Korea Post-Marketing Surveillance for Xeljanz® in Ulcerative Colitis Patients

Sponsor	:	Pfizer Pharmaceuticals Korea Ltd.
Protocol No.	:	A3921343
Product Name	:	Xeljanz® (5 mg: contains tofacitinib citrate 8.078 mg in 1 tablet) (10 mg: contains tofacitinib citrate 16.155 mg in 1 tablet)
Version No.	:	1.1

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Statistical Analysis Plan for rPMS

Amendment Log

Version	Date	Updated by	Reason
1.0	23/Aug/2021	PPD	Initial version
1.1	02/Nov/2022	PPD	Change the imputation for end date of treatment from "The date of the final evaluation of the efficacy" to "The last follow-up date"

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1. 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 patients 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.

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2. Study Objectives and Others

2.1. Objectives

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

2.2. 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 (i.e., 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 or partial Mayo score [Table 1].

[Table 1] Mayo Score for ulcerative colitis

Variable/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 occurred between the first dose of Xeljanz® to the next visit.

As a secondary endpoint, the investigator will perform the final efficacy 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 efficacy 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.

2.3. Study Population

2.3.1. 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

2.3.2. 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.

2.4. Sample Size Considerations

Sample size calculations are not applicable for this study. At least 600 patients will be enrolled in this study to meet MFDS requirements.

3. Analysis Populations

3.1. Safety Analysis Set

Safety analysis set will be included 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.

The cases below shall be excluded from the safety analysis set in the following order:

1) Subjects who have been administered Xeljanz® prior to the contract date
2) Subjects who have not been administered Xeljanz®
3) Subjects who have not met the inclusion/exclusion criterion
4) Subjects who have not been evaluated for any safety-related endpoints

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5) Subjects who have any other significant protocol violation

3.2. Efficacy Analysis Set

The Efficacy analysis set will be included all patients entering this study for the safety analysis whose efficacy 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.
The cases below shall be excluded from the efficacy analysis set in the following order:

1) Subjects who are excluded from the safety analysis set
2) Subjects without general efficacy assessment by the investigator
3) Subjects who are evaluated general efficacy assessment as 'Not assessable' by the investigator
4) Subjects who are have been administrated Xeljanz® for less than 8 weeks (56 days)

3.3. Special Patient Population

As required by MFDS guidelines, if any of the following special patient population is identified, sub-group analysis will be conducted for:

- Geriatric subjects (aged ≥ 65 years)
- Subjects with renal impairment
- Subjects with hepatic impairment

3.4. Long-Term Surveillance Case

Subjects who are treated with Xeljanz® for at least 52 weeks will be classified as long-term users.

3.4.1. Long-Term Safety Analysis Set

Subjects belonging to the safety analysis set and who are treated with Xeljanz® for at least 52 weeks will be classified as long-term safety analysis set.
The cases below shall be excluded from the long-term safety analysis set in the following order:

1) Subjects who are excluded from the safety analysis set
2) Subjects who have been administrated Xeljanz® for less than 52 weeks (364 days)

3.4.2. Long-Term Efficacy Analysis Set

Subjects belonging to the long-term safety analysis set and whose efficacy data are available after 52 weeks (±15 days) of treatment will be classified as long-term efficacy analysis set.
The cases below shall be excluded from the long-term efficacy analysis set in the following order:

1) Subjects who are excluded from the long-term safety analysis set

2) Subjects without general efficacy assessment by the investigator
3) Subjects who are evaluated general efficacy assessment as 'Not assessable' by the investigator

3.5. Population Excluded from Safety Analysis

Population excluded from safety analysis will be reported separately with descriptive analysis only (number, percentage of subjects with adverse events and number of adverse events). However, subject who have not been administered for Xeljanz® will be excluded from this analysis set.

4. Study Endpoints

4.1. Safety Endpoints

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.

4.2. Efficacy Endpoints

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

- 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 assessable

1) Mayo score or partial Mayo score
   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. Partial Mayo score is calculated by the sum of the remaining evaluations, except for the findings of endoscopy score.
2) Mucosal healing (If endoscopy was done)
   Mucosal healing is defined as an endoscopic score of 0 or 1.

- Achieved
- Not achieved

3) Remission

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.

- Achieved
- Not achieved

4) Clinical response

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 30% from the baseline and decrease of 1 or more in rectal bleeding score or rectal bleeding score of 0 or 1.

- Achieved
- Not achieved

5) The final efficacy evaluation determined by the investigator

- Effective
  - Improved
- Not-effective
  - Unchanged
  - Aggravated

5. General Consideration

5.1. Analysis Principles

Statistical analysis will be conducted after database is locked and performed using SAS software version 9.4 or higher according to this Statistical Analysis Plan (SAP). If statistical analysis methods are changed, it will be described in the final clinical study report.

In case of statistical testing, two-sided tests will be conducted at a 5% significance level and the p-value of each test result will be presented in the summary table.

5.2. Handling of Missing and Incomplete Data

5.2.1. Handling of Missing Data

If data are missing or if a subject decided to discontinue form the study, there will be no imputation applied except as specified in section 5.2.2. The impact of missing data will be evaluated as appropriate.

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5.2.2. Handling of Missing and Incomplete Dates

Missing or incomplete dates will be handled by following rule:

	Missing	Imputation
Disease duration	YYYY	0 year
	MM	0 month
	YYYY/MM	No imputation
End date of treatment	'Taking Xeljanz®'	The last follow-up date

6. Statistical Analyses

6.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics, past/present disease, concomitant medications, administration status for the study drug will be summarized with descriptive statistics.

6.1.1. Demographic and Baseline Characteristics

1) Sex will be presented in frequency and percentage.
2) Age (year) will be presented in n, mean, SD, median, minimum and maximum. Also, frequency and percentage of each group categorized according to the distribution for age will be presented.
3) Geriatric subjects (≥ 65 years) will be presented in frequency and percentage.
4) Height (cm) will be presented in n, mean, SD, median, minimum and maximum.
5) Weight (kg) will be presented in n, mean, SD, median, minimum and maximum.
6) Disease duration* (month) will be presented in n, mean, SD, median, minimum and maximum. Also, frequency and percentage of each group categorized according to the distribution for disease duration will be presented.

   *The duration from when ulcerative colitis was first diagnosed until the day that first dose of Xeljanz® is taken.

   $$\text{Disease duration (month)} = (\text{Year of disease duration} \times 12) + \text{Month of disease duration}$$
7) Disease severity will be presented in frequency and percentage.
8) Latent tuberculosis will be presented in frequency and percentage.
9) Herpes zoster vaccination will be presented in frequency and percentage.
10) Smoking will be presented in frequency and percentage.

6.1.2. Previous Ulcerative Colitis Treatment

Previous ulcerative colitis treatment will be analyzed as treatment which purpose is to treatment UC and checking 'Yes' for "terminated prior to administration of Xeljanz®", on 'concomitant medication' page of eCRF.

1) Previous ulcerative colitis treatment will be presented in frequency and percentage.
2) Previous ulcerative colitis treatment classified by Level 1 and Level 2 according to the latest version of Anatomical Therapeutic Chemical (ATC) classification system in detail will be summarized with the number of subjects having concomitant medication, percentage and the number of concomitant medication.

6.1.3. Medical History

1) Other past/present diseases will be presented in frequency and percentage.
2) Other past/present diseases classified by System Organ Class (SOC) and Preferred Term (PT) according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be summarized with the number of subjects having other past diseases, percentage and the number of other past diseases.
3) Renal impairment will be presented in frequency and percentage.
4) Hepatic impairment will be presented in frequency and percentage.

6.1.4. Concomitant Medication

Concomitant medication will be analyzed as all treatment included present ulcerative colitis treatment and other concomitant medication except previous ulcerative colitis treatment.

1) Concomitant medication will be presented in frequency and percentage.
2) Concomitant medication classified by Level 1 and Level 2 according to the latest version of ATC classification system in detail will be summarized with the number of subjects having concomitant medication, percentage and the number of concomitant medication.

6.1.5. Administration Status of Xeljanz®

1) Total duration of administration (day) will be presented in n, mean, SD, median, minimum and maximum. Also, frequency and percentage of each group categorized according to the distribution for total duration of administration will be presented.

$$\text{Total duration of administration (day)} = \sum_{\text{First}}^{\text{Last}} (\text{End treatment} - \text{Start treatment} + 1)$$

2) Total dose of administration (mg) will be presented in n, mean, SD, median, minimum and maximum.

$$\text{Total dose of administration (mg)} = \sum_{\text{First}}^{\text{Last}} \{\text{Dose per administration} \times \text{Daily dosing frequency} \times (\text{End treatment} - \text{Start treatment} + 1)\}$$

3) Daily average dose of administration (mg/day) will be presented in n, mean, SD, median,

minimum and maximum. Also, frequency and percentage of each group categorized according to the distribution for daily average dose of administration will be presented.

$$\text{Daily average dose of administration (mg/day)} = \frac{\text{Total dose of administration (mg)}}{\text{Total duration of administration (day)}}$$

6.1.6. Completion of the treatment and reasons of discontinuaion

Completion of the 24 weeks treatment (52 week of treatment for long-term user) will be presented in frequency and percentage. For the subjects who have not completed the 24 weeks of treatment (52 week of treatment for long-term user), the reasons of discontinuation will be presented in frequency and percentage.

6.2. Safety Analyses

Safety analyses will be performed based on data of safety analysis set. All adverse events in CRF will be classified by SOC and PT according to the latest version of MedDRA.

1) All adverse events investigated after administration of Xeljanz® during the study will be summarized with the number of subjects having adverse events, incidence of adverse events with 95% confidence interval (C.I) and the number of adverse events by categorizing as follows:
   - Serious adverse events and serious adverse drug reactions
   - Unexpected serious adverse events and unexpected serious adverse drug reactions
   - Unexpected adverse events and unexpected adverse drug reactions
   - Adverse events and adverse drug reactions
   - Adverse events of safety concerns*

     *Adverse event with important identified risks and important potential risks in relation to the safety specification under the risk management plan
2) All adverse events investigated after administration of Xeljanz® during the study will be summarized with the frequency and percentage of adverse events by categorizing as follows:
   - Occurrence status of adverse events by their severity
     - Mild
     - Moderate
     - Severe
   - Occurrence status of adverse events by their outcome
     - Recovered
     - Recovered with sequelae
     - Recovering
     - Not recovered
     - Unknown

- Occurrence status of adverse events by their seriousness

  [SAE]
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of hospitalization
  - Results in persistent or significant disability/incapacity
  - Results in congenital anomaly/birth defect
  - Other important medical event

  [Non-SAE]
- Occurrence status of adverse events by action taken
  - Permanently discontinued
  - Temporary discontinued or delayed
  - Dose reduced
  - Dose increased
  - No change
  - Not applicable
- Occurrence status of adverse events by their causality assessment to Xeljanz®
  - Related to Xeljanz®: ① Certain
    ② Probable/likely
    ③ Possible
    ⑤ Conditional/unclassified
    ⑥ Unassessable/unclassifiable
    ⑦ Not applicable
  - Not related to Xeljanz®: ④ Unlikely
- Occurrence status of adverse events by their other causality assessment (In case of 'Unlikely')
  - Disease under the study
  - Other diseases
  - Concomitant treatment-medication or non-medication
  - Other

3) Occurrence status of adverse events by demographic and other baseline characteristics
   - The incidence of adverse events and 95% C.I will be presented by categorical variables of demographic and other baseline characteristics.
   - To identify statistically significant difference in the incidence of adverse events by categorical variables of demographic and other baseline characteristics, Chi-square test (χ^2 test) or Fisher's exact test (if the expected frequency for each cell under 5 is more than 20%) will be performed.

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4) Analysis of factors that affect the safety
   - In the re-examination report, logistic regression of multivariate analysis will be performed and an odds ratio with 95% C.I and p-value will be presented to identify the factors that affect incidence of adverse events in demographic and other baseline characteristics.
5) Analysis for special patient populations [geriatric subjects (aged ≥ 65 years), subjects with renal impairment, subjects with hepatic impairment]
   - Adverse events and adverse drug reactions collected in each special patient population will be presented the number of subjects having adverse events, incidence of adverse events and the number of adverse events for each SOC and PT.
6) Analysis for population excluded from safety analysis
   - All adverse events investigated after administration of Xeljanz® for population excluded from safety analysis will be summarized with the number of subjects having adverse events, incidence of adverse events with 95% C.I and the number of adverse events by categorizing as follows.
     - Serious adverse events and serious adverse drug reactions (in the re-examination report only)
     - Unexpected serious adverse events and unexpected serious adverse drug reactions (in the re-examination report only)
     - Unexpected adverse events and unexpected adverse drug reactions (in the re-examination report only)
     - Adverse events and adverse drug reactions

6.3. Efficacy Analyses

Efficacy analyses will be performed based on data of efficacy analysis set

1) Mayo index, Mayo score and partial Mayo score
   - Mayo index (stool frequency, rectal bleeding, physician's global assessment and finding of endoscopy), Mayo score or partial Mayo score at baseline, week 8 (±15 days), week 16 (±15 days), week 24 (±15 days) and changes from the baseline to last value will be presented in n, mean, SD, median, minimum and maximum. And changes from the baseline to last values will be tested by using paired t-test (or Wilcoxon signed rank test).
2) Mucosal healing (If endoscopy was done)
   - Mucosal healing at week 8 (±15 days), week 16 (±15 days), week 24 (±15 days) will be presented in frequency and percentage.
     - Achieved
     - Not achieved
3) Remission
   - Remission at week 8 (±15 days), week 16 (±15 days), week 24 (±15 days) will be

presented in frequency and percentage.

- Achieved
- Not achieved

4) Clinical response
   - Clinical response at week 8 (±15 days), week 16 (±15 days), week 24 (±15 days) will be presented in frequency and percentage.
     - Achieved
     - Not achieved
5) Final efficacy assessment by the investigator
   - Final efficacy assessment by the investigator classified as follows will be presented in frequency and percentage.

     [Effective]
     - Improved

     [Not-effective]
     - Unchanged
     - Aggravated
6) Effective rate by demographic and other baseline characteristics
   - Effective rate and 95% C.I will be presented by categorical variables of demographic and other baseline characteristics.
   - To identify statistically significant difference in the effective rate by categorical variables of demographic and other baseline characteristics, Chi-square test (χ^2 test) or Fisher's exact test (if the expected frequency for each cell under 5 is more than 20%) will be performed.
7) Analysis of factors that affect the efficacy
   - In the re-examination report, logistic regression of multivariate analysis will be performed and an odds ratio with 95% C.I and p-value will be presented to identify the factors that affect effective rate in demographic and other baseline characteristics.

6.4. Long-Term Surveillance Case Analyses

The following analyses will be performed for long-term user who are treated with Xeljanz® for at least 52 weeks.

1) Safety analyses for long-term user

   Safety analyses for long-term user will be performed based on data of long-term safety analysis set.

   Repeated [6.2. Safety Analyses] - 1) ~ 4).
2) Efficacy analyses for long-term user

   Efficacy analyses for long-term user will be performed based on data of long-term efficacy analysis set and analysis at week 52 (±15 days) will be added.

Repeated [6.3. Efficacy Analyses] - 1) ~ 7).

7. Reporting Conventions

Continuous variables will be summarized by descriptive statistics including n, mean, SD, median, minimum and maximum, and categorical variables will be presented in frequency and percentage. Summary statistics including mean, SD, median, minimum and maximum, etc. will be reported to two decimal places using rounding off.

The p-values through the statistical test will be reported to four decimal place and if p-values smaller than 0.0001 will be written as '<0.0001'.

8. Attachments

8.1. Attachment 1: Dummy Table