NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**Korea Post-marketing Surveillance for Xeljanz® in Ulcerative Colitis Patients**
Protocol number	A3921343
Protocol version identifier	Amendment 7
Date	25 Mar 2022
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz® (5 mg: contains tofacitinib citrate 8.078 mg in 1 tablet) (10 mg: contains tofacitinib citrate 16.155 mg in 1 tablet)
Research question and objectives	To identify any safety and effectiveness of Xeljanz in Ulcerative Colitis patients during the post-marketing period as required by the regulation of Ministry of Food and Drug Safety (MFDS).
Country(-ies) of study	Korea, Republic of.
Author	PPD Pfizer BiopharmaceuticalsKorea Ltd.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AEM	adverse event monitoring
ANC	absolute neutrophil count
CRF	case report form
CRP	C-reactive protein
CYP	cytochrome P450
EDP	exposure during pregnancy
ESR	erythrocyte sedimentation rate
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
HDL	high density lipoprotein
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LDL	low density lipoprotein
MFDS	Ministry of Food and Drug Safety
NIS	non-interventional study
PhRMA	Pharmaceutical Research and Manufacturers Association
PMS	post-marketing surveillance
pANCA	perinulclear anti-neutrophil cytoplasmic antibodies
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
TC	total cholesterol
UC	ulcerative colitis
VAS	visual analogue scale
MedDRA	Medical Dictionary for Regulatory Activities

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD	Non-Interventional Study Lead	Pfizer BiopharmaceuticalsKorea Ltd.	PPD

3. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reasons
Amendment 1	23 Jul 2019	2. Responsible parties	Change of responsible parties	NISL change
		5. Rationale and background	Least number of patients to be followed until the end of 52weeks mentioned	Amendment recommended by the MFDS
		7.1. Study design	Included how to clinically assess the efficacy Added the content of the follow-up for long-term users.	
		7.2.5. Study Procedures 7.2.5.1. Basic Information	Added the content of the follow-up for long-term users	
		7.2.5.2. Demography and baseline characteristics	Included Partial Mayo Score	
		7.3.1. Safety variables 7.3.2. Efficacy variables 7.3.3. Efficacy evaluation	Added the content of the follow-up for long-term users	
		7.7.2. Efficacy analysis		

Amendment 2	26 Aug 2019	7.3.1.1. Adverse event	Added the 'not applicable' in the Causality assessment	Amendment recommended by the MFDS
		7.7.1. Safety analysis	Added the definition of patients entering this study for the safety analysis Described the special popluations in detail	
		7.7.2 Efficacy analysis	Added the definition of the patients enterting this study for the efficacy analysis Added the efficacy anlaysis for incompleted long-term users	
		7.7.4. Statistical consideration	Described the statistical analysis in detail	
Amendment 3	19 Sep 2019	7.3.2. Efficacy variables 7.3.3. Efficacy evaluation	Added the final efficacy variable in efficacy variables	Added the final efficacy variable by investigator
Amendment 4	15 Oct 2019	7.1. Study design	Removed the Truelove and Witts's Score	Mayo score is more frequently used in actual medical practice
		7.3.1.1. Adverse events 7.6. Data management	Changed the criteria of AE terminology from the WHO-ART to MedDRA	Changed for digitalization and standardization of AE terminology
		7.3.2. Efficacy variables 7.3.3. Efficacy evaluation	Clarified the final efficacy evaluation	To reflect the actual medical practice

Amendment 5	06 Feb 2020	4.Milestones	Add RMP report submission timeline	Amended according to the MFDS comments
		7.7.1.Safety analysis	Add analysis and evaluation methods for safety specification according to RMP	
Amendment 6	23 Mar 2021	5. Rationale and background	Modify number of patients in the study Add retrospective data collection method	Change of research methods
		7.1 Study design		
		7.2.1. Inclusion criteria		
		7.2.5. Study procedures		
		7.2.5.1. Basic information		
		7.2.5.2. Demography and baseline characteristics		
Amendment 7	25 Mar 2022	Total	Change 'Efficacy' to 'Effectiveness' if it is evaluated under usual clinical practice	To clarify the definition of terms
		5. Rationale and background	Remove retrospective data collection method	Change of research methods
		7.1 Study design		

		7.2.1. Inclusion criteria		
		7.2.5. Study procedures		
		7.2.5.1. Basic information		
		7.2.5.2. Demography and baseline characteristics		
		7.3.1.2. Laboratory test	Remove laboratory normal ranges of the center	Change of data collection methods
		7.4.2. Record retention	Add record retention period	To align with regulation
		7.5. Study Size	Modify number of patients in the study	Change of research methods

4. MILESTONES

Milestone	Planned date
Start of data collection	27 May 2019
End of data collection	19 September 2022
First year (1-1) periodic report (MFDS)	19 May 2019
First year (1-2) periodic report (MFDS)	19 November 2019
Second year (2-1) periodic report (MFDS)	19 May 2020
Second year (2-2) periodic report (MFDS)	19 November 2020
Third year annual report (MFDS)	19 November 2021
Final study report (MFDS)	19 December 2022

- Abbreviations: MFDS=Ministry of Food and Drug Safety.

- RMP periodic report will be submitted every year after RMP approval, and final report will be submitted after December 2022 considering completion schedule of xeljanz post-marketing surveillance final report in patients with ulcerative colitis.

5. RATIONALE AND BACKGROUND

Xeljanz® (tofacitinib) is a potent, oral janus kinase inhibitor. Xeljanz was initially approved by the Ministry of Food and Drug Safety (MFDS) on 02 April 2014 for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. On 20 September 2019, new indications for the treatment of adult paitens with moderately to severely active ulcerative colitis (UC) and psoriatic arthritis (PsA).

In clinical trials conducted on patients with moderately to severely active ulcerative colitis, the Xeljanz® (tofacitinib) demonstrated its efficacy and safety in adult patients who have had an inadequate response or intolerance to the basic treatments or biological agents. Ulcerative colitis has the chronic nature of relapse and improvement, most patients experience a number of acute deterioration throughout their life, and in the course of treatment with various drugs, they become resistant to or lose response to the treatment. Currently, there are very limited treatment options available to patients with moderately to severely active ulcerative colitis in terms of efficacy, safety, convenience of administration and quality of life (QoL). Therefore, for patients with limited options who do not respond to current available drugs, there are still many unmet needs for effective and rapid medications with new mechanisms of action.

CCI [redacted] Patients who are treated with Xeljanz for at least 52 weeks will be classified as long-term users. Out of all the enrolled patients, at least 18 cases (20%) of long-term users will be followed up to see the long term safety and effectiveness of Xeljanz. This non-interventional post-marketing surveillance (PMS) study is a commitment to MFDS.

6. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to identify any safety and effectiveness of Xeljanz during the post-marketing period as required by the regulation of MFDS.

7. RESEARCH METHODS

7.1. Study design

This is an open-label, non-comparative, non-interventional, prospective, and multi-center study conducted in Korean health care centers by accredited physicians (ie, investigators). The study population will be adult patients with moderately to severely active UC who have had an inadequate response or intolerance to the basic treatments or biological agents. Clinical Severity of Ulcerative Colitis is classified as mild, moderate, or severe based on the Mayo score of Partial Mayo score. (Table 1).

Table 1. Mayo Score for ulcerative colitis[4]

Variables/Score		Criteria
Stool frequency	0	Normal number of stool
	1	1-2 stools more than normal
	2	3-4 stools more than normal
	3	≥5 stools more than normal
Rectal bleeding	0	No blood seen
	1	Streaks of blood with stool less than half the time
	2	Obvious blood with stool most of the time
	3	Blood alone passed
Findings of proctosigmoidoscopy	0	Normal or inactive disease
	1	Mild disease (erythema, decreased vascular pattern, mild friability)
	2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
	3	Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	0	Normal
	1	Mild
	2	Moderate
	3	Severe

Xeljanz will be administered according to the "Dosage and Administration" of the approved labeling. There is no visit or activity mandated by this study. The investigator will collect patient data and record the information on each patient's case report form (CRF).

Each investigator will sequentially enroll all patients to whom Xeljanz is prescribed for the first time according to the local product label, and who agree to participate in this study by signing the data privacy statement. Safety is the primary endpoint of this study, which will be assessed based on adverse events (AEs) that have occured between the first dose of Xeljanz to the next visit.

As a secondary endpoint, the investigator will performe the final effectiveness evaluation based on the clinical impression plus the Mayo score or Partial Mayo score. The Mayo score or the Partial Mayo Score at week 8, 16 and 24(also 52 for the long-term users) is assessed to see the remission, clinical response or mucosal healing. To assess the effectiveness of the Xeljanz. Mayo score is based on a total score of 12 points by evaluating and calculating the four clinical evaluation criteria: Stool frequency, Rectal bleeding, Findings of endoscopy, and Physician's global assessment. (Table 1) Partial Mayo Score is calculated by the sum of the remaining evaluations, except for the findings of endoscopy score.

7.2. Setting

7.2.1. Inclusion criteria

To be included in the study all patients will have received at least 1 dose of Xeljanz for the treatment of the following indication as per local labelling:

- Moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to the basic treatments or biological agents

7.2.2. Exclusion criteria

Patients meeting any of the following criteria as per the local labeling will not be included in the study:

1. Patients with a history of hypersensitivity to any ingredients of this product.
2. Patients with serious infection (sepsis, etc.) or active infection including localized infection.
3. Patients with active tuberculosis.
4. Patients with severe hepatic function disorder.
5. Patients with an absolute neutrophil count (ANC) <1,000 cells/mm^3.
6. Patients with a lymphocyte count <500 cells/mm^3.
7. Patients with a hemoglobin level <9 g/dL.
8. Pregnant or possibly pregnant women.
9. Because of lactose contained in this drug, it should not be administered to patients with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

7.2.3. Duration of the study

According to the MFDS re-examination regulation, the analyzed study report based on 4 years of collected data has to be submitted to MFDS within 3 months after the end of specified re-examination period (from the indication approval date to 4 years afterwards). The re-examination period is from 20 September 2018 to 19 Septmber 2022, and the final study report should therefore be submitted by 19 December 2022.

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7.2.5. Study procedures

Patients will be enrolled by continuous registration method. The investigator should enroll all patients to whom Xeljanz is prescribed for the first time according to the local product label and who agree to participate in this study by signing the data privacy statement (used in place of the informed consent form). Xeljanz will be medicated by the investigator's prescription under usual clinical practice. Pfizer Korea will not provide the medicinal product for this study.

There will be no mandatory visit during the study. The investigators will collect relevant data from the time of initiating administration of Xeljanz until 24 weeks of treatment (52 weeks of treatment for the long-term users). If the patient does not complete 24 or 52 weeks of treatment, relevant data should be collected based on the last assessment performed at the time of treatment discontinuation. The investigator should record the following information on the patient's CRF.

7.2.5.1. Basic information

The following will be recorded on the CRF for each patient:

- Name of institution: Enter the name of the institution.
- Department: Enter the department name of the institution.
- Name of investigator: Enter the name of the contracted physician.
- Patient number: The investigator will sequentially assign each patient a patient identification number, which will be a 4-digit number. The total number of cases that need

to be collected will be allocated to each study site by Pfizer at the time of execution of a contract with each site.

- Completion of the study: If the patient completed 24 weeks of treatment (52 weeks for the long-term users), check "yes". Otherwise, check "no" and choose reason for the discontinuation: AE; lack of effectiveness; others.

- Date of CRF completion: Record the date of CRF completion.

- Signature of investigator: Contracted investigator must sign after identifying the CRF.

- Confirmation of data privacy statement: If the patient has signed the data privacy statement to indicate agreement for using his/her personal and medical information, check the box of "yes" on the CRF. If not, check "no" and exclude the case from the study.

7.2.5.2. Demography and baseline characteristics

The following will be recorded on the CRF for each patient:

- Age: Record actual age of the patient at the time of enrollment. The age should be calculated by the date of birth.

- Sex: Check the box next to "male" or "female" on the CRF.

- Height: Record by unit of cm.

- Weight: Record by unit of kg.

- Herpes zoster vaccination: Record if the patient had received vaccine of herpes zoster: yes; no; unknown.

- Smoking: Record smoking status of the patient: ex-smoking; current smoking; non-smoking; unknown.

- Duration of the disease: Record the duration of disease since the date that the patient was initially diagnosed with UC.

- Severity of disease activity: Assess the severity (Mild, Moderate, Severe) by measuring Mayo or partial Mayo score and calcuating the total score of 12 or 9 points based on clinical evaluation criteria: Stool frequency, rectoral bleeding, findings of endoscopy, and physician's global assessment. Partial Mayo score excludes the findings of endoscopy. The severity for partial Mayo score is defined as 0-1 for remission, 2-4 for mild, 5-6 for moderate and 7-9 for severe disease activity.

- Previous UC treatments: Only record UC treatments received 6 months prior to the initiation of Xeljanz. Record name of the medication/therapy, route and duration of the administration, and overall response, if possible.

- Latent tuberculosis: Record if the patient has latent tuberculosis: yes; no; unknown.

- Renal impairment: Record if the patient has renal disorder: yes (severe/moderate/mild); none.

- Hepatic impairment: Record if the patient has hepatic disorder: yes (severe/moderate/mild); none.

- Other past/present diseases: Record "yes" or "no" for medical history. If "yes", record adequate full name of the past or present disease according to the Medical Terminology Dictionary written by the Korean Medical Society. Past or present disease will be determined based on the date of the first dose of Xeljanz.

7.2.5.3. Administrative status for medicinal product

The following will be recorded on the CRF for each patient:

- Treatment duration: Record start date and stop date (year/month/day) of the treatment of Xeljanz. If the medication is being continued at the completion of the study, record the start date only.

- Daily dose: Record single dose of Xeljanz in mg.

- Daily dosing frequency: Record dosing frequency per day.

- Reason for dose adjustment: If there are any dose adjustments during the study, record the reason(s).

7.2.5.4. Concomitant treatments

Any concomitant treatments should be recorded on the CRF for each patient. The information should include:

- Name of the drug: Record generic name of the concomitant medication.

- Daily dose: Record single dose and dosing frequency of the concomitant medication.

- Duration of the treatment: Record the start date and stop date (year/month/day) of the concomitant medication. If the medication is being continued at the completion of the study, record the start date only and check "ongoing".

- Purpose of the treatment: Record purpose of the concomitant treatment in detail.

7.2.5.5. Safety and effectiveness data

Please refer to Section 7.3 for safety and effectiveness assessment and data collection.

7.3. Variables

7.3.1. Safety variables

Safety will be assessed by the investigator based on all AEs that occur during the 24 weeks (52 weeks for the long-term users) from the first treatment for all patients who have received at least 1 dose of Xeljanz according to the local product document.

7.3.1.1. Adverse events

Please refer to Section 9 for the definition of non-serious and serious adverse events (SAEs).

Any AEs observed and reported within the reporting period will be recorded on the CRF by the investigator, regardless of the causal relationship with Xeljanz (see Section 9.2). The AEs can be reported by the patients. The investigator will also collect AE data by asking the patient questions such as "Have you had any health problem since the last visit?"

Check either "yes" or "no" in the AE section of CRF. If "yes", record the following information:

Event name: Record the name of the AE according to the MedDRA(Medical Dictionary for Regulatory Activities). If there is no appropriate term in the MedDRA, record the name of the AE according to the Medical Terminology Dictionary written by the Korean Medical Society. If possible, specify diagnosis, not individual symptoms.

Date of onset: Record the onset date of the AE. Record approximate date if an actual date is unknown.

Date of recovery: Record the stop date of the AE if the outcome of the AE is recovered or recovered with sequelae (see below). Record approximate date if an actual date is unknown.

Seriousness: Check either "yes" or "no" to indicate if the event is a SAE. If "yes' record appropriate category of the seriousness (see Section 9for the definition and reporting of SAEs).

Severity: Evaluation of AE severity must be done according to the following categories:

- Mild: Not causing any significant problem to the patient. Administration of medicinal product continues without dose adjustment.
- Moderate: Causes a problem that does not interfere significantly with usual activities or the clinical status. Dose of the medicinal product is adjusted or other therapy is added due to the AE.

- Severe: Causes a problem that interferes significantly with usual activities or the clinical status. The medicinal product is stopped due to the AE.

If the severity of an AE changes, the AE must be entered separately. Record the stop date of the previous severity and onset date of the new severity – along with completion of all other related items.

Causality assessment: The causal relationship of AEs to the medicinal product must be allocated by the investigator according to the following criteria in alignment with the requirements of MFDS:

- Certain
    - It follows a reasonable time sequence from administration of the drug (before and after the study medication);
    - It could not be explained by other drugs, chemical substances or accompanying diseases;
    - It has clinically reasonable reaction on cessation of the drug;
    - It has pharmacological or phenomenological reaction to re-administration of the drug, where necessary.
- Probable/likely
    - It follows a reasonable time sequence from administration of the drug (before and after the study medication);
    - It could not be explained by other drugs, chemical substances or accompanying diseases;
    - It has clinically reasonable reaction on cessation of the drug (no information on re-administration).
- Possible
    - It follows a reasonable time sequence from administration of the drug;
    - It could also be explained by other drugs, chemical substances or accompanying diseases;
    - It lacks information or has unclear information on discontinuation of the drug.
- Unlikely

  - It is not likely to have a reasonable causal relationship from administration of the drug. Rather, it seems to be temporary;
  - It could also be reasonably explained by other drugs, chemical substances or latent diseases.

- Conditional/unclassified
  - It needs more data to make an appropriate assessment or its additional data are being reviewed.

- Unassessible/unclassifiable
  - Lack of sufficient information or conflicting information hampers accurate causality assessment or supplementation or confirmation.

- Not applicable
  - Causality is assessed but does not fall into any categories

All AEs, except for those with a causality of "unlikely", are considered as AEs whose causal relationship to the study drug can not be excluded (ie, adverse drug reaction [ADR]).

Action taken: With regard to the medicinal product, actions will include:

- Permanently discontinued;
- Temporarily discontinued or delayed;
- Dose reduced;
- Dose increased;
- No change;
- Not applicable.

Outcome: Evaluation of outcome will include:

- Recovered;
- Recovered with sequelae;
- Recovering;
- Not recovered;

- Unknown.

Please refer to Section 9 for the requirements for reporting safety events to Pfizer Safety during the study.

7.3.1.2. Laboratory test

Recommended laboratory tests and time points are included in Table 4. Test results of chest X-ray, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), other blood chemistry, hematology, and tuberculin test should be recorded, if conducted.

Table 4 Recommended Laboratory Test

	Lymphocyte	Neutrophils	Hemoglobin	Lipids (TC, HDL, LDL)
Baseline	X	X	X	X
4 to 8weeks after treatment		X	X	X
Every 3 months	X	X	X	

Abbreviations: TC=total cholesterol, HDL= high density lipoprotein, LDL=low density lipoprotein.

In case there are any clinically significant laboratory abnormalities (as per the investigator's judgment) that occur after the treatment of Xeljanz compared to baseline, the tests should be recorded in detail on the CRF, including test results before and after Xeljanz treatment, a causal relationship to Xeljanz, and any comments from the investigator.

Please refer to Section 9.4.1 for the criteria for determining whether an abnormal objective test finding should be reported as an AE.

7.3.2. Effectiveness variables

The Mayo score or the Partial Mayo score at week 8, 16, 24 and also 52 for the long-term users is assessed is assessed to see the remission, clinical response or mucosal healing. Investigator will perform the final effectiveness evaluation of the drug into 4 categories based on the clinical impression plus Mayo score or Partial Mayo score ('Improved', 'Unchanged', 'Aggravated', 'Not assessible').

7.3.3. Effectiveness evaluation

Effectiveness assessment will be performed by the accredited investigator in the Korean health care center. The investigator will perform the final effectiveness evaluation at baseline and after 8, 16 and 24 weeks of treatment based on the clinical impression and any of the commonly used effectiveness assessment criteria such as Mayo score or Partial Mayo score, and record the assessment results in each patient's CRF. 52nd week will be added for the long-term users. If the patient does not complete the 24 or 52 weeks of treatment, relevant data should be collected based on the last assessment performed at the time of treatment discontinuation. The final evaluation of the effectiveness will be determined by the investigator into 4 categories('Improved', 'Unchanged', 'Aggravated', 'Not assessible').

- Improved (Symptoms of ulcerative colitis have improved or showed adequate maintenance effect after taking Xeljanz)
- Unchanged (Symptoms have not changed much since taking Xeljanz)
- Aggravated (Symptoms have worsened after taking Xeljanz)
- Not assessible (Reason :)

If the overal effectiveness assessment is evaluated as 'Improved', 'Unchanged' or 'Aggrevated', it is analyzed to be clinically significant. If the overall effectiveness assessment is evaluated as 'Not assessible', it is analyzed as not clinically significant. Among the 4 categories, 'Improved' is considered that the drug is effective. 'Unchanged' and 'Aggravate' are considered that there is a lack of effectiveness.

The Mayo score or the Partial Mayo score, which is referred in the effectiveness evaluation, are commonly used in actual medical practice. The Mayo score or the Partial Mayo Score at 8, 16 and 24 weeks(also 52 for the long-term users) will be assessed after the administration of Xeljanz, and Mayo Score measures the number of stool frequency, rectal bleeding, findings of endoscopy, and physician's global assessment. In total, based on the total score of 12 points, 0-2 points is rated as Remission, 3-5 as Mild, 6-10 as Moderate, and 11-12 as Severe. Partial Mayo Score is calculated by the sum of the remaining evaluations, except for the findings of endoscopy score. Based on the total score of 9 points, 0-1 is rated as Remission, 2-4 as Mild, 5-6 as Moderate and 7-9 as Severe.

Remission is defined as Mayo score being less than or equal to 2 (in case of partial Mayo score, the score is less than or equal to 1) and other subscores not greater than 1 and rectal bleeding score of 0. Clinical response is defined as a decrease of Mayo score of more than 3 points and 30% from the baseline and a decrease of 1 or more in rectal bleeding score or rectal bleeding score of 0 or 1. Clinical response per partial Mayo score is a decrease of partial Mayo score of 2 or more and 30 % from the baseline and a decrease of 1 or more in rectal bleeding score or rectal bleeding score of 0 or 1. Clinical remission is defined as Mayo score being less than or equal to 2 and other subscores not bigger than 1. Endoscopic remission is endoscopic subscore of 0 and mucosal healing is defined as an endoscopic score of 0 or 1.

7.4. Data sources

7.4.1. Case report forms

The investigator will review source documents and complete an electronic CRF for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to the third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

7.4.2. Record retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or as required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

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7.6. Data management

CRF data collected by the investigator will be entered into the clinical database. Verifications will be performed after comparison of the double data entry. All missing data or data to be checked will be reported on a query sheet for further verification at the study site. Any data modification will be recorded.

AEs and Medical history will be coded using the MedDRA(Medical Dictionary for Regulatory Activities). Concomitant medication will be coded via ATC code.

Statistical analysis will be carried out with SAS software version 9.2 or a more recent version.

7.7. Data analysis

Analysis will be performed for the pooled data collected by each investigator during the re-examination period. Total number of centers participating, total number of cases enrolled and retrieved, and total number of cases included in the analysis will be presented in summary tables. Evaluation of data will primarily consist of summary displays (eg, descriptive statistics, tables, and graphs).

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 Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment.

7.7.1. Safety analysis

The primary interest of this study is the incidence of AEs investigated during the re-examination period. Incidence of each AE will be presented with 95% confidence interval. Serious, related, and/or unexpected AEs will be summarized separately.

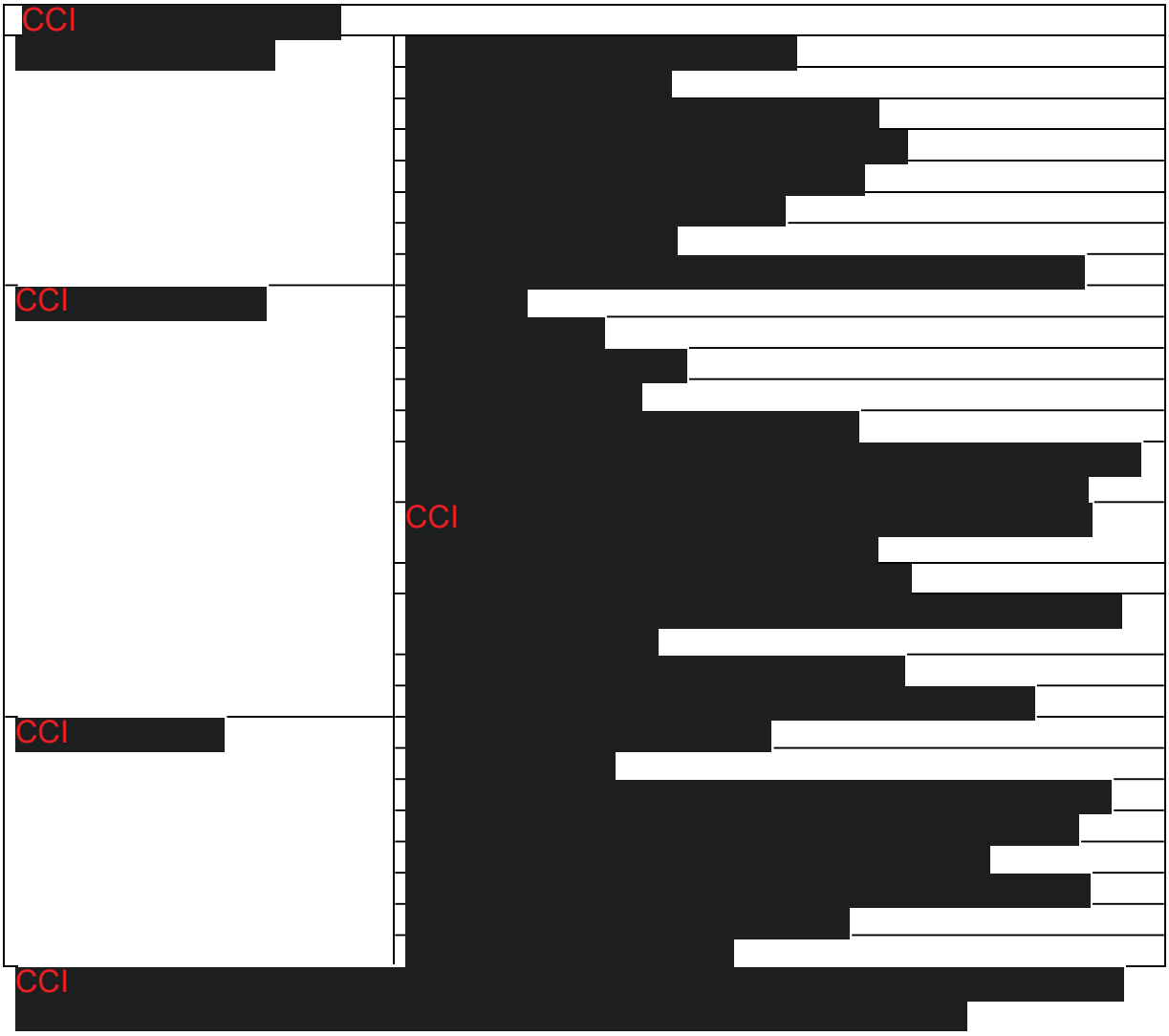
Safety analysis will be performed for all patients registered for this study who are prescribed at least 1 dose of Xeljanz according to the local label and followed up for safety data.

To identify the factors that affect safety, subgroup analysis for various factors will be performed, including the classification of AEs by body system, and comparison of incidence of AEs by sex, age, presence of concurrent diseases, presence of concomitant medications, baseline disease activity, etc.

In case the drug was administered to special populations such as elderly people over 65, or patients with renal or hepatic disorders during the study, subgroup analysis will also be performed for each of those populations. The safety and effectiveness of Xeljanz in pediatric patients have not been established.

Unexpected AEs/ADRs will be classified by medical review with reference to the local product document. Events already included in the “Precautions for use” section of the local product document will be classified as “expected”. All other events that are not included in the “Precautions for use” section of the local product document will be classified as “unexpected”. An unexpected AE includes any events that may be symptomatically and patho-physiologically related to an event listed in the labeling, but differs from the labeled event because of greater severity or specificity.

In the case of an adverse event with important potential risks and important identified risks in relation to the safety specification under the risk management plan, or if missing information patient group is recruited, actions according to the label will be taken, and the safety information is presented separately.



7.7.2. Effectiveness analysis

Effectiveness analysis will be performed for all patients entering this study for the safety analysis whose effectiveness data are available after 24 weeks of treatment, or based on the last assessment performed at the time of treatment discontinuation if the patient does not complete the 24 weeks of treatment. If the patient does not complete the 24 weeks of treatment, the cause of discontinuation will be assessed. For the long-term users, effectiveness analysis will also be performed after the 52 week of the treatment. Cause of discontunation will also be performed for the long term users if the patient does not complete the 52 weeks of treatment.

7.7.3. Quality control

Quality assurance audits will be performed at study centers by Pfizer's own independent quality assurance group or by the clinical research organization. These audits will be

conducted according to Pfizer's procedures and the guidelines for Good Pharmacoepidemiology Practices (GPP) (see Section 8.4).

7.7.4 Statistical consideration

For the safety and effectiveness outcome variables, the statistically significant differences for each classification group are statistically processed using the $\chi 2$ test ($p \leqslant 0.05$). The incidence of each anomaly is presented with a 95% confidence interval. In order to analyze the factors affecting safety, a list of abnormal case expressions was prepared by the types of abnormal cases and by the background factors of the subjects (by gender, age and the presence or absence of accompanying diseases). Analyze the factors using a categorical data analysis method (Chi-square test, Fisher's Exact test). For statistically significant items, the pharmacological significances are described, and major adverse events, drug adverse reactions, and unexpected adverse events will be summarized in a table.

7.8. Limitations of the research methods

This is a non-interventional PMS study conducted in the Republic of Korea to satisfy the requirements of MFDS: The protocol is determined by regulation of MFDS and not the specific disease and drug characteristics. The observational, non-controlled, and non-randomized design of this study has intrinsic limitations.

7.9. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The data privacy statement (in place of an informed consent form) must be in compliance with local regulatory requirements and legal requirements.

The data privacy statement used in this study, and any changes made during the course of the study, must be prospectively approved by both Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible

risks associated with participation. The investigator, or a person designated by the investigator, will obtain the written data privacy statement from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed data privacy statement.

8.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Pfizer for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document the patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be submitted to MFDS prior to the study. The ethical consideration on this study will be evaluated by the IRB/ IEC in each clinical site prior to the study, if the site has an approval process for this PMS study according to the local standard operation procedure of the site.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for GPP issued by the International Society for Pharmacoepidemiology (ISPE), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines, and Korea PMS regulations and/or guidelines.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) SAEs; (2) non-serious AEs (as applicable); and (3) scenarios involving drug

exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in Section 9.4.

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Xeljanz or the time of the patient's data privacy statement if s/he is already exposed to

Xeljanz, and lasts through the end of the observation period of the study which must include at least 28 calendar days following the last administration of Xeljanz; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

Most often, the date of data privacy statement is the same as the date of enrollment. In some situations, there may be a lag between the dates of data privacy statement and enrollment. In these instances, if a patient provides data privacy statement but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Xeljanz, the SAE must also be reported to Pfizer Safety.

9.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to Xeljanz, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Xeljanz caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Xeljanz caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Xeljanz did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

9.4. Definition of safety events

9.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;

- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.4.2. Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In this study, the onset of disease includes but is not limited to the following, which should be considered as medically important SAEs of special interest: serious infection, tuberculosis, cancer, or lymphocyte proliferative disorders. These events will be monitored, analyzed, and reported.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

<u>Hospitalization</u>

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) Xeljanz or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Xeljanz (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to Xeljanz prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable, irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Xeljanz, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Xeljanz in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs includes:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

  An identifiable reporter;

  A suspect product;

The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.5. Single reference safety document

The local product document will serve as the SRSD during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For the first 2 years, 6-month reports will be submitted to MFDS (ie, reports 1-1, 1-2, 2-1, and 2-2,). Thereafter, data collected in the 3rd and finally 4th year will be reported to MFDS annually. The final study report (ie, re-examination report) will be submitted to MFDS in the 4th year to include all data collected during the whole study period (see Section 4).

11. REFERENCES

1. MFDS. Basic standards for the re-examination of new medicines. Notification No. 2013-185.

2. MFDS. Guidelines for re-examination of new medicines. July 2012.

3. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2:1041–8.

4. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–9.

12. LIST OF TABLES

13. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable