <20 years, ≥20 years]
- Range of UC [pancolitis, left-sided disease, proctitis, right-sided or segmental disease, other]
- Severity of UC [mild, moderate, severe]
- Refractory UC based on treatment responsiveness [absent, present]
- Refractory UC based on treatment responsiveness [absent, steroid-resistant, steroid-dependent, present but not steroid-resistant or steroid-dependent]
- Past history [absent, present]
- Infections [absent, present]
- Past history of malignancy [absent, present]
- Past history of an autoimmune disease [absent, present]
- Past history of a cardiovascular disease [absent, present]
- Past history of lung disorder [absent, present]
- Past history of gastrointestinal disorder [absent, present]
- Past history of hepatic function disorder [absent, present]
- Hepatic function disorder: past history of hepatitis B [absent, present]
- Hepatic function disorder: past history of hepatitis C [absent, present]
- Hepatic function disorder: past history of hepatitis B virus carrier [absent, present]

- Hepatic function disorder: past history of hepatitis C virus carrier [absent, present]
- Past history of renal impairment [absent, present]
- Past history of metabolic abnormality [absent, present]
- Metabolic abnormality: past history of diabetes mellitus [absent, present]
- Past history of anaemia [absent, present]
- Complications [absent, present]
- Complication of an infection [absent, present]
- Complication of malignancy [absent, present]
- Complication of an autoimmune disease [absent, present]
- Complication of a cardiovascular disease [absent, present]
- Complication of lung disorder [absent, present]
- Complication of gastrointestinal disorder [absent, present]
- Complication of hepatic function disorder [absent, present]
- Complication of hepatic function disorder: hepatitis B [absent, present]
- Complication of hepatic function disorder: hepatitis C [absent, present]
- Complication of hepatic function disorder: hepatitis B virus carrier [absent, present]
- Complication of hepatic function disorder: hepatitis C virus carrier [absent, present]
- Complication of renal impairment [absent, present]
- Complication of metabolic abnormality [absent, present]
- Complication of metabolic abnormality: diabetes mellitus [absent, present]
- Complication of anaemia [absent, present]
- Smoking [non-smoker, former smoker, present smoker, unknown]
- Family history of malignancy (including lymphoma) [absent, present, unknown]
- Family history of malignancy (including lymphoma) [absent, present (colorectal cancer absent), present (colorectal cancer present), present (colorectal cancer unknown), unknown]
- Prior treatment with a biologic agent [absent, present, unknown]
- Prior treatment with a biologic agent [absent, infliximab, adalimumab, golimumab, other, unknown]
- Effectiveness of prior biologics (no prior use, 1st line ineffective, 2nd line ineffective, prior use unknown)
- Baseline partial Mayo score (continuous)
- Baseline Mayo score (continuous)
- Baseline Mayo score [<6, ≥6]
- Baseline stool frequency subscore [0, 1, 2, 3]
- Baseline rectal bleeding subscore [0, 1, 2, 3]
- Baseline findings of flexible sigmoidoscopy subscore [0, 1, 2, 3]
- Baseline physician's global assessment subscore [0, 1, 2, 3]
- Baseline faecal calprotectin [≤50 mg/kg, >50 to ≤300 mg/kg, >300 mg/kg, not tested]
- Starting daily dose of Xeljanz [5 mg, 10 mg, 15 mg, 20 mg, >20 mg]
- Prior treatment with a 5-aminosalicylic acid preparation [absent, present]
- Prior treatment with steroid [absent, present]
- Prior treatment with azathioprine [absent, present]
- Prior treatment with 6-mercaptopurine [absent, present]

- Prior treatment with an immunomodulator (azathioprine or 6-mercaptopurine) [absent, present]
- Prior treatment with tacrolimus [absent, present]
- Prior treatment with infliximab [absent, present]
- Prior treatment with adalimumab [absent, present]
- Prior treatment with golimumab [absent, present]
- Prior vaccination with a herpes zoster vaccine [absent, present]
- Prior vaccination with a pneumococcal vaccine [absent, present]
- Prior vaccination with a tuberculosis vaccine [absent, present]
- Prior vaccination with a pneumocystis jirovecii pneumonia vaccine [absent, present]
- Prior vaccination with a hepatitis B vaccine [absent, present]
- Prior treatment with a non-drug therapy [absent, present]
- Prior treatment with a non-drug therapy: blood cell component removal therapy [absent, present]
- Prior treatment with a non-drug therapy: surgery [absent, present]
- Baseline neutrophil count [<2000/μL, ≥2000/μL, not tested]
- Baseline lymphocyte count [<1000/μL, ≥1000/μL, not tested]
- Baseline hemoglobin [<8 g/dL, ≥8 g/dL, not tested]

Using the SAS, patients will be summarized according to the following factors in terms of n and proportion by SOC and PT:

- Past history (diseases and syndromes recorded as past history in the CRF entry “Medical history”)
- Complications (diseases and syndromes recorded as present illness in the CRF entry “Medical history”)

Using the SAS, patients will be summarized according to the following factors in terms of n and proportion:

- Pre-treatment testing for hepatitis virus [absent, present]
- Pre-treatment HBs antigen test [positive, negative, not tested]
- Pre-treatment HBs antibody test [positive, negative, not tested]
- Pre-treatment HBc antigen test [positive, negative, not tested]
- Pre-treatment HCV antibody test [positive, negative, not tested]
- Pre-treatment imaging [absent, present]
- Pre-treatment imaging: chest X-ray [normal, abnormal, not tested]
- Pre-treatment imaging: chest CT [normal, abnormal, not tested]
- Pre-treatment interferon gamma release assay [absent, present]
- Pre-treatment interferon gamma release assay: QuantiFERON [positive, equivocal, negative, indeterminate, not tested]
- Pre-treatment interferon gamma release assay: T-Spot. TB [positive, equivocal, negative, indeterminate, not tested]
- Pre-treatment tuberculin reaction [-, 1+, 2+, 3+, indeterminate, not tested]
- Pre-treatment diastolic blood pressure [<60 mmHg, ≥60 to <80 mmHg, ≥80 to <100 mmHg, ≥100 to <120 mmHg, ≥120 mmHg, not measured]

- Pre-treatment systolic blood pressure [<120 mmHg, ≥120 to <140 mmHg, ≥140 to <160 mmHg, ≥160 to <180 mmHg, ≥180 mmHg, not measured]

Using the SAS and EAS, a breakdown of patients by each of the following factors will be presented in terms of n and proportion. Concomitant medications and non-drug therapies will be defined in align with the data collection period for adverse reactions and AEs so that relationship to adverse reactions and AEs can be assessed.

- Concomitant medications (drugs recorded in the CRF entry "Drug therapies for UC – prior treatment and concomitant therapies" that were used in the period from the start of the treatment with this drug to the discontinuation of treatment or 60 weeks after the start of treatment, whichever came first)
- Non-drug therapies (non-drug therapies recorded in the CRF entry "Non-drug therapies for UC – prior treatment and concomitant therapies" that were used in the period from the start of the treatment with this drug to the discontinuation of treatment or 60 weeks after the start of treatment, whichever came first)
- Prior medications (medications recorded in the CRF entry "Past history of treatment for UC – biological therapeutics", and medications recorded in the CRF entry "Drug therapies for UC – prior treatment and concomitant therapies" of which administration had been started by the day before the start of the treatment with this drug)

- **Dosing status of Xeljanz tablets**

Using the SAS (including the subgroups by mean daily dose) and the set of patients treated for a long term (including the subgroups by mean daily dose), dosing data for this drug will be summarized with respect to the following aspects:

- Starting daily dose [5 mg, 10 mg, 15 mg, 20 mg, >20 mg]
- Duration of treatment [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks]
- Total duration of treatment (patient-years) [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks] (The total duration of treatment in each category and the accumulated total duration of treatment will be presented.)
- Mean daily dose by duration of treatment (mg) (summary statistics) [<15 mg, ≥15 mg] [<17 mg, ≥17 mg], with the following categories for the duration of treatment:
  - Any duration of treatment
  - Duration of treatment ≤15 weeks
  - Duration of treatment >15 to ≤30 weeks
  - Duration of treatment >30 to ≤45 weeks
  - Duration of treatment >45 to ≤60 weeks
  - Duration of treatment >60 to ≤75 weeks
  - Duration of treatment >75 to ≤90 weeks

- Duration of treatment >90 to ≤105 weeks
- Duration of treatment >105 to ≤120 weeks
- Duration of treatment >120 to ≤135 weeks
- Duration of treatment >135 weeks

The duration of treatment is defined as the period from the start date of the treatment with this drug to the last observed administration date of this drug, including non-dosing days.

8.2.3. Safety analyses

Adverse reactions or AEs included in a summarization will be those that developed from the start of treatment to the end of the observation period or 60 weeks after the start of treatment, whichever came first, except for malignancy, for which all events occurring by the end of observation period will be included in a summarization. All adverse reactions and AEs reported in this study will be included in a listing.

8.2.3.1. Adverse reactions

- **All adverse reactions**

Adverse reactions will be summarized by SOC and PT in terms of number and proportion of patients.

- **Serious adverse reactions**

Serious adverse reactions will be summarized by SOC and PT in terms of number and proportion of patients.

- **Details of adverse reactions**

Adverse reactions in different categories defined with respect to the following factors will be summarized by SOC and PT in terms of number and proportion of patients. For the factor time to onset, the number of patients who took at least one dose during each time category will be used as the denominator to calculate the proportion.

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Time to onset [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks]
- Action taken [permanent discontinuation of treatment, temporary discontinuation or dose reduction, dose increase, no change]
- Outcome [not recovered, resolved/recovered, recovered with sequelae, improved, death, unknown]

Patients who experienced multiple adverse reactions of the same adverse reaction (identical PT) will be summarized as follows:

- For seriousness: Patients who experienced both serious and non-serious adverse reactions of the same PT will be handled as having experienced a serious event.
- For known/unknown: Priority will be given to "unknown" if both experienced.
- For time to onset: The day to the first onset will be used.
- For action taken: If multiple actions were taken, only one kind of action will be adopted with the order of priority being permanent discontinuation, temporary discontinuation/dose reduction, and other (no change or dose increase).
- For outcome: The outcome for the last event will be used.

- **Safety specification**

The following adverse reactions included in the scope of the safety specification will be summarized in terms of number and proportion of patients, as well as incidence and its 95% CI.

- Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection)
- Herpes zoster
- Neutrophils decreased, lymphocytes decreased, haemoglobin decreased
- Hepatic function disorder
- Hepatitis B virus reactivation (in patients with past history or complication of hepatitis B virus carrier)
- Gastrointestinal perforation
- Interstitial lung diseases
- Venous thromboembolism
- Malignancy
- Cardiovascular events (including lipids increased and hyperlipidaemia)
- Cardiovascular events (excluding lipids increased and hyperlipidaemia)
- Lipids increased and hyperlipidaemia
- Rhabdomyolysis and myopathy

In addition, patients who experienced adverse reactions in the scope of the safety specification will be summarized in terms of n and proportion by SOC and PT, for different kinds of action taken and outcome.

- **Timing of onset of elements in the safety specification**

Patients who experienced adverse reactions of each element in the safety specification will be summarized by timing of first onset, in terms of n and proportion as well as incidence and its 95% CI. For the purpose of summarization by time to onset, the denominator to calculate the proportion will be the number of patients who took at least one dose during each time category, and the denominator to calculate the incidence will be the duration of exposure in each time category. The categories for onset timing will be given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks], except for malignancy, for which given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks].

- **Relationship between concomitant drugs and adverse reactions**

To investigate the relationship between concomitant biologics/immunosuppressants or concomitant CYP3A4 inhibitors/CYP2C19 inhibitors and adverse reactions included in the scope of the safety specification, development of those adverse reactions will be summarized in patients with and without concomitant use of a biologic/immunosuppressant and in patients with and without concomitant use of a CYP3A4 inhibitor/CYP2C19 inhibitor, by PT in terms of number of patients. Concomitant drugs used after the first onset of a target event will be excluded from the summarization. Concomitant drugs considered in this investigation include:

- Biologics (including recombinants)/immunosuppressants: abatacept, adalimumab, anakinra, azathioprine, baminercept, canakinumab, certolizumab, certolizumab pegol, cyclosporine, efalizumab, etanercept, golimumab, infliximab, ofatumumab, rituximab, Syk kinase inhibitors, tacrolimus hydrate, tocilizumab, sarilumab, zanolimumab, vedolizumab, ustekinumab, secukinumab, ixekizumab, and 6-mercaptopurine
- CYP3A4 inhibitors/CYP2C19 inhibitors: clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, tacrolimus hydrate, cyclosporine, amitriptyline, clomipramine, fluconazole, fluvoxamine, imipramine, ticlopidine, esomeprazole, fluoxetine, moclobemide, omeprazole, and voriconazole

- **Adverse reactions in patients excluded from and included in the SAS**

Adverse reactions occurring in CRF-collected patients who are excluded from the SAS will be listed in tabular form. In addition, adverse reactions occurring in patients included in the SAS and in patients excluded from the SAS will be summarized by SOC and PT in terms of n and proportion of patients.

8.2.3.2. Adverse events

- **All adverse events**

Adverse events will be summarized by SOC and PT in terms of number and proportion of patients.

- **Serious and non-serious adverse events**

SAEs will be summarized by SOC and PT in terms of number and proportion of patients. Similarly, non-serious AEs will be summarized by SOC and PT in terms of number and proportion of patients.

- **Safety specification**

The following AEs included in the scope of the safety specification will be summarized in terms of number and its proportion of patients, as well as incidence and its 95% CI.

- Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection)
- Herpes zoster
- Neutrophils decreased, lymphocytes decreased, haemoglobin decreased
- Hepatic function disorder

- Hepatitis B virus reactivation (in patients with past history or complication of hepatitis B virus carrier)
- Gastrointestinal perforation
- Interstitial lung diseases
- Venous thromboembolism
- Malignancy
- Cardiovascular events (including lipids increased and hyperlipidaemia)
- Cardiovascular events (excluding lipids increased and hyperlipidaemia)
- Lipids increased and hyperlipidaemia
- Rhabdomyolysis and myopathy

In addition, patients who experienced AEs in the scope of the safety specification will be summarized in terms of n and proportion by SOC and PT, for different kinds of action taken and outcome.

- **Timing of onset of elements in the safety specification**

Patients who experienced AEs of each element in the safety specification will be summarized by timing of first onset, in terms of n and proportion as well as incidence and its 95% CI. For the purpose of summarization by time to onset, the denominator to calculate the proportion will be the number of patients who took at least one dose during each time category, and the denominator to calculate the incidence will be the duration of exposure in each time category. The categories for onset timing will be given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks], except for malignancy, for which given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks].

- **Relationship between concomitant drugs and adverse events**

To investigate the relationship between concomitant biologics/immunosuppressants or concomitant CYP3A4 inhibitors/CYP2C19 inhibitors and AEs included in the scope of the safety specification, development of those AEs will be summarized in patients with and without concomitant use of a biologic/immunosuppressant and in patients with and without concomitant use of a CYP3A4 inhibitor/CYP2C19 inhibitor, by PT in terms of number of patients. Concomitant drugs used after the first onset of a target event will be excluded from the summarization. Concomitant drugs considered in this investigation include:

- Biologics (including recombinants)/immunosuppressants: abatacept, adalimumab, anakinra, azathioprine, baminercept, canakinumab, certolizumab, certolizumab pegol, cyclosporine, efalizumab, etanercept, golimumab, infliximab, ofatumumab, rituximab, Syk kinase inhibitors, tacrolimus hydrate, tocilizumab, sarilumab, zanolimumab, vedolizumab, ustekinumab, secukinumab, ixekizumab, and 6-mercaptopurine
- CYP3A4 inhibitors/CYP2C19 inhibitors: clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, tacrolimus hydrate, cyclosporine, amitriptyline, clomipramine, fluconazole, fluvoxamine, imipramine, ticlopidine, esomeprazole, fluoxetine, moclobemide, omeprazole, and voriconazole

8.2.3.3. Subgroup analyses

- **Analyses by dosage subgroup**

(1) Safety analysis of the treatment with 10 mg BID

To evaluate the safety of the treatment with this drug administered mainly at a dose of 10 mg BID, the following analyses will be performed in the patients treated mainly at 10 mg BID defined in Section 5.4.1 and results will be compared with those in the entire SAS. To eliminate the effect of including patients who discontinued treatment during the induction phase, similar analyses will also be performed in patients treated mainly at 10 mg BID for a long term and results will be compared with those in the patients treated for a long term defined in Section 5.4.1:

● Adverse reactions of each element in the safety specification will be summarized in terms of number and proportion of patients as well as incidence and its 95% CI.

● Adverse reactions will be summarized by SOC and PT in terms of number and proportion of patients.

In addition, to investigate the temporal change in the risk of occurrence of each event, the following analyses will be performed in the patients treated mainly at 10 mg BID and results will be compared with those in the SAS:

● Patients who experienced adverse reactions of each element in the safety specification will be summarized by timing of first onset, in terms of n and proportion as well as incidence and its 95% CI. For the purpose of summarization by time to onset, the denominator to calculate the proportion will be the number of patients who took at least one dose during each time category, and the denominator to calculate the incidence will be the duration of exposure in each time category. The categories for onset timing will be given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks], except for malignancy, for which given by [≤15 weeks, >15 to ≤30 weeks, >30 to ≤45 weeks, >45 to ≤60 weeks, >60 to ≤75 weeks, >75 to ≤90 weeks, >90 to ≤105 weeks, >105 to ≤120 weeks, >120 to ≤135 weeks, >135 weeks].

● A Kaplan-Meier plot will be presented for the time to first onset of each element in the safety specification.

(2) Evaluation of dose response of the safety

To evaluate the dose-response relationship concerning the safety of the treatment with this drug, the following analyses will be performed in the patients treated at a higher dose level defined in Section 5.4.1 and in the patients treated at a lower dose level. To eliminate the effect of including patients who discontinued treatment during the induction phase, similar analyses will also be performed in patients treated at a higher dose level for a long term and in patients treated at a lower dose level for a long term:

● Adverse reactions of each element in the safety specification will be summarized in terms of number and proportion of patients as well as incidence and its 95% CI. In addition, the risk ratio and risk difference with their 95% CI will be presented for the patients treated at a higher dose level compared with those at a lower dose level.

● Adverse reactions will be summarized by SOC and PT in terms of number and proportion of patients.

In addition, to investigate the temporal change in the risk of the occurrence of each event, the following analyses will be performed in the patients treated at a higher dose level and patients treated at a lower dose level:

● Patients who experienced adverse reactions of each element in the safety specification will be summarized by timing of first onset, in terms of n and proportion as well as incidence and its 95% CI. As for the denominator to calculate the proportion, the denominator to calculate the incidence, and the categories used for onset timing, the corresponding descriptions in (1) should be followed.

● A Kaplan-Meier plot will be presented for the time to first onset of any adverse reaction included in each element in the safety specification.

- **Subgroup analyses regarding patient characteristics**

According to Section 8.1.3, the risk ratio based on the proportion of patients who experienced adverse reactions of each element in the safety specification will be determined and graphically presented for different subgroups regarding each of the patient factors defined in Section 8.2.2 in which events developed in ≥10 patients. Risk ratios will not be calculated for subgroups in which events developed in <10 patients.

For each relevant subgroup defined in Section 5.4.2, patients who experienced adverse reactions will be summarized by SOC and PT in terms of n and proportion.

Adverse reactions that developed in patients with a contraindication to Xeljanz will be listed in tabular form. Patients with a contraindication to Xeljanz who experienced adverse reactions will be summarized by SOC and PT in terms of n and proportion, as necessary.

CCI [redacted]

8.2.4. Effectiveness analyses

In this study, the proportion of patients who achieved the remission based on the partial Mayo score will be the primary effectiveness endpoint.

8.2.4.1. Effectiveness assessment based on the partial Mayo score

● Proportions of patients who achieved study endpoints based on the partial Mayo score

The proportion of patients who achieved each study endpoint based on the partial Mayo score (remission or clinical response) will be calculated with its 95% CI for each study visit. The definition of the study visits should follow “10.1. Appendix 1: Details of Data Handling”.

The definition of the endpoints based on the partial Mayo score is shown in Table 1.

Table 1. Endpoints Based on the Partial Mayo Score

Endpoint	Definition
Remission based on the partial Mayo score	The patient is called to have achieved remission if they meet all the following criteria: ● Partial Mayo score ≤2 ● Stool frequency subscore ≤1 ● Rectal bleeding subscore ≤1 ● Physician's global assessment subscore ≤1
Clinical response based on the partial Mayo score	● The decrease from baseline in the partial Mayo score ≥2

● Changes in the partial Mayo score

Summary statistics will be presented for each study visit regarding the partial Mayo score and the change from baseline in the partial Mayo score. For the change from baseline, its 95% CI will also be presented. The definition of the study visits should follow "10.1. Appendix 1: Details of Data Handling".

8.2.4.2. Effectiveness assessment based on the Mayo score

● Proportions of patients who achieved the responses based on the partial Mayo score

The proportion of patients who achieved each response based on the Mayo score (remission, mucosal healing, clinical response, clinical remission, endoscopic response, endoscopic remission, symptomatic remission, or deep remission) will be calculated with its 95% CI for each study visit. The definition of the study visits should follow "10.1. Appendix 1: Details of Data Handling".

The definition of the endpoints based on the Mayo score is shown in Table 2.

Table 2. Endpoints Based on the Mayo Score

Endpoint	Definition
Remission	The patient is called to have achieved remission if they meet all the following criteria: ● Mayo score ≤2 ● All Mayo subscores ≤1 ● Rectal bleeding subscore = 0
Mucosal healing	● Findings of flexible sigmoidoscopy subscore ≤1
Clinical response	The patient is called to have achieved clinical response if they meet all the following criteria: ● The decrease from baseline in the Mayo score ≥3 and ≥30% ● Rectal bleeding subscore ≤1 or the decrease from baseline in the rectal bleeding subscore ≥1

Table 2. Endpoints Based on the Mayo Score

Endpoint	Definition
Clinical remission	The patient is called to have achieved clinical remission if they meet all the following criteria: ● Mayo score ≤2 ● All subscores ≤1
Endoscopic response	● The decrease from baseline in the findings of flexible sigmoidoscopy subscore ≥1
Endoscopic remission	● Findings of flexible sigmoidoscopy subscore = 0
Symptomatic remission	The patient is called to have achieved symptomatic remission if they meet all the following criteria: ● Mayo score ≤2 ● All subscores ≤1 ● Rectal bleeding subscore = 0 ● Stool frequency subscore = 0
Deep remission	The patient is called to have achieved deep remission if they meet all the following criteria: ● Mayo score ≤2 ● All subscores ≤1 ● Rectal bleeding subscore = 0 ● Findings of flexible sigmoidoscopy subscore = 0

● Changes in the Mayo score

Summary statistics will be presented for each study visit regarding the Mayo score and the change from baseline in the Mayo score. For the change from baseline, its 95% CI will also be presented. The definition of the study visits should follow “10.1. Appendix 1: Details of Data Handling”.

8.2.4.3. Effectiveness assessment based on individual Mayo subscores

● Changes in each Mayo subscore

Summary statistics will be presented for each study visit regarding each Mayo subscore and the change from baseline in the Mayo subscore. For the change from baseline, its 95% CI will also be presented. The definition of the study visits should follow “10.1. Appendix 1: Details of Data Handling”.

8.2.4.4. Changes in faecal calprotectin

Summary statistics will be presented for each study visit regarding the faecal calprotectin level and the change from baseline in the faecal calprotectin level. For the change from baseline, its 95% CI will also be presented. The definition of the study visits should follow “10.1. Appendix 1: Details of Data Handling”.

8.2.4.5. Subgroup analyses

For each relevant subgroup defined in Section 5.4.2, the proportion of patients who achieved the remission based on the partial Mayo score at the end of treatment will be analyzed.

CCI [redacted]

[redacted]

9. LISTINGS

The following patients and events will be listed in tabular form:

- Patients included in the study
- Patients who experienced AEs
- Patients who experienced adverse reactions
- Patients excluded from the safety analysis who experienced adverse reactions
- Patients with a contraindication to this drug who experienced adverse reactions
- Patients who experienced serious adverse reactions
- Patients who experienced SAEs
- Patients with hepatic impairment who experienced adverse reactions
- Patients with renal impairment who experienced adverse reactions
- Aged patients who experienced adverse reactions
- Events included in the scope of the safety specification
- AEs considered as out of collection-period

The following documents required for application of re-examination (of which forms are presented in PSEHB/PED Notification No. 1128-2 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated November 28, 2017) will also be prepared.

- Attachment Form 2 (Development Status of Adverse Reactions/Infections by the Time of Approval)
- Attachment Form 12 (Development Status of Adverse Reactions/Infections in an Additional Pharmacovigilance Plan)
- Attachment Form 15 (Development Status of Adverse Reactions/Infections in Post-marketing Surveillance etc.)
- Attachment Form 16 (Summary of Patients Reported in Post-marketing Surveillance etc.)

In addition, the following documents required for periodic safety reporting (of which forms are presented in Joint PSEHB/PED Notification No. 1128-5 issued by the Director of the PDE, PSEHB, MHLW and the Director of Pharmaceutical Safety Division, PSEHB, MHLW dated November 28, 2017) will be prepared for the purpose of periodic safety reporting.

- Attachment Form 1-2 (Development Status of Adverse Reactions/Infections by the Time of Approval)
- Attachment Form 2 (Development Status of Adverse Reactions/Infections in Post-marketing Surveillance etc.)

10. APPENDICES

10.1. Appendix 1: Details of Data Handling

A1.1 Definition of Study Visits 1

For the endpoints the partial Mayo score, stool frequency subscore, rectal bleeding subscore, and physician's global assessment subscore, the study visits are defined as follows:

Visit	Definition [time window]
Baseline	From 6 months before Day 1 (= the day of first dose of Xeljanz in this study = the day of the start of treatment) to Day 1 (pretreatment)
Week 2	Day 2 to Day 22
Week 4	Day 23 to Day 43
Week 8	Day 44 to Day 71
Week 12	Day 72 to Day 99
Week 16	Day 100 to Day 141
Week 24	Day 142 to Day 197
Week 32	Day 198 to Day 253
Week 40	Day 254 to Day 309
Week 48	Day 310 to Day 379
Week 60	Day 380 to Day 463
End of treatment	From 2 weeks before to 2 weeks after the day of last dose If the day two weeks before the last dose is Day 1 or earlier, the time window is from Day 2 to 2 weeks after the day of last dose.

A1.2 Definition of Study Visits 2

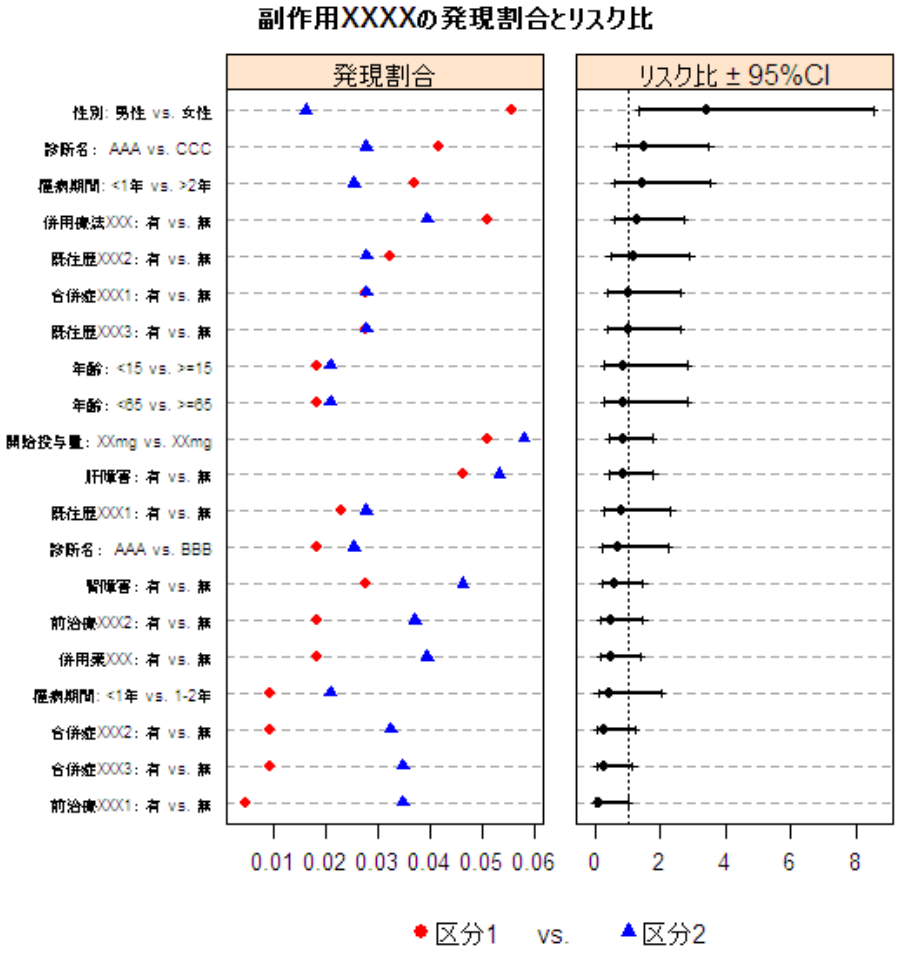
For the endpoints the Mayo score, findings of flexible sigmoidoscopy subscore, and faecal calprotectin, the study visits are defined as follows:

Visit	Definition [time window]
Baseline	From 6 months (or 3 months for faecal calprotectin) before Day 1 (= the day of first dose of Xeljanz in this study = the day of the start of treatment) to Day 1 (pretreatment)
Week 8	Day 2 to Day 85
Week 16	Day 86 to Day 141
Week 24	Day 142 to Day 197

Visit	Definition [time window]
Week 32	Day 198 to Day 253
Week 40	Day 254 to Day 309
Week 48	Day 310 to Day 379
Week 60	Day 380 to Day 463
End of treatment	From 2 weeks before to 2 weeks after the day of last dosing If the day two weeks before the last dose is Day 1 or earlier, the time window is from Day 2 to 2 weeks after the day of last dose.

10.2. Appendix 2: Example of Tabulated and Graphical Presentations of Risk Ratios Regarding the Proportion of Patients with an Adverse Reaction in Different Subgroups

事象名：XXXの上昇	区分1		区分2		リスク比（RR）	
	例数/N	(%)	例数/N	(%)	RR	95 %CI
性別（男性 vs. 女性）	18/ 2220	(0.8)	3/ 1099	(0.3)	2.97	(0.88 - 10.06)
65歳以上 vs. 65歳未満	19/ 2788	(0.7)	2/ 531	(0.4)	1.81	(0.42 - 7.74)
診断（疾患A vs.疾患B）	3/ 221	(1.4)	18/ 3098	(0.6)	2.34	(0.69 - 7.87)
罹病期間（1年未満 vs. 1年以上）	9/ 771	(1.2)	7/ 866	(0.8)	1.44	(0.54 - 3.86)
薬剤A 併用（あり vs. なし）	9/ 798	(1.1)	12/ 2521	(0.5)	2.37	(1.00 - 5.60)
薬剤A 前治療（あり vs. なし）	1/ 148	(0.7)	20/ 3171	(0.6)	1.07	(0.14 - 7.93)
疾患B 合併（あり vs. なし）	16/ 1614	(1.0)	5/ 1703	(0.3)	3.38	(1.24 - 9.20)
疾患B 既往（あり vs. なし）	7/ 674	(1.0)	14/ 2643	(0.5)	1.96	(0.79 - 4.84)
肝障害（あり vs. なし）	0/ 80		18/ 2056	(0.9)		
腎障害（あり vs. なし）	1/ 140	(0.7)	17/ 2004	(0.8)	0.84	(0.11 - 6.28)



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