XELJANZ® Tablets 5 mg Special Investigation

(Investigation of Long-term Use in Patients with Ulcerative Colitis)

STUDY PROTOCOL SYNOPSIS

Pfizer Inc.

STUDY INFORMATION

Title	XELJANZ® Tablets 5 mg Special Investigation (Investigation of Long-term Use in Patients with Ulcerative Colitis)
Protocol number	A3921248
Protocol version identifier	Version 5
Date of last version of protocol	17 September, 2019 (Version 4)
Active substance	Tofacitinib citrate
Medicinal product	XELJANZ® Tablets 5 mg
Research question and objectives	This investigation aims to examine the safety and effectiveness of XELJANZ Tablets in post-marketing clinical settings when it is administered chronically to patients with ulcerative colitis.
Author	PPD

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1. LIST OF ABBREVIATIONS

acronym	Tittle
k4ST (GOT)	aspartate transaminase
k4LT (GPT)	alanine transaminase
k4L-P	alkaline phosphatase
[DH	lactate dehydrogenase isozyme
'iHDL-C	high-density lipoprotein cholesterol
[DL-C	low-density lipoprotein cholesterol
y-GTP	y-glutamyl transpeptidase
'iKL-6	Krebs von den Lungen-6 (sialylated carbohydrate antigen)
'!BUN	blood urea nitrogen
'!EDC	electronic data capture
l!AK	Janus kinase
WDA	new drug application

2. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Reason
Version 5	13 December 2019	Other amendment(s)	7.2.3Planned investigation period 7.6.1Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record 7.6.4.1Procedures for registration	Change target of CRF collection
Version 4	17 September 2019	Other amendment(s)	6.1.limportant identified risks 9NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Revistion of RMP Change of outsourced work

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Reason
Version 3	17 April, 2019	Other amendment(s)	7.2.4.2 . Distribution management Deleted 7.6Data management 13.2Contact information for the EDC system (in the case of study using EDC)	Change distribution meshod Improvements of descriptions Change mail addess
Version 2	01 December, 2018	Other amendment(s)	9NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Description revision maintenance accompanying establishment of Pfizer R & D
Final	25 May, 2018	Other amendment(s)	6 RESEARCH QUESTION AND OBJECTIVES 7.3 Variables (Table 2) 7.3.1 Background 7.3.2 Pre-dosing observation 7.3.3 XELJANZ use record 7.3.4.1 Drug therapy 7.3.5 Status of vaccination 7.3.7.1 Clinical laboratory tests 7.3.7.6 Colonoscopy 7.3.10 Status of treatment with XELJANZ 9 NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS 14 REFERENCES	Action against direction by the authorities Improvements of descriptions Improvements of descriptions Improvements of descriptions Improvements of descriptions Improvements of descriptions Improvements of descriptions Addition of footnotes Improvements of descriptions Improvements of descriptions Change in the outsourced operations Improvements of descriptions
NDA_ Amended 3	17 April, 2018	Other amendment(s)	"7.3.12 Major investigation items" deleted	Direction by the authorities
NDA_ Amended 2	13 April, 2018	Other amendment(s)	5 RATIONALE AND BACKGROUND 6.1 Safety Specifications	Ordinance revision Change to RMP

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Reason
			7.2.1 Registration criteria	Improvements of descriptions
			7.2.4.2 Distribution management	Improvements of descriptions
			7.2.5 Observation period	Action against PMDA inquiry
			7.3 Variables (schedule)	Action against PMDA inquiry
			7.3.3 XELJANZ use record	Action against PMDA inquiry
			7.3.9 9 Status of pregnancy (female patients only)	Action against PMDA inquiry
			7.3.10 Status of treatment with XELJANZ	Action against PMDA inquiry
			7.3.11 Adverse events	Action against PMDA inquiry
			7.6 Data management	Improvements of descriptions
			9 NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Clarification of the outsourcing contractors
			13 CONTACT INFORMATION	Clarification of contact information
			14 REFERENCES	Addition of attached documents
NDA_ Amended 1	13 Febru ary, 2018	Other amendment(s)	6.1 Safety Specifications	Change to RMP
			7.3.1 Background	Reconsidera tion of the variables
			7.3.2 Pre-dosing observation	Reconsideration of the variables
			7.3.4 Concomitant therapy for ulcerative colitis	Reconsideration of the variables
			7.3.5 5 Status of vaccination	Addition of an applicable vaccine
			7.3.7.1 Clinical laboratory tests	Reconsideration of the parameters
			7.3.7.6 Colonoscopy	Reconsideration of the parameters
			7.3.10 Status of treatment with XELJANZ	Reconsideration of the variables
NDA First	10 May, 2017	ot applicable	Not aoolicable	Not aoolicable

4. MILESTONES

Milestone	Planned date
Start of data collection	May 2018
End of data collection	June 2021
Interim report	At the time of submission of Japan Periodic Safety Report
Final study report	Augast 2022

5. RATIONALE AND BACKGROUND

XELJANZ® Tablets 5 mg (non-proprietary name: tofacitinib citrate) (hereinafter "XELJANZ") is a potent inhibitor of Janus kinase (JAK) created by Pfizer Inc. In Japan, XELJANZ received marketing approval for the indication of "rheumatoid arthritis with inadequate response to existing therapy" in March 2013 and the indication of "induction and maintenance therapy for moderate or severe active ulcerative colitis (limited to cases with inadequate response to existing therapy)" in May 2018.

"XELJANZ® Tablets 5 mg Special Investigation (Investigation of Long-term Use in Patients with Ulcerative Colitis)" (hereinafter "Investigation") will be conducted based on the approval conditions in order to understand the safety and effectiveness of long-term use of XELJANZ in patients with ulcerative colitis in clinical settings. Information obtained in this study shall be used to report Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), and Pfizer Inc. which is the corporate parent of marketing authorization holder (or sponsor) of XELJANZ. And also, it shall be used for application of re-examination (including Japan Periodic Safety Report), re-evaluation, preparation of material for proper use information of XELJANZ, publications and activities for information service.

This Study shall be conducted in strict compliance with the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated December 20, 2004), "MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 26, dated March 11, 2013), the "Enforcement of the MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices, and on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and

Clinical Trials of Medical Products" (PFSB Notification No. 0311-7, dated March 11, 2013), "MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 116, dated October 26, 2017), and "Announcement of the MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products (Regarding the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products)" (PSEHB Notification No. 1026-1, dated October 26, 2017).

6. RESEARCH QUESTION AND OBJECTIVES

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

6.1. Safety Specifications

The safety specifications included in the Risk Management Plan of XELJANZ are as shown below.

6.1.1. Important identified risks

- Serious infection (including tuberculosis, pneumonia, Pneumocystis pneumonia, sepsis, and opportunistic infection)
- Herpes zoster
- Neutropenia, lymphopenia, oligochromemia
- Hepatic impairment
- Reactivation of hepatitis B virus
- Gastrointestinal perforation
- Interstitial lung disease
- Venous thrombosis

6.1.2. Important potential risks

- Malignant tumor
- Cardiovascular event
- Rhabdomyolysis, myopathy

6.1.3. Important missing information

Not applicable.

7. RESEARCH METHODS

7.1. Study design

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

7.2. Setting

7.2.1. 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

For the "indications" and "dosage and administration" of XELJANZ, refer to the latest package insert of the drug.

7.2.2. Sites for this study

This investigation is planned to be conducted at approximately 500 medical institutions of gastrointestinal medicine or gastrointestinal surgery that satisfy the following requirements.

7.2.2.1. Site requirements

- Sites that are able to cooperate with this investigation
- Sites that are sufficiently capable of taking emergency actions (including those that are capable of such actions in collaboration with other institutions*)

  *: If the diagnosis and treatment are conducted in collaboration with other institutions, the information on safety measures, procedures of adverse reactions, etc. of XELJANZ must be shared with the sites in collaboration and the cooperation system must be confirmed.

- Sites with physicians who satisfy the investigator requirements below:

[Investigator requirements]

- Physicians with sufficient knowledge of XELJANZ (including knowledge of adverse reactions)
- Physicians with experience in treatment of ulcerative colitis
- Physicians who are able to cooperate with this investigation
- Physicians who can have an interview with Sponsor

7.2.3. Planned investigation period

The planned period covered by this study is as follows.

- Investigation period: May 2018 to June 2021

- Registration period: May 2018 to until the approval conditions for all cases investigations are lifted

However, when PMDA has accepted to continuing registration only, it is not necessary to enter new CRF.

7.2.4. Study procedures

7.2.4.1. Study method

This investigation will be conducted with all patients surveillance system that register all patients treated with XELJANZ for ulcerative colitis.

This investigation will study patients who use XELJANZ at contract sites after the date of approval of the dosage and administration for ulcerative colitis.

7.2.4.2. Distribution management

Sponsor, upon confirming the completion of contract for this study, shall set up logistics necessary to deliver XELJANZ to the site.

7.2.5. Observation period

The duration of observation will be 60 weeks (14 months) from the date of treatment commencement (Day 1). However, patients who are treated with XELJANZ for more than 60 weeks after the date of treatment commencement will be continuously followed up until the end of the investigation period * (June 2021). For patients who discontinue XELJANZ, information until the discontinuation will be collected.

*: Date of the last observation before June 2021

This study will be conducted using booklet type CRF. Investigator will complete each booklet of CRFs for each observation period in Table 1. However, for patients who discontinue XELJANZ, information until the discontinuation will be collected.

Table 1. Name of CRF and observation period

Name of CRF	Observation period
Booklet 1	Treatment commencement to Week 26 (Month 6) of treatment
Booklet 2	Week 27 (Month 7) to Week 60 (Month 14) of treatment
Booklet 3	Week 61 (Month 15) to end of the investigation period (June 2021)

7.3. Variables

This study will be conducted according to the schedule of observation in Table 2. However, when PMDA accepted to continuing the case registration only, the information in 7.3.2 to 7.3.11 does not need to be entered in the new CRF.

Table 2. Schedule of observation

Observation item	Patient registration[1]	Baseline[11]	Date of treatment commencement[11]	Week 26 of treatment[11]	Week 60 of treatment[11]	End of investigation period[11]
ID number, gender, age[2]	●					
Planned first day of treatment with XELJANZ[3]	●					
Confirmation of eligibility for XELJANZ treatment	●					
Confirmation of eligibility for the investigation	●					
Height, body weight[4]			●			
Information on ulcerative colitis		●				
Status of pregnancy (female patients only)		●				
Disease history		●				
Prior treatment for ulcerative colitis		●				
Smoking history		●				
Family history of malignant tumor including lymphoma)		●				
XELJANZ use record			✓	✓	✓	
Concomitant therapy for ulcerative colitis			✓	✓	✓	
Status of vaccination[5]		✓	✓	✓	✓	
Status of prophylactic treatment[6]	✓	✓	✓	✓	✓	
Clinical laboratory tests		✓	✓	✓	✓	
Chest X-ray or chest CT[7]	✓	✓	✓	✓	✓	
Tuberculosis screening tests		✓	✓	✓	✓	
Blood pressure	✓	✓	✓	✓	✓	
Hepatitis B and C virus tests	✓	✓	✓	✓	✓	
Colonoscopy[8]		✓	✓	✓	✓	
Clinical evaluation on effectiveness[9]		✓	✓	✓	✓	
Status of treatment with XELJANZ			✓	✓	✓	
All adverse events			✓	✓	✓	
Malignant tumor and adverse events leading to discontinuation[10]			✓	✓	✓	✓

1. Record the information in the registration form
2. Age at the time when the treatment of XELJANZ is commenced
3. Date when treatment with the commercial product of XELJANZ is started for patients who participated in clinical trials

4. Name and duration of the disease. extent of the lesion, severity. status of refractory ulcerative colitis based on treatment response
5. Information on vaccination with herpes zoster vaccine and pneumococcal vaccine from baseline to the date of completion of the observation period (or date of discontinuation)
6. Information on prophylactic treatment for tuberculosis. Pneumocystis jiroveci i pneumonia and hepatitis B given from 3 months before commencement of XELJANZ treatment to the date of completion of the observation period (or date of discontinuation)
7. lofonnation on chest X-ray and chest CT conducted from 3 months before commencement of XELJANZ treatment to the date of completion of the observation period (or date of discontinuation)
8. Information on colonoscopy conducted from 6 months before commencement of XELJANZ treatment to the date of completion of the observation period (or date of discontinuation)
9. Frequency of defecation. rectal bleeding. findings of colonoscopy (if conducted), and investigator's global assessment
10. For patients who continue treatment beyond Week 60 of treatment. collect information on malignant tumor and adverse events leading to treatment discontinuation that occur at and after Week 61 of treatment
11. When PMDA has accepted to continuing registration only, it is not necessary to enter new CRF.

7.3.1. Background

The following information should be recorded in the registration foml for patient registration (see 7.6.4).

1. ID number
2. Gender
3. Month of birth or age (at the time when the treatment of XELJANZ is planned to be commenced)
4. Planned first day of treatment with XELJANZ•

   *: Date when treatment with the couunercial product of XELJANZ is started for patients who participated in clinical trials

5. . Confirmation of eligibility for XELJANZ treatment (confirm that patients do not meet the contraindications in the latest package insert)
6. Confirmation of eligibility for the investigation

7.3.2. Pre-dosing observation

The following information should be recorded in CRF.

1. Height
2. . Body weight
3. Information on ulcerative colitis
   a. Name of the disease
   b. Date of diagnosis or duration of the disease
   c. Extent of the lesion· (total colitis, left-sided colitis, proctitis, right-sided or segmental colitis)
   d. Severity* (sever, moderate, mild; See Table 3.)

Table 3. Classification of ulcerative colitis by severity•

	Severe	Moderate	Mild..
l) Frequency of stool	6 times or more	Intermediate	4 times or less

2) Obvious bloody stool	(+++)	between severe and mild	(+) to (-)
3) Fever	37.5°C or higher		(-)
4) Tachycardia	90/min or more		(-)
5) Anemia	Hb 10 g/dL or less		(-)
6) Erythrocyte sedimentation rate	30 mm/h or more		Normal

Note:

- Rated as severe when criteria 1), 2), and one of the systemic symptoms 3) a11d 4) are satisfied, and at least 4 of the 6 criteria are satisfied.
- Rated as mild when all of the 6 cliteria are satisfied.
- Among patients with severe disease, those showing extremely severe symptoms are classified as having fu lulinant disease, and, depending on the rapidity of the disease onset. fuhninant disease is subdivided into acute fuhninant and relapsing fuhninan t disease.
- Patients satisfying all of the following 5 criteria are classified as having fulminant disease.
  1. Satisfying the criteria for severe disease
  2. Bloody diarrhea occurring at a frequency of 15 times/day or more
  3. Persistent high fever (38°C or higher)
  4. Increase of the leukocyte count to 10,000 /mm^3 or more
  5. Severe abdominal pa in

*: Criteria for diagnosis and treatment strategy for ulcerative colitis and Crohn's disease 2016 revised version (supplementary volume of the 2016 annual report of "Research Group of Intractable Inflammatory Bowel Disease" [Suzuki Group], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health and Labom Sciences Research Grants)

**: Patients with nlild disease ale not eligible for XELJANZ treatment.

e. Status of refractory ulcera tive colitis based on treatment response (statu s of steroid dependency or resistance in the last episode before commencement of XELJANZ treatment)

4. Status of pregnancy (female patients only)
5. Medical history (name of disease or syndrome (diagnosis], classification of history or concurrent disease..)

* History: Chronic disease (including allergy), disease requiring treatment, disease or disorder with surgery, hospitalization or sequelae, and other relevant disease or syndrome that are cured before commencement of XELJANZ treatment (no treatment and no symptoms)

* Concurrent disease: Chronic disease (including allergy), disease requiring treatment. disease or disorder with surgery, hospitalization or sequelae, and other relevant disease or syndrome that require any treatment or requ ire no treatment but have residual symptoms at the time of commencement of XELJANZ treatment

6. Prior treatment for ulcerative colitis
   The status of prior treatment (drug and non-drug therapy) for the last episode before commencement of XELJANZ treatment (an episode treated with XELJANZ) should be recorded.

   For biological products, the status of use throughout the past treatment of ulcerative colitis should be recorded, and if any biological product was used, the name of the product and the classification of primary failure or secondary failure• should be recorded.

   *: Primary failure: Lack of effectiveness or insufficient effectiveness with treatment for an appropriate period at the approved dosage and administration
   Secondary failure: Loss of effectiveness (relapse) with continued treatment after achieving a clinical response (remission) with treatment for an appropriate period at the approved dosage and administration
   Indeterminate: Treatment is discontinued due to any reason other than "not effective" (e.g., adverse events) and determination whether it is primary failure or secondary failure cannot be made
7. Smoking history (status of smoking at the start of the investigation)
8. Family history of malignant tumor (including lymphoma)

7.3.3. XELJANZ use record

The record of the status of XELJANZ treatment from the date of treatment commencement to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the following information.
However, for patients who are treated with XELJANZ for more than 60 weeks after the date of treatment commencement, information until the end of the investigation period (or date of XELJANZ discontinuation) should also be recorded.

1. Dose
2. Number of doses per day
3. Reason for change or intenuption•
   *: Reason for a change in the dose or the number of doses per day if any
4. Duration of treatment
5. Reason for continued treatment at Week 16 of treatment*
   *: Reason for continuation of XELJANZ treatment beyond Week 16 despite no therapeutic response in induction therapy at Week 16 based on clinical symptoms, endoscopy and other findings

7.3.4. Concomitant therapy for ulcerative colitis

7.3.4.l. Drug therapy

The record of treatments• for ulcerative colitis used from the date of commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the following information.

1. Drug name
2. Route of administration
3. Dosage form (topical agents only)
4. Duration of treatment

*: 5-ASAs (oral, enema, suppository), steroids (oral, enema, suppository, injection), immunomodulators (oral, injection), biological products (injection)

7.3.4.2. Non-drug therapy

The record of non-drug treatments given from the date of commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the following information.

1. Name of the therapy
2. Period of administration
3. Reason for the administration of non-drug therapy

7.3.5. Status of vaccination

The record of vaccines given in relation to the treatment of ulcerative colitis should include the following information from baseline to the date of completion of the observation period (or date of XELJANZ discontinuation).

1. Herpes zoster vaccine: Status and date of vaccination, drug name (vaccine name)
2. Pneumococcal vaccine: Status and date of vaccination

7.3.6. Status of prophylactic treatment

The record of the status of prophylactic treatment given from 3 months before the commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the following information.

1. Classification: Tuberculosis, Pneumocystis jirovecii pneumonia, hepatitis B
2. Drug name (product name)
3. Duration of treatment

7.3.7. Tests/clinical laboratory tests

The record of the following tests conducted from baseline to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the status, dates and results (or findings) of the tests. If the abnormal change is clinically

significant compared to the baseline value, this information should also be recorded in the adverse event field.

7.3.7.1. Clinical laboratory tests

Results of the following clinical laboratory tests conducted from baseline (within 1 month before treatment commencement, including the date of treatment commencement*) to the date of completion of the observation period (or date of XELJANZ discontinuation).

1. Hematology White blood cell count, neutrophil, eosinophil, lymphocyte, monocyte, red blood cell count, platelet count, hemoglobin
2. Blood chemistry AST (GOT), ALT (GPT), AL-P, LDH, total cholesterol, HDL-C, LDL-C, y-GTP, total bilirubin, triglyceride, serum creatinine, creatine kinase, albumin
3. Other tests KL-6, -D-glucan, BUN, fecal calprotectin, CRP

*: Within 3 months before treatment commencement for fecal calprotectin

7.3.7.2. Chest X-ray test or chest CT test

Findings of chest X-ray or chest CT conducted from baseline (within 3 months before treatment commencement, including the date of treatment commencement) to the date of completion of the observation period (or date of XELJANZ discontinuation).

7.3.7.3. Tuberculosis screening tests

Results of the following tests conducted from baseline (within 6 months before treatment commencement, including the date of treatment commencement) to the date of completion of the observation period (or date of XELJANZ discontinuation).

1. Interferon *y* release assay (QuantiFERON, T-SPOT)
2. Tuberculin skin test

7.3.7.4. Blood pressure (systolic/diastolic)

Results of measurements from baseline to the date of completion of the observation period (or date of XELJANZ discontinuation).

7.3.7.5. Hepatitis B and C virus tests

Results of the following tests conducted within 3 months before treatment commencement should be recorded. For patients who are HBV carriers, the status of HBV-DNA test conducted up to the completion of the observation period (or date of XELJANZ discontinuation) should be recorded.

1. Hepatitis B virus test: HBs antigen, HBs antibody, HBc antibody, and HBV-DNA test
2. Hepatitis C virus test: HCV antibody

7.3.7.6. Colonoscopy

Results of colonoscopy (inflammation site and findings) conducted from 6 months before commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation).

7.3.8. Clinical evaluation on effectiveness

The record of the clinical evaluation on effectiveness against ulcerative colitis from baseline (including the date of treatment commencement) to the date of completion of the observation period (or date of XELJANZ discontinuation) should include the results of evaluations based on the following rating scales.

1. 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
2. Rectal bleeding:
   0 point = No 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
3. Findings of flexible sigmoidoscopy:
   0 point = Normal or inactive disease
   1 point = Mild disease (erythema, decreased vascular pattern, mild fragility)
   2 points = Moderate disease (marked erythema, absent vascular pattern, any friability, erosion)
   3 points = Severe disease (spontaneous bleeding, ulceration)
4. Physician's global assessment:
   0 point = Normal
   1 point = Mild disease
   2 points = Moderate disease
   3 points = Severe disease

7.3.9. Status of pregnancy (female patients only)

The status of pregnancy from the date of commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation) should be recorded. However, for patients who are treated with XELJANZ for more than 60 weeks after the date of treatment commencement, the status of pregnancy until the end of the investigation period (or date of XELJANZ discontinuation) should also be recorded.

7.3.10. Status of treatment with XELJANZ

The status of treatment with XELJANZ at the completion of the observation period for each booklet (Week 26, Week 60, end of the investigation) should be confirmed, and the following information should be recorded. Ifthe reason for discontinuation at the last observation is an adverse event or patient's death, its details should be recorded in the adverse event field.

1. Date of the last observation
2. Completion of treatment or reason for discontinuation
   - Completed (treatment continued)
   - Adverse events (Record the details in the adverse event field)
   - Patient's death (Record the date of death)
   - Remission
   - Insufficient clinical effectiveness
   - Failure to show up
   - Other

7.3.11. Adverse events

The status of occurrence of adverse events from the date of commencement of XELJANZ treatment to the date of completion of the observation period (or date of XELJANZ discontinuation) should be confirmed, and the following information should be recorded. However, for patients who are treated with XELJANZ for more than 60 weeks after the date of treatment commencement, the record of malignant tumor and adverse events leading to discontinuation that occur at and after Week 61 should include the following information.

Occurrence of a serious adverse reaction, an unexpected adverse reaction or other adverse reactions should be separately investigated in detail if determined necessary by Sponsor.

- Presence/absence of adverse event
- Name of adverse event
- Diagnosis of malignant tumor (only if malignant tumor occurs)
- Date of occurrence
- Intervention
- Seriousness
- Outcome at the completion of observation period
- Causal relationship

Ifthe adverse event is associated with abnormal laboratory values, i.e., clinical laboratory tests, the following information should also be recorded.

- Laboratory parameter
- Site reference value
- Unit
- Date measured

- Results

Supplemental remarks: An adverse event is any unfavorable event (including a clinically significant abnormal laboratory change) occurring after administration of XELJANZ, whether or not related to XELJANZ. A serious adverse event is any event that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or any other medically important event that may lead to disability.

7.4. Data sources

In this study, the investigators extract the necessary information using medical charts, medical records and other information in accordance with the protocol.

7.5. Study size

7.5.1. Planned sample size

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

7.5.2. Rationale for sample size

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.

7.6. Data management

7.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF[/DCT] should be understood to refer to either a paper form or an electronic data record, or both, depending on the data collection method used in this study (when PMDA has accepted to continuing registration only, it is not necessaly to enter new CRF).

A CRF[/DCT] is required and should be completed for each included patient. The completed original CRFs[/DCTs] are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory

authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs[/DCTs] are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs[/DCTs] and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs[/DCTs] must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs[/DCTs] are true. Any corrections to entries made in the CRFs[/DCTs] or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs[/DCTs] must match those charts.

7.6.2. Record retention

The records related to this study should be retained at the study site until the End of Study Letter by Pfizer is received or during the period defined by the study site, whichever is longer.

7.6.3. Data collection method

The data for this study will be collected and confirmed by using electronic data capture (EDC). However, if EDC is not available, designated paper registration form and CRF provided by Sponsor will be used to collect data.

7.6.4. Patient registration

7.6.4.1. Procedures for registration

Necessary information should be recorded in EDC registration form (patient registration screen), and patients should be registered at least 1 week before the commencement of XELJANZ treatment in principle.

If EDC is not available and when the PMDA has accepted to continuing the case registration only, information should be recorded in a paper registration form, and the form should be faxed to the Patient Registration Center at least 1 week before the commencement of XELJANZ treatment in principle.

In addition, as this investigation will be conducted with all patients surveillance system, all patients who are confirmed to be treated with XELJANZ should be registered.

7.6.5. Reminders concerning completing, revising, and submission of case report form

7.6.5.1. Completing

The investigator shall, upon confirming the study items, input the data in this system based on medical charts, and save the data. If EDC is not available, data should be recorded in a paper CRF.

7.6.5.2. Revising

Upon receiving Sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records, and as required, correct relevant sections.

7.6.5.3. Submitting

After completing and revising the CRF, the investigator will again confirm the completed CRF and the contents of confirmation and affix an electronic signature. If EDC is not available, signature or name/seal should be affixed to the cover page of a paper CRF after the completion of the observation period for each booklet, and the CRF should be sent to Sponsor using a designated envelop.

7.7. Data analysis

7.7.1. Definition of analysis set

The safety analysis set will include a group of patients who receive at least 1 dose of XELJANZ and have post-treatment information. The effectiveness analysis set will be a set of patients for whom the efficacy evaluation is considered possible among the safety analysis set according to the separately prescribed Statistical Analysis Plan (SAP).

7.7.2. Method of analysis

7.7.2.1. Analysis for safety evaluation

In the safety analysis set, the onset of major adverse reactions (adverse events for which the causal relationship with XELJANZ cannot be ruled out), incidence of adverse reactions (number/percentage of patients with adverse reactions), and incidence of adverse events per duration of exposure (100 x 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.

7.7.2.2. 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.

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

7.8. OTHER NECESSARY MATTERS

Not applicable.

8. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

Regarding the organizational system in this study, refer to the appendix I of "the risk management plan".

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

Name: PPD
Address: PPD
Scope of the outsourced operations: Drafting of study protocol and management of operation study, etc.

Name: PPD
Address:
Scope of the outsourced operations: Establishment, operation and maintenance of the EDC system.

Name: PPD
Address: PPD
Scope of the outsourced operations: Contract-related operations, reception of registration forms, delivery/reception of CRFs, data management , medical writing etc.

Name: PPD
Address: PPD
Scope of the outsourced operations: Establishment of the EDC system, data management , tabulation analysis

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

Review the risk management plan including the following contents at the scheduled timing of milestones.

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

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

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

Review and report the safety and effectiveness at the time of reporting the Periodic Safety Reports and completion of the study.

12. OTHER NECESSARY MATTERS

1. Amendment of the Study Protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the protocol will be examined and the Study Protocol will be amended if necessary. Also, the need for amendment of the Study Protocol will be examined and the protocol will be amended even if the partial change in the dosage and administration or indication is approved during the reexamination period (except the case when the reexamination period is newly designated), etc.

2. Actions to be taken if any problem or question is observed

In the cases where the onset of any serious and unknown adverse reaction is suggested, a significant increase in the frequency of adverse reactions is observed, any problem is found in the effectiveness and safety of the drug compared to those prior to the approval, the onset of a different kind of adverse reaction is suggested, etc., the amendment of the package insert and implementation of a new Special Investigation or Post-marketing Clinical Trial should be considered.

13. CONTACT INFORMATION

13.1. Contact information for the contents of the study

Name	rpn
Address	rPD
FAX	fPD
E-mail address	rPD

13.2. Contact information for the EDC system (in the case of study using EDC)

Name	PPD
Open Hours	PPD
TEL	PPD
E-mail address	PPD

14. REFERENCES

1. Clinical practice guidelines for inflammatory bowel disease (IBD) 20 16 (The Japanese Society of Gastroenterology)
2. Criteria for diagnosis and treatment strategy for ulcerative colitis and Crohn's disease 2016 revised version (supplementary volume of the 2016 annual report of "Research Group of Intractable Inflammatory Bowel Disease" [Suzuki Group], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health and Labour Sciences Research Grants)
3. Special Investigation protocol
4. Special Investigation registration form
5. Special Investigation case record form

15. LIST OF TABLES

16. LIST OF FIGURES

Not applicable.

17. LIST OF STAND ALONE DOCUMENTS

Not applicable.

18. ADDITIONAL INFORMATION

Not applicable.

19. ADDITIONAL TABLE (NAME OF THE TABLE)

Not applicable.