Statistical Analysis Plan

Korean Post-marketing Surveillance for Xeljanz®

Sponsor : Pfizer Pharmaceuticals Korea Ltd.
Protocol No. : A3921249
Product Name : Xeljanz®
Version No. : Ver.2.0

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Amendment Log

Version	Date	Updated by	Reason
Ver.1.0	02/Mar/2016	PPD	Initial version
Ver.1.1	11/Mar/2019	PPD	Modify in the medical coding of drugs (concomitant drugs and previous RA drugs)
Ver.1.2	27/Feb/2020	PPD	● Modify in the medical coding of past/present diseases and adverse events ● Add serious unexpected adverse events/serious unexpected adverse drug reactions analysis ● Add adverse events of special interest/adverse drug reactions of special interest analysis
Ver.2.0	24/Feb/2021	PPD	● Modify in the protocol amendment ● Add sub group analyses set

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1. Rationale and Background

Xeljanz® (tofacitinib) is a potent, oral janus kinase inhibitor. Xeljanz® was 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. It may be used as monotherapy or in combination with methotrexate or other non biologic disease-modifying anti-rheumatic drugs (DMARDs).

In addition, MFDS approved new indications for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to previous antirheumatic drugs (DMARDs) on 20 Sep 2018. It may be used in combination with methotrexate or other nonbiologic disease-modifying anti-rheumatic drugs (DMARDs). The efficacy of Xeljanz as a monotherapy has not been studied in psoriatic arthritis.

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Background information on Xeljanz® can be obtained from the current version of the local product document (ie, local labelling), which is the single reference safety document (SRSD) for information relating to Xeljanz® in this study.

2. Study Objective(s) and Others

2.1. Study Objective

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

2.2. Study Design

2.2.1. General 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 RA who have had an inadequate response or intolerance to methotrexate. 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).

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Also, investigators collect data on the Xeljanz retrospectively from the subjects who have been administered the Xeljanz according to the local product documents but not participated in this study for 2 years after completion of re-examination.

Safety is the primary interest of this study, which will be assessed based on adverse events (AEs) that occur during the 6 months from the first dose of Xeljanz®. The efficacy endpoints will be the modified Disease Activity Score using 28 joint counts (DAS28) change from baseline, European League Against Rheumatism (EULAR) response, and American College of Rheumatology 20% improvement criteria (ACR20) response after treatment.

2.2.2. Duration of the Study

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CCI The re-examination period is from 02 April 2014 to 01 April 2020, and the final study report should therefore be submitted by 01 July 2020. Additional safety and effectiveness result report from prospective and retrospective studies for additional 2 years would be submitted as part of RMP in accordance with local regulations.

2.3. Study Population

2.3.1. Inclusion Criteria

All patients will have received at least 1 dose of Xeljanz® for the treatment of the following indication as per local labelling. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study.

- Moderately to severely active RA in adult patients who have had an inadequate response or intolerance to methotrexate.
- Active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or intolerance to previous antirheumatic drugs (DMARDs).
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study (In case of subjects to be collected data retrospectively, whether or not to obtain the informed consent document depends on the decision by the institutional review board

(IRB)/independent ethics committee (IEC).).

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.

* For patients who develop the laboratory abnormalities as follows, it should be discontinued Xeljanz® dosing according to the 'warning and precautions' in the local labelling.

- Patients with an ANC <500 cells/mm^3.
- Patients with a hemoglobin level <8 g/dL.

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3. Analysis Populations

3.1. Safety Analysis Set

Safety analysis set will be included all patients who have received at least 1 dose of Xeljanz® according to local product document and have been assessed for safety information including AEs by investigator.

The following cases will be excluded from the safety analysis set.

- Patients who have been enrolled and completed before contracting with health care center.
- Patients who have not been administered for Xeljanz®.
- Patients who have not met the inclusion/exclusion criterion.
- Patients who have experienced off-label use against Xeljanz® local product document.

3.2. Efficacy Analysis Set

Efficacy analysis set will be included all patients who received at least 1 dose of Xeljanz® according to the local product document, and are available for an efficacy assessment performed after 6 months of treatment, or based on the last assessment performed at the time of treatment discontinuation if the patient dose not complete 6 months of treatment.

The following cases will be excluded from the efficacy analysis set in the following order:

- Patients who are excluded from the safety analysis set
- Patients without overall assessment as efficacy assessment item

3.3. Special Patient Population

Special patient population will include elderly people (age ≥ 65) or patient with renal or hepatic disorders who have been administered Xeljanz® during the study, respectively.

3.4. Sub-group Analysis set by Indication

The following sub-groups are defined for sub-group analysis of safety and efficacy by indication:

- Sub-group 1: Subjects with RA indication.
- Sub-group 2: Subjects with PsA indication.

3.5. Off-label Evaluation Patients

Off-label evaluation patients will be included patients who have experienced off-label use against Xeljanz® local product document during the study.

4. Study Endpoints

4.1. Demography and Baseline Characteristics

Demography and baseline characteristics include the following.

- Demography characteristic (Age, Sex, Height, Weight)
- Herpes zoster vaccination

- Smoking
- Indication (RA, PsA)
- Duration of the disease
- Severity of disease activity
- Radiologic progression
- Previous treatments (Status (yes/no), previous RA or PsA drugs classified by latest version of Anatomical Therapeutic Chemical (ATC) code as level 1 and level 2)
- Latent tuberculosis
- Renal/hepatic disorder
- Other past/present diseases (Status (yes/no), past/present disease classified by latest version of MedDRA)
- Allergic history

4.2. Administrative Status for Medicinal Products

- Treatment duration
- Daily dose

4.3. Concomitant Treatments

Assessment variable for concomitant treatments of patients will be included the following.

- Concomitant medication status
- Concomitant drugs classified by latest version of ATC code as level 1 and level 2

4.4. Safety Endpoints

The incidence and number with 95% confidence interval for all adverse events/adverse drug reactions investigated within 6 months from initial dosing after at least 1 dose of Xeljanz® during the study.

- Seriousness
- Severity
- Causality assessment
- Action taken
- Outcome

4.5. Efficacy Endpoints

Efficacy variables will be included DAS28, EULAR response, and ACR20 response. Also, overall assessment will be performed as 'Improved', 'No change', 'Aggravated' and 'Not Done' based on the variables, tests and clinical discretion by investigator.

1) DAS28

DAS28, a modified version of the original Disease Activity Score (DAS), is a quantitative measure of disease activity used to monitor the treatment of RA. DAS28 is calculated using the following formula that includes the number of tender joints and swollen joints (28 joints maximum).

$$DAS28(ESR) = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.014 \times VAS + 0.70 \times \ln(ESR)$$

or,

$$DAS28(CRP) = 0.56 \times \sqrt{TJC28} + 0.28 \times \sqrt{SJC28} + 0.014 \times VAS + 0.36 \times ln(CRP + 1) + 0.96$$

Abbreviations: ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, TJC28=28 tender joint count, SJC28=28 swollen joint count, VAS=visual analogue scale

2) EULAR response

The DAS-based EULAR response criteria classify individual patients as none, moderate, or good responders, depending on the extent of change and the level of disease activity reached (refer to the Figure 1).

[Figure 1] DAS28-based EULAR response criteria

DAS28 at endpoints	Improvement in DAS28 from baseline		
	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good		
>3.2 and ≤5.1		Moderate	
>5.1			None

3) ACR20 response

An ACR20 response is defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in 3 of the 5 other disease activity measures (item 3 to 7) listed in Table 1. If ACR20 is assessed in the usual clinical practice, the results should be recorded as "done-achieved" or "done-not achieved". If ACR20 is not assessed, the investigator records "not done" in the CRF.

[Table 1] American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis

Disease activity measures:
1. Tender joint count
2. Swollen joint count

3. Patient's assessment of pain
4. Patient's global assessment of disease activity
5. Physician's global assessment of disease activity
6. Patient's assessment of physical function
7. Acute-phase reactant value: ESR or CRP level

Abbreviations: ESR=erythrocyte sedimentation rate, CRP=C-reactive protein

4) Overall assessment

Overall assessment will be performed as 'Improved', 'No change', 'Aggravated' and 'Not Done' based on the variables, tests and clinical discretion by investigator.

5. General Consideration

5.1. Handling of Missing and Incomplete data

5.1.1. Handling of Missing data

If data are missing or if a subject decides to discontinue from the study, there will be no imputation applied. The impact of missing data will be evaluated as appropriate.

5.1.2. Handling of Missing and Incomplete date

Missing or incomplete dates will be handled by following rule:

	Missing	Imputation
Date of treatment stop date	DD	01
	MM/DD	01/01
	YYYY/MM/DD	No imputation

6. Statistical Analyses

6.1. Demography and Baseline Characteristics

Demography and baseline characteristics will be demonstrated by descriptive statistics.
Continuous variables will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum) and categorical variables will be presented in frequency and percentage (n, %).

- Age will be presented in n, mean, standard deviation, median, minimum and maximum and frequency and percentage of categorized age groups (exact age will be calculated based on birth year and month).
- Sex will be presented in the frequency and percentage.
- Height (cm) and weight (kg) will be presented in the frequency and percentage of

categorized height and weight groups.

- Herpes zoster vaccination status and smoking status will be presented in frequency and percentage.
- Indication (RA, PsA) will be presented in the frequency and percentage.
- Duration of the disease will be presented in n, mean, standard deviation, median, minimum and maximum.
- Severity of disease activity and radiological progression status will be presented in frequency and percentage.
- Previous RA or PsA treatment will be presented in frequency and percentage and specifically, previous RA or PsA drugs classified by latest version of ATC code will be presented in frequency and percentage.
- Status of latent tuberculosis will be presented in frequency and percentage.
- Past/present disease status will be presented in frequency and percentage and past/present disease classified by latest version of MedDRA in detail will be presented in each frequency and percentage.
- Renal/hepatic disorder status and allergic history will be presented in frequency and percentage.

6.2. Administrative Status for Medicinal Product

- Treatment duration and daily dose will be presented by descriptive statistics as n, mean, standard deviation, median, minimum and maximum. If treatment is ongoing, the date of final efficacy evaluation will replace the treatment stop date. But, if the treatment is ongoing after the date of final efficacy evaluation, the date of signature of investigator will replace the treatment stop date.

$$Total\ \ treatment\ \ duration(day) = \sum_{First}^{Last} \{(Stop\ \ date) - (Start\ \ date) + 1\}$$

- Total dose (mg) will be presented by descriptive statistics as n, mean, standard deviation, median, minimum and maximum.

$$Total\ \ dose(mg) = \sum_{First}^{Last} \{(Daily\ \ dose)\} \times \{(Stop\ \ date) - (Start\ \ date) + 1\}$$

- Daily average dose (mg/day) will be presented by descriptive statistics as n, mean, standard deviation, median, minimum and maximum.

$$Daily\ \ average\ \ dose(mg/day) = \frac{Total\ \ dose}{\sum_{First}^{Last}\{(Stop\ \ date) - (Start\ \ date) + 1\}}$$

6.3. Concomitant Treatments

- Concomitant medication status will be presented in frequency and percentage.
- Concomitant drugs classified by latest version of ATC code will be presented in n, percentage and frequency.

6.4. Safety Analyses

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

1) All adverse events investigated after administration of Xeljanz® during the study will be summarized by frequency and percent (n, percentage) by categorizing as follows. Also, it will be presented in n, incidence rate, 95% confidence interval of incidence rate and number of events for each SOC and PT.
   - Frequency analysis of adverse events/adverse drug reactions
   - Frequency analysis of serious adverse events/serious adverse drug reactions
   - Frequency analysis of serious unexpected adverse events/serious unexpected adverse drug reactions
   - Frequency analysis of unexpected adverse events/unexpected adverse drug reactions
   - Frequency analysis of adverse events of special interest/adverse drug reactions of special interest
   - Occurrence status of adverse events/adverse drug reactions by its seriousness
     - 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
     - Important medical event: 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
   - Occurrence status of adverse events/adverse drug reactions by its severity
     - Mild
     - Moderate
     - Severe
   - Occurrence status of adverse events/adverse drug reactions by its causality assessment
     - Related to this medicinal product: ① Certain

② Probable/likely
③ Possible
⑤ Conditional/unclassified
⑥ Unassessable/unclassifiable

- Not related to this medicinal product: ④ Unlikely

- Occurrence status of adverse events/adverse drug reactions by its action taken
  - Permanently discontinued
  - Temporarily discontinued or delayed
  - Dose reduced
  - Dose increased
  - No change
  - Not applicable
- Occurrence status of adverse events/adverse drug reactions by its outcome
  - Recovered
  - Recovered with sequelae
  - Recovering
  - Not recovered
  - Unknown

2) Occurrence status of adverse events by demography and baseline characteristics

Occurrence status of adverse events will be presented in frequency and percentage and incidence rate with 95% confidence interval based on categorical variables of demography and baseline characteristics of the patients. To identify statistically significant difference in occurrence of adverse events by demography and baseline characteristics, Chi-square test or Fisher's exact test will be performed.

3) Occurrence status of adverse events by concomitant treatment

Occurrence of adverse events will be presented in frequency and percentage and incidence rate of adverse events with 95% confidence interval by concomitant treatment status. To identify statistically significant difference in occurrence of adverse events by concomitant treatment status, Chi-square test or Fisher's exact test will be performed.

4) Analysis of factors that affect the safety

In the re-examination report, logistic regression analysis of multivariate analysis will be performed and presented an odds ratio with 95% confidence interval to identify the factors that affect occurrence of adverse events in demography and baseline characteristics, or concomitant treatment status, etc.

5) Distribution for special patient populations (elderly (age over 65 years old), renal disorder, hepatic disorder) will be presented. Also, adverse events and adverse drug reactions collected

by these groups will be presented in incidence rate and number events of it for each SOC and PT.

- For children and pregnant women, it will be performed in off-label patient analysis because administration of children (age less than 19 years old) and pregnant women is contraindicated according to the local product document.

6) Distribution for off-label evaluation patients will be presented. Also, adverse events and adverse drug reactions collected by these groups will be presented in incidence rate and number events of it for each SOC and PT.

6.5. Efficacy Analyses

Analysis of efficacy assessment will be performed based on data of efficacy analysis set.

1) DAS28 (ESR) or DAS28 (CRP) which measured at baseline and final assessment after follow-up visits will be presented by descriptive statistics. And the changes in it from baseline to final assessment will be tested by using paired t-test (or Wilcoxon signed rank test).
2) EULAR response (none, moderate, good) by DAS28 which measured at baseline and final assessment after follow-up visits will be presented in frequency and percentage.
3) ACR20 response which measured at baseline and final assessment after follow-up visits will be presented in frequency and percentage.
4) Overall assessment will be classified with effective/not-effective as follows, presented in frequency and percentage of it.
   - Effective
     - Improved
   - Not-effective
     - No change, Aggravated

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6.6. Sub-group Analyses by Indication

Analysis of safety and efficacy assessment will be performed based on sub-group analysis set.

6.6.1. Sub-group Analyses by RA

- [6.4. Safety Analyses] - 1)
- [6.5. Efficacy Analyses] - 1) ~ 4)

6.6.2. Sub-group Analyses by PsA

- [6.4. Safety Analyses] - 1)
- [6.5. Efficacy Analyses] - 1), 2), 4)

7. Reporting Principles

All results of analysis will be reported table and graph to assist the understanding for the study results. Continuous variables will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum) and categorical variables will be presented in frequency and percentage (n, %). Summary statistics including n, mean, standard deviation, median, minimum and maximum, frequency, etc will be reported to two decimal places using rounding off.

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