NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**Korean Post-marketing Surveillance for Xeljanz® in Rheumatoid arthritis and Psoriatic arthritis patients**
Protocol number	A3921249
Protocol version identifier	Amendment 11
Date of last version of protocol	26 Apr 2022
Active substance	Tofacitinib citrate Selective immunosuppressant (L04AA29)
Medicinal product	Xeljanz® (5 mg: contains tofacitinib citrate 8.078 mg in 1 tablet)
Research question and objectives	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 Ministry of Food and Drug Safety (MFDS).
Author	PPD Pfizer Pharmaceuticals Korea Ltd. PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR20	American College of Rheumatology 20% improvement criteria
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
DAS	Disease Activity Score
DAS28	Disease Activity Score using 28 joint counts
DMARD	disease-modifying anti-rheumatic drug
EDP	exposure during pregnancy
EULAR	European League Against Rheumatism
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
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SRSD	single reference safety document
SJC28	28 swollen joint count
TC	total cholesterol
TJC28	28 tender joint count
VAS	visual analogue scale
WHO-ART	World Health Organization - Adverse Reaction Terminology
Xeljanz®	tofacitinib citrate

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD, MD	Non-Interventional Study Lead	Pfizer Pharmaceuticals Korea Ltd.	PPD

3. AMENDMENTS AND UPDATES

Protocol Amendments 1 to 11 are summarized in the table below.

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	14 April 2015	Substantial	Section 5 Rationale and background Section 7 Research methods Section 8 Protection of human subjects Section 9 Management and reporting of adverse events/adverse reactions Section 11 References	• Change study design from retrospective to prospective. • Add more detailed data collection procedures. • Add the description of data privacy statement requirement and patient withdrawal. • Change safety language to prospective study. • Correct indication as per local product document. • Add MFDS guidelines as references.	The design of the original protocol dated 28 October 2014 was not accepted by the MFDS. The protocol is amended to satisfy MFDS' requirements
Amendment 2	29 October 2015	Substantial	Section 1 List of abbreviations Section 4 Milestones Section 7.1 Study design Section 7.2.5.2 Demography and baseline characteristics Section 7.3.1.2 Laboratory test Section 7.3.2 Efficacy variables Section 7.7.1 Safety analysis Section 7.7.2 Efficacy analysis Section 9.4.2 Serious adverse events Section 11 References Section 12 List of tables	• Add some abbreviations. • Change planned date for end of data collection from 01 March 2020 to 01 April 2020. • Add recording medical histories of latent tuberculosis, renal disorder and hepatic disorder. • Add recommended laboratory tests. • Add efficacy variable ACR20, its definition, and assessment. • Add statement that SAEs such as serious infection, tuberculosis, cancer, or lymphocyte proliferative disorders will be considered as SAEs of special interest and summarized separately. • Add a reference about ACR20. • Add a list of tables.	The protocol is amended to reflect MFDS' comments on Amendment 1.

Amendment 03	25 January 2016	Substantial	Section 7.2.2 Exclusion criterial Section 7.3.2 Efficacy Variables Section 7.6 Data management	• Change for exclusion criteria to clarify the standard according to dosage and administration • Add the investigators overall assessment about efficacy based on DAS 28 or ACR 20 • Change the coding dictionary for Disease to WHO-ART.	Clarification of exclusion criteria and efficacy assessment
Amendment 04	01 August 2016	Substantial	Section 7.2.2 Exclusion criterial Section 7.3.1.2 Laboratory Test Section 7.7.2. 7.7.2. Efficacy analysis	• Change the contents from exclusion criterial to Laboratory Test about drug discontinuation criterial in accordance with laboratory test result by MFDS requirements. • Include the contents of effectiveness ratio and less effectiveness ratio about overall efficacy assessment by MFDS requirement	Amended to reflect MFDS' comments on Amendment 3
Amendment 05	11December 2018	Substantial	Section 5 Rationale and background Section 7.1 Study design Section 7.5 Study size	• Considering the disease prevalence and status of administration, the number of target subjects is amended	Amended to adjust the number of target subjects

		Administrative	Section 7.6 Data management	• Specified coding dictionary of concomitant medication as an ATC code.	Specified con-med coding dictionary
Amendment 06	21 February 2019	Substantial	Section 7.2.1 Inclusion criteria Section 7.2.2 Exclusion criteria Section 7.2.4 Dosage and administration Section 7.2.5.2 Demography and baseline characteristics Section 7.3.2.1 Efficacy evaluation 7.4.1 Case report forms Section 8.1 Patient information Section Patient concent Section 8.4 institutional Review Board(IRB)/Independent Ethics Committee (IEC)	• Add new indications according to the updated label	Add new indications (for psoriatic rheumatoid arthritis (PsA))
Amendment 07	17 June 2019	Substantial	Section 7.2.5.2 Demography and baseline characteristics	• Add the severity criteria of disease activity for PsA indication	The protocol is amended to reflect MFDS' comments on Amendment 6.
Amendment 08	07 August 2019	Substantial	Study title Section 5 Rationale and background Section 7.1 Study design Section 7.2.3 Duration of the study Section 7.2.5 Study procedures Section 7.5 Study size	• Specify the indication in the title • Add abbreviationsSample size adjust, add RMP scope • Add retrospective data collection method	Target sample size adjustment, add RMP scope according to the MFDS comments.

Amendment 09	14 January 2020	Substantial	Section 4 Milestones Section 7.7.1 Safety analysis	• Add RMP report submission timeline • Add analysis and evaluation methods for safety specification according to RMP	Amended according to the MFDS comments
Amendment 10	19 March 2020	Administrative Substantial	Section 2 Responsible parties Section 7.2.1 Inclusion criterial Section 7.2.2 Exclusion criterial Section 7.2.5.1 Information of Institution Section 7.2.5.2 Demography and baseline characteristics	• Change the non-interventional study lead • Add the abbreviation • Change the collected data • Guidance for obtaining the data privacy statement in the subjects to be collected data retrospectively • Change the collected data	Coordination of internal task Change of research methods
Amendment 11	26 Apr 2022	Minor	Section 2 Responsible parties Section 4 Milestones Section 5 Rationale and Background Section 7.1 Study design Section 7.2.3 Duration of the study Section 7.5 Study size	• Change of NISL • Change of study period	Coordination of internal task Amended according to MFDS' comments

Abbreviations: ACR20=American College of Rheumatology 20% improvement criteria, MFDS=Ministry of Food and Drug Safety, SAE=serious adverse event.

4. MILESTONES

Milestone	Planned date
Start of data collection	01 May 2015
End of data collection	01 April 2020
First year (1-1) periodic report (MFDS)	01 December 2014
First year (1-2) periodic report (MFDS)	01 June 2015
Second year (2-1) periodic report (MFDS)	01 December 2015
Second year (2-2) periodic report (MFDS)	01 June 2016
Third year annual report (MFDS)	01 June 2017
Fourth year annual report (MFDS)	01 June 2018
Fifth year annual report (MFDS)	01 June 2019
Final study report (MFDS)	01 July 2020
RMP periodic report will be submitted every year after RMP approval	

Abbreviations: MFDS=Ministry of Food and Drug Safety.

5. 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 nonbiologic 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.

6. RESEARCH QUESTION AND OBJECTIVES

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.

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 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 until 26 June 2022.

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 (see Section 7.3).

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:

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)).

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 an absolute lymphocyte count(ALC) <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

CCI [redacted] The re-examination period is from 02 April 2014 to 01 April 2020, and the final re-examination report should therefore be submitted by 01 July 2020. Additional safety and effectiveness result

report from prospective and retrospective studies until 26 June 2022 would be submitted as part of RMP.

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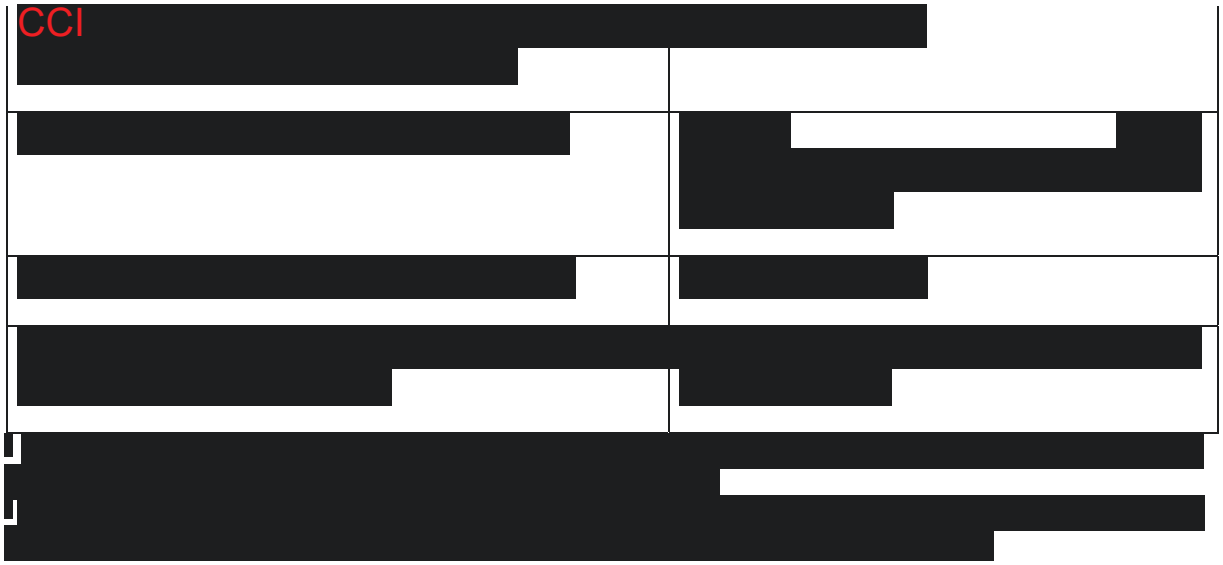

7.2.5. Study procedures

The investigator should enroll all patients to whom Xeljanz is prescribed for the first time according to the local product document and who agree to participate in this study by signing the data privacy statement (used in place of the informed consent form) by continuous registration method. In case of the patients who already have been administered Xeljanz but not participated in this study, study related information from the first administration until the last day of the observation period should be collected retrospectively. Xeljanz tablets 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 6 months of treatment. If the patient does not complete 6 months 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. Information of institution

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

- Name of institution: Enter the code number assigned to each institution.
- 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 6 months treatment, check "yes". Otherwise, check "no" and choose reason for the discontinuation: AE; lack of efficacy; 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 in case of subjects to be collected data prospectively. If not, check "no" and exclude the case from the study. If the patient has signed the data privacy statement, check the box of "yes" on the CRF in case of subjects to be collected data retrospectively, and if not, check "no" on the CRF and check if it is available for the exempt of the data privacy statement according to the IRB/IEC's decision

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 in case of subjects to be collected data prospectively. Record age of the patient at the first dosing of Xeljanz in case of subjects to be collected data retrospectively. The age should be calculated by the year of birth.

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

- Height: Record by unit of 'cm' in case of subjects to be collected data prospectively. Check the box indicated to the range of height(unit of 'cm') in case of subjects to be collected data retrospectively

- Weight: Record by unit of 'kg' in case of subjects to be collected data prospectively. Check the box indicated to the range of weight(unit of 'kg') in case of subjects to be collected data retrospectively

- 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 RA and PsA.

- Severity of disease activity:

  RA: Disease activity should be assessed by initial DAS28. DAS28 >5.1 is considered to be indicative of high disease activity; DAS28 >3.2 and ≤5.1 indicates moderate disease activity; DAS28 ≤3.2 indicates low disease activity. A patient scoring less than 2.6 is defined as being in remission.

PsA: Disease activity should be assessed by initial DAS28. DAS28 >5.1 is considered to be indicative of high disease activity; DAS28 >3.2 and ≤5.1 indicates moderate disease activity; DAS28 ≤3.2 indicates low disease activity. A patient scoring less than 2.6 is defined as being in remission.

- Radiologic progression: Radiologic progression based on clinically relevant evaluation methods, such as X-ray, ultrasonography, or magnetic resonance imaging, should be recorded, if evaluated.

- Previous treatments: Only record RA and PsA 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 disorder: Record if the patient has renal disorder: yes (severe/moderate/mild); no.

- Hepatic disorder: Record if the patient has hepatic disorder: yes (severe/moderate/mild); no.

- 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.

- Allergic history: Check either "yes" or "no" on the CRF. If "yes", record the trigger factors and the corresponding symptoms.

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 total daily 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 total daily dose 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 efficacy data

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

7.3. Variables

7.3.1. Safety variables

Safety will be assessed by the investigator based on AEs that occur during 6 months 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 Korean Version of World Health Organization - Adverse Reaction Terminology (WHO-ART) distributed by Korean Ministry of Health and Welfare. If there is no not an appropriate term in the WHO-ART, 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 9 for 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.

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 1. 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 1 Recommended Laboratory Test

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

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 the laboratory normal ranges of the center, test results before and after Xeljanz treatment, a causal relationship to Xeljanz, and any comments from the investigator.

According to Contraindication on label, the investigator should discontinue the patient's treatment if the laboratory test results are as below

- Patients with an absolute neutrophil count (ANC) <500 cells/mm^{3*}

- Patients with a hemoglobin level <8 g/dL

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. Efficacy variables

Efficacy variables include DAS28, EULAR response, and ACR20 response. The investigator can make an assessment of the overall efficacy – improved, no change, aggravated - based on each test results and clinical judgment.

7.3.2.1. Efficacy evaluation

Efficacy assessment will be performed by the accredited investigator in the Korean health care center. In the case of RA, The investigator will perform the efficacy assessment at baseline and after 6 months of treatment by any of the commonly used efficacy assessment criteria such

as DAS28 and American College of Rheumatology 20% improvement criteria (ACR20), and record the assessment results in each patient's CRF. If the patient dose not complete 6 months of treatment, relevant data should be collected based on the last assessment performed at the time of treatment discontinuation.

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)[3].

DAS28 (ESR) = 0.56×√(TJC 28) + 0.28×√(SJC 28) + 0.014×VAS+ 0.70×ln(ESR)

or,

DAS28 (CRP) = 0.56×√(TJC 28) + 0.28×√(SJC 28) + 0.014×VAS + 0.36×ln(CRP+1)+0.96

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

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

Figure 1 DAS28-based EULAR response criteria

DAS28 at endpoint	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

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 (items 3 to 7) listed in Table 2. 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.

In the case of PsA, the number of active joints, including number of tender and swollen joints at 3 months of treatment is measured. DAS28 can be calculated based on the number of active joints, and DAS28 calculation is the same as calculation of RA above.

Table 2 American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis[4]

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

7.4. Data sources

7.4.1. Case report forms

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed 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 shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs, any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made on the CRFs or source documents 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.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

7.4.2. Record retention

To enable evaluations and/or inspections 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), all original signed

informed consent documents copies of all CRFs, safety reporting 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. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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 for longer if 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 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

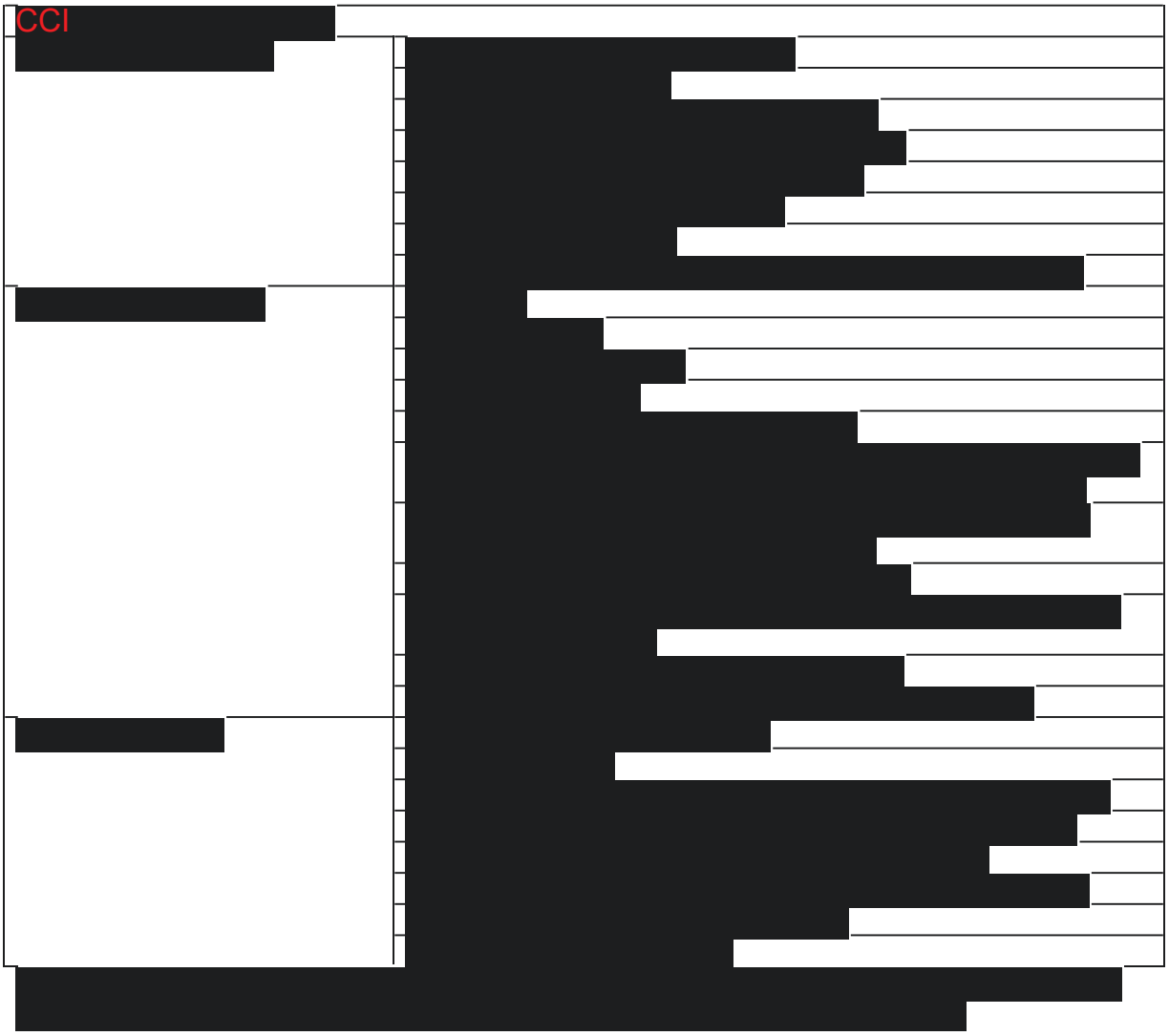
The primary interest of this study is the incidence of AEs investigated during the re-examination period. Incidence of each AE will be presented with 95% confidence interval. Serious, related, and/or unexpected AEs will be summarized separately.

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 children, elderly people, or patients with renal or hepatic disorders during the study, subgroup analysis will also be performed for each of those populations.

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. Efficacy analysis

Efficacy analysis will be performed on an intent-to-treat basis. It will be analyzed for all patients entering this study, 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.

Analysis with effectiveness of treatment based on change from baseline in DAS28, after a treatment EULAR response and after a treatment ACR20 response. Evaluation of overall

assessment including 'Improve', 'Changeless', 'Aggravated' - based on each test results and clinical judgment analysis. As a result of evaluation, 'Without any assessment' remains with not available effectiveness result. 'Improve', 'Changeless', 'Aggravated' remain with available effectiveness. Overall assessment evaluation conclude with 'Improve' that Xeljanz is effective. Overall assessment evaluation conclude with 'Changeless' or 'Aggravated' that Xeljanz is less effective.

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If the patient discontinues prematurely without completing the 6 months treatment, the reason of discontinuation will be analyzed.

7.8. 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 8.5).

7.9. 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.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.
The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staffs have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient

names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

8.2. Patient concent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

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 the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. 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. The investigator further must ensure that each study patient or his or her legally acceptable representative, or parent(s) is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative/parent(s), the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

8.3. 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.

8.4. 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 informed consent forms, and other relevant documents (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.5. 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), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), 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

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
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.

Hospitalization

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.

<u>Exposure during breastfeeding</u>

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.

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COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

11. REFERENCES

CCI [redacted]

3. DAS-score.nl. Home of the DAS: Disease activity score and DAS28, http://www.das-score.nl/das28/en/(accessed 16 October 2014).

4. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology: preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.

5. Eypasch E, et al. Probability of adverse events that have not yet occurred: a statistical reminder. BMJ. 1995 Sep 2;311(7005):619-20.

12. LIST OF TABLES

13. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.