For Application for Reexamination

Xeljanz® Tablets 5 mg

Special Investigation

(All-cases surveillance)

Surveillance protocol

(Version 2.1)

Pfizer Japan, Inc.

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Introduction

Xeljanz® Tablets 5 mg (nonproprietary name: tofacitinib citrate; hereinafter referred to as “Xeljanz”) is a strong inhibitor of Janus kinase (JAK) created by Pfizer U.S., and has been approved as an antirheumatic drug. It has also been approved overseas, particularly in the U.S.in November 2012.

The approval of the indication, “treatment for patients with rheumatoid arthritis who showed inadequate response to conventional treatments” was granted under approval conditions to “conduct a use-result surveillance in all patients receiving Xeljanz until post-marketing data on a certain number of cases is accumulated so as to collect safety and effectiveness data as early as possible to take measures necessary for proper use” and “conduct appropriate post-marketing surveillance to adequately evaluate the safety of this product, and investigate the safety and effectiveness of long-term use including possible development of infections and related events.” Also, malignant tumors such as malignant lymphoma and solid cancer have been reported in clinical studies, while the causal relationship with Xeljanz is unknown. Therefore, in accordance with the approval conditions, and taking into consideration the fact that Xeljanz is a new drug with a new mechanism of action, and that serious infection has been identified as a risk associated with Xeljanz, “Xeljanz® Tablets 5 mg Specific Use-result Surveillance (all-cases survey)” (hereinafter referred to as "Surveillance") with a control group shall be conducted.

This Surveillance is conducted by Pfizer Japan Inc. (hereinafter referred to as “Sponsor”), and is intended to investigate the actual use status of Xeljanz to confirm the occurrence of each adverse reaction associated with Xeljanz (for which, malignant tumors and serious infections will be compared with a control group), and to detect or confirm effectiveness and other safety data concerning Xeljanz. The information collected in this Surveillance will be used to prepare documents to be included in the Proper-Use Information and prepare documents to be included in the application for reexamination.

This Surveillance shall be conducted in compliance with the “Ordinance concerning Standards for Conducting Post-Marketing Surveillance and Studies on Pharmaceutical Products” (MHLW Ordinance No. 171 dated December 20, 2004). Data obtained from the patients enrolled in this Surveillance will be reported to the MHLW pursuant to the Pharmaceuticals and Medical Devices Act; pertinent to which, data may be publicly posted in MHLW’s “Pharmaceutical and Medical Device Safety Information” and Pharmaceuticals and Medical Devices Agency’s “Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)” as a listing of patients, which will present the names of drugs, adverse reactions, gender, age (increment of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the “Act on Access to Information Held by Administrative Organs” (Law No. 42 dated May 14, 1999); provided that in no event will the names of physicians, medical institutions, and other personal information be subject to such disclosure, nor will it be posted or disclosed in any form or shape.

1 Objective

The objective of this Surveillance is to verify the following subject matters concerning Xeljanz® Tablets (hereinafter referred to as "Xeljanz") under post-marketing actual status of use.

1) Occurrence of adverse reactions, factors that may potentially affect safety, and effectiveness
2) Long-term safety (particularly, malignant tumors and serious infections) and effectiveness

Occurrences of malignant tumors and serious infections will be compared with a control group.

[Approval conditions]

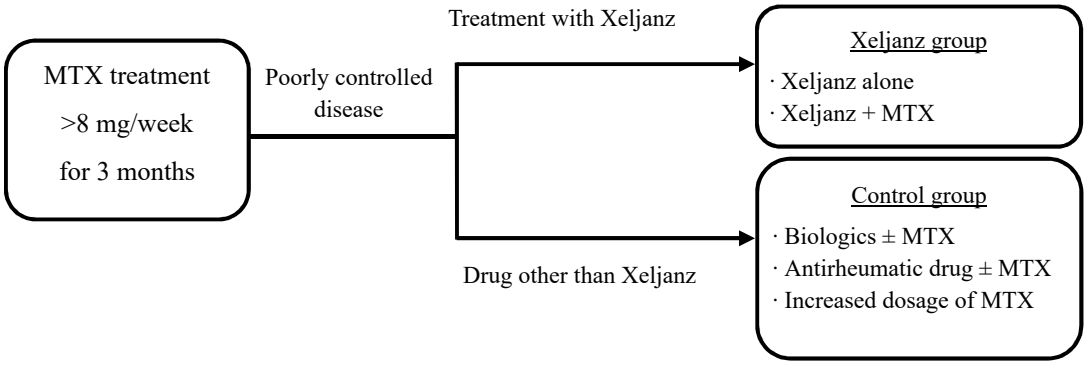
1. To conduct a use-result surveillance in all patients receiving Xeljanz until post-marketing data on a certain number of cases is accumulated so as to collect safety and effectiveness data as early as possible to take measures necessary for proper use.
2. To conduct appropriate post-marketing surveillance to adequately evaluate the safety of Xeljanz, and investigate the safety and effectiveness of long-term use including possible development of infections and related events.

2 Subjects

Among rheumatoid arthritis patients with poorly controlled disease in spite of continuous use of a methotrexate preparation (hereinafter, MTX) in a dosage exceeding 8 mg/week for 3 months or more, those meeting the following criteria:

1) All patients who receive Xeljanz (Xeljanz group)
2) Patients who have begun pharmacotherapy with another drug* (control group)

*Patients with no experience of treatment with Xeljanz (Patients participating in clinical trial cannot be registered in the control group)



When using Xeljanz, refer to "Guidelines for the use of tofacitinib in all-cases post-marketing surveillance" (revised version on June 29, 2014) (Japan College of Rheumatology) (hereinafter, "tofacitinib use guidelines"). Please consider using a pharmacotherapy other than Xeljanz for patients who do not meet the criteria shown below.

[Target patients]

1. Rheumatoid arthritis patients with poorly controlled disease in spite of continuous use of a methotrexate preparation (MTX) in a dosage exceeding 8 mg/week for 3 months or more. Patients with the above treatment history after February 23, 2011 when the approved dosage for MTX was increased to 16 mg/week are targeted. However, it is desirable not to target patients to whom MTX cannot be administered from the safety perspectives at this point, in principle.
   - Painful joint count of 6 or more
   - Swollen joint count of 6 or more
   - CRP of 2.0 mg/dL or more or ESR of 28 mm/hr or more

   Even if patient does not meet the 3 criteria above, consider use if there is moderate or higher activity for any of
   - DAS28-ESR, SDAI, and CDAI.
2. Moreover, out of consideration for safety with respect to opportunistic infections, it is strongly recommended that the following 3 criteria be met.
   - Peripheral blood count of 4000/mm^3 or more
   - Peripheral lymphocyte count of 1000/mm^3or more
   - Negative for blood β-D-glucan

Excerpted from "tofacitinib use guidelines"

The indication and dose regimen for this Surveillance are as follows: (This surveillance targets rheumatoid arthritis patients with poorly controlled disease in spite of continuous use of a methotrexate preparation (MTX) in a dosage exceeding 8 mg/week for 3 months or more.)

- Indication: Patients with rheumatoid arthritis who showed inadequate response to conventional treatments
- Dosage and Administration: As a standard therapy, a patient should receive a daily oral administration of tofacitinib 5 mg BID.

Refer to the most updated package insert and "tofacitinib use guidelines" when administering Xeljanz.

3 Target sample size

Target sample size: Subjects who meet the conditions in "2. Subjects" for each group and the sample size is shown below.

1) Xeljanz group: 4000 subjects for safety analysis

· The target sample size is set to be 4000 subjects by adding a certain sample size [a) b)] of ≥3000 subjects beginning from the start of registration (3-year observation) to the subsequent number of subjects (6-month observation period). See "6.5 observation period" for more information. However, even if Xeljanz is administered to subjects who do not meet the conditions described in "2. Subjects" for inevitable reason(s), while such subjects will not be included in the above sample size, the request to enroll subjects and complete survey forms will be made for subjects in the Xeljanz group for the sake of all-cases survey.

2) Control group: A certain sample size [a) b)] of ≥2000 subjects for safety analysis

[Remarks]

a) The sample size in both groups will be set to be the number of subjects for whom the degree of statistical accuracy described in [Rationale for sample size] is maintainable. See the Appendix for more information.

b) The registration period until a certain sample size is reached will be the same period for both groups.

[Rationale for sample size]

The incidence of malignant tumor associated with Xeljanz in a domestic long-term administration study (Study No. A3921041) was 1.16 (/100 person-year). The drop-out rate in clinical studies was 31% among subjects who transferred from the domestic Phase II study (Study No. A3921039) to the domestic long-term administration study (Study No. A3921041) (treatment period: approximately 3 years), and 14% among subjects who transferred from another domestic Phase II study (Study No. A3921040) (treatment period: approximately 1.4 years); based on which, the drop-out rate at the completion of 3-year observation in daily medical practice is estimated to be approximately 50%.

If 4000 patients were to be enrolled in the Xeljanz group, the target events should be confirmable in 104 patients based on the incidence of malignant tumor in Japanese subjects, which was 1.16 (/100 person-year).

Next, assuming that 4000 patients would be enrolled in the Xeljanz group and the incidence of malignant tumor in the control group would be equivalent to the Xeljanz group, at least 2000 subjects would need to be enrolled in the control group in order to enable a statistically appropriate inter-group comparison; thus, a sample size of 2000 subjects was selected for control.

Depending on the progress of registration, if the registered number of patients in either group significantly exceeds the above number earlier than the other group, a sample size with 3-year observation period can be changed to the combination of a sample size for whom the degree of statistical accuracy is maintainable if it is compared with 4000

patients in the Xeljanz group and 2000 patients in the control group (see the Appended Table). Also, the registration period for patients in the inter-group comparison needs to be the same.

4 Sites conducting this Surveillance

This Surveillance will be conducted in all sites (departments) where Xeljanz is prescribed; provided that doctors prescribing Xeljanz must meet the below criteria and consent to "Confirmation of Cooperation to Surveillance."

4.1 Site requirements:

Sites must meet both of the following conditions 1) to 2):

1) Cooperate with Xeljanz Tablets 5mg Specific Use-result Surveillance (hereinafter referred to as "Surveillance");
2) Provide urgent medical intervention, etc. to adverse reactions that may occur in patients using Xeljanz (including the sites* which may provide in cooperation with other medial facilities).

   *When diagnosing and treating serious infections, tuberculosis, or malignant tumors in collaboration with other medial facilities, information on safety measures and treatment for adverse drug reactions associated with Xeljanz will be shared with the collaborating medial facilities, and the system of cooperation will be confirmed.

4.2 Doctor requirements:

Doctors must meet all of the following conditions [1] to [5]:

[1] A doctor must meet all of the following Items (1) to (3):

(1) Is a rheumatologist certified by the Japan Rheumatism Association;
(2) Is a rheumatologist certified by the Japanese Orthopaedic Association; or
(3) Has taken part in clinical study(s) of Xeljanz.

[2] Doctors with abundant experience in using methotrexate drug

[3] Doctors with abundant experience in using biological drugs

[4] Doctors who can cooperate with this Surveillance

[5] Doctors who are available for interview with Medical Sponsor

5 Duration of surveillance

Duration of surveillance:

From the date marketing of Xeljanz begins to the completion of assessment by regulatory authorities

Enrollment period: From initial marketing for Xeljanz to lifting approval conditions for all-cases survey

Completion of survey forms for the Xeljanz group will no longer be mandated after reaching the registration of 4000 subjects[c)] in the Xeljanz group, which is the target sample size, after the approval from regulatory authorities is obtained. Meanwhile, registration will be continued until the final assessment is made by regulatory authorities.

For the control group, both completion of survey forms and registration will no longer be mandated after the target sample size is reached and the approval from regulatory authorities is obtained.

*The results of collecting and analyzing 6-months data on the 4000 subjects[c)] in the Xeljanz group will be submitted to the regulatory authorities together with the results of collecting and analyzing 6-months data on the subjects in the Xeljanz group who do not meet the conditions described in "2. Subjects" and the control group.

c) Subjects who meet the conditions described in “2. Subjects”.

6 Surveillance procedures

6.1 Surveillance method

Subjects in this Surveillance will be enrolled with a central registration system.

6.2 Data collection method

Registration and surveillance data for this Surveillance will be collected and recorded in the registration form and survey forms to be supplied by Sponsor.

6.3 Contract and logistics

A contract for this Surveillance must be concluded in writing with the head of each site. Contract templates of surveillance site shall be used if available.

[1] The Medical Representative (hereinafter referred to as "MR") shall provide Xeljanz Proper-use Information to doctors, pharmacists, and other relevant site staff who will handle/use Xeljanz.

[Safety information kit] Product Summary, Proper Use Guide, explanation of “Precautions” for new pharmaceuticals, literature for use by patients, package inserts, etc.

[2] Sponsor will explain the proper use of Xeljanz to each investigator taking part in this Surveillance; after which, the investigator will sign or name/seal the "Confirmation of Cooperation to Surveillance", and submit it to the MR (this document is also required when the investigator is relocated to another site).

[Confirmation of Cooperation to Surveillance] · Cooperation to diagnosis and treatment of serious infection, tuberculosis and malignant tumor · Requirements for sites and doctors · Other relevant items requiring confirmation · Signature or name/seal of the investigator taking part in this Surveillance

[3] Upon receiving “Confirmation of Cooperation to Surveillance,” a contract for this Surveillance will be concluded between the site and Sponsor.

[4] The sample size ratio between the Xeljanz group and the control group to be specified in the contract will be in principle 2 to 1. However, depending on the conditions at the medical facility, the case ratio may be adjusted between 2:1 and 1:1.

[5] Sponsor, upon confirming the conclusion of contract for this Surveillance, shall set up logistics necessary to deliver Xeljanz to the site.

6.4 Patient registration

[1] After the date on which the contract for this Surveillance is concluded, the investigator conducting surveillance will complete the registration form provided by Sponsor, and submit the form to Patient Registration Center via FAX.

[Patient Registration Center]	
FAX	0120-077176
Business hours:	9:00 to 17:15 (except for Saturdays, Sundays, National Holidays, and New Year Holidays)
	*FAX transmission after 16:00 will be responded during the following business day.

[2] Definition of start date

(1) Xeljanz group

The date on which administration of Xeljanz begins will be considered the "start date of treatment." However, for patients participating in the clinical trial, the start date will be considered the date on which administration of the commercially available Xeljanz product begins, and in the case of subjects administered Xeljanz at other medical facilities, it will be the date on which treatment at the physician's own hospital begins.

(2) Control group

For rheumatoid arthritis patients with poorly controlled disease in spite of continuous use of a methotrexate preparation (MTX) in a dosage exceeding 8 mg/week for 3 months or more, the date on which the change in pharmacotherapy began is regarded as the "start date of surveillance."

[3] Enrollment method

(1) Xeljanz group

The registration form should be submitted to the Patient Registration Center via FAX in principle no later than 1 week prior to the start of Xeljanz therapy.

If the sponsor has made the judgment that there has been a deviation from the scope of proper use of Xeljanz on the basis of the registration information, this will be checked with the physician in charge of surveillance, and the proper use information will be explained. If any of the patients registered in the control group has been administered Xeljanz during the registration period, the patient will also need to be registered in the Xeljanz group.

(2) Control group

The registration form should be faxed to the Case Registration Center within 2 weeks after surveillance start in the control group.

In principle, case selection in the control group should be performed according to the prescribing conditions for routine medical care under actual use conditions.

Patients to whom any of the following apply will be excluded from candidates for registration in the control group.

- Patients with past experience of treatment with Xeljanz (Patients participating in clinical trial cannot be registered in the control group)
- Patients already registered as part of the control group (Patients switching to another type of pharmacotherapy, excluding Xeljanz will be handled as continued surveillance cases in this survey)

(3) Completion of subject registration

The Case Registration Center will fax the results of registration (eligible/ineligible) to the physician in charge of surveillance.

In the Xeljanz group, the physician in charge of surveillance will begin prescribing after accepting the results on registration eligibility.

(4) Confirmation of cases registered in Xeljanz group

The sponsor will periodically confirm with the physician in charge of surveillance that all Xeljanz cases are

registered. If there are unregistered cases, the physician in charge of surveillance will immediately register the said cases.

6.5 Observation period

[1] Xeljanz group:

(1) Registered subjects up to a certain sample size exceeding 3000 subjects from the start of registration: 3 years (36 months) from the date of treatment start

(2) Registered subjects after the above (1): Only 6 months from the date of treatment start

[2] Control group: 3 years (36 months) from the date of treatment start

[3] Type of survey form

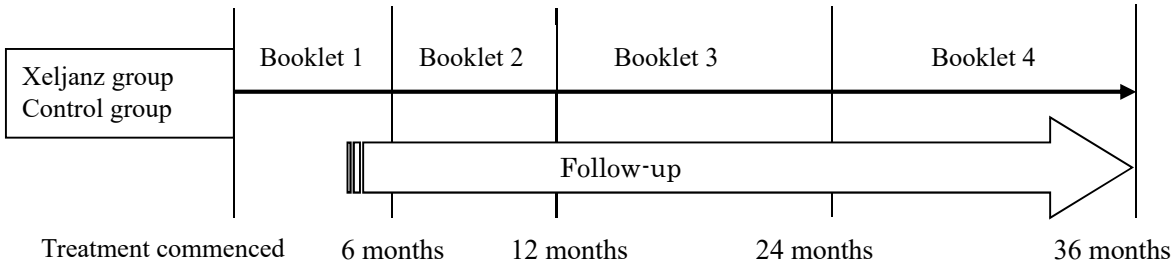
Booklet-type survey form will be used for this Surveillance.

Safety and effectiveness will be evaluated on the day of the initial office visit after the end of the observation period for each booklet (including the day on which the observation period ends). However, the safety and effectiveness will be evaluated based on the information from the last known visit if the subject is lost to follow up during the treatment period.

The effectiveness evaluation will be performed on Xeljanz group only.

[4] Follow-up surveillance

For a period of 3 years from the date of treatment start, follow-up surveillance for subjects in the Xeljanz group (1) and the control group will be conducted on the information related to the drug administration conditions and adverse events after discontinuation (serious infections [12 months], malignant tumors, adverse events leading to death).

<table>
<tr><th rowspan="2">Booklet No.</th><th rowspan="2">Observation period</th><th colspan="2">Safety</th><th colspan="2">Effectiveness</th></tr>
<tr><th>Xeljanz group</th><th>Control group</th><th>Xeljanz group</th><th>Control group</th></tr>
<tr><td>Booklet 1[d)]</td><td>Treatment start to Month 6[d)]</td><td rowspan="4">All adverse events</td><td rowspan="2">Serious infection, Malignant tumor, Death</td><td>Before treatment start, At Month 6</td><td rowspan="4">-</td></tr>
<tr><td>Booklet 2</td><td>Months 7 to 12</td><td>At Month 12</td></tr>
<tr><td>Booklet 3</td><td>Months 13 to 24</td><td rowspan="2">Malignant tumor, Death</td><td>At Month 24</td></tr>
<tr><td>Booklet 4</td><td>Months 25 to 36</td><td>At Month 36</td></tr>
<tr><td>Follow-up survey form[d)]</td><td colspan="5">Performed for 3 years from the start of treatment for subjects who prematurely discontinue treatment[d)]</td></tr>
<tr><td colspan="6"> 
</td></tr>
</table>

d) For subjects who correspond to "[1] Xeljanz group (2)"; the observation period will be only the duration of 6 months from the date of treatment start (Booklet 1) and no follow-up surveillance will be conducted.

6.6 Reminders concerning completing, revising, and submission of survey form

[1] Completing

The doctor shall, upon confirming the survey items, complete the survey form based on medical charts and other medical records such as relevant test results, using a pen, or ballpoint pen.

[2] Revising

Upon receiving Sponsor's inquiry on the contents of the survey form (resurvey), the investigator will again confirm the contents of medical records described earlier, and as required, correct relevant contents and resubmit the form. Corrections in the survey form should be struck out with a double line (=) with a "correction seal" on the double line; the double line should be drawn so that the original contents prior to correction are legible.

[3] Submission method

Survey forms should be submitted promptly upon completion in accordance with the procedures set out by Sponsor.

7 Survey items and schedule

This Surveillance should be conducted in accordance with the following observation schedule.

Survey item \ Observation period		Subject	Registration form	Survey form						
				Booklet 1 *6				Booklet 2	Booklet 3	Booklet 4
			Pre-dose*1 During treatment*2	Start of surveillance	Month 1	Month 3	Month 6	Month 12	Month 24	Month 36
Registration form	Confirmation of target patients, prior treatment of MTX, drugs to be investigated, ID number, patient's initials, gender, date of birth or age at the start of treatment, and start date of treatment (or surveillance)	Xeljanz group Control group	●	-	-	-	-	-	-	-
	Contraindication, tuberculosis check, hepatitis B virus test, and clinical laboratory	Xeljanz group	●	-	-	-	-	-	-	-
Survey Form	Patient characteristics	Both groups	-	●	-	-	-	-	-	-
	Dose record	Both groups	-	←	—	—	—	—	—	→
	Concomitant therapy (Pharmacotherapy)	Xeljanz group	-	←	—	—	—	—	—	→
	Pneumococcus vaccination*3	Both groups	-	←	—	—	—	—	—	→
	Prophylactic administration*4	Both groups	-	←	—	—	—	—	—	→
	Chest X-rays or CT	Xeljanz group	-	●	←	—	→	●	●	●
	Tuberculosis check	Xeljanz group	-	●	-	-	-	-	-	-
	Hepatitis B/C virus test	Xeljanz group	-	●	←	—	—	—	—	→
	Blood pressures (systolic/diastolic)	Xeljanz group	-	●	-	-	●	●	●	●
	Clinical laboratory	Xeljanz group	-	●	●	●	●	●	●	●
	Tender/swollen joint count, patient/doctor-reported outcome, CRP, and ESR	Xeljanz group	-	●	-	-	●	●	●	●
	Adverse events*5	Xeljanz group	-	←	—	—	—	—	—	→
		Control group	-	Serious infection						-
				← Malignant tumor/adverse events leading to death	—	—	—	—	—	→
	Tests/examinations related to adverse events	Xeljanz group	-	←	—	—	—	—	—	→
Follow	Follow-u*6	Both groups	-	Periodically performed for 3 years from the start of treatment for subjects who prematurely discontinue treatment*6						

●: Essential data

*1: Patients in the Xeljanz group should be registered in principle no later than 1 week prior to the start of treatment.

*2: Patients in the control group should be registered in principle no later than 2 weeks after the start of surveillance.

*3: Information on patients in the control group should be collected until 12 months after the start of surveillance.

*4: Prophylactic administration to prevent tuberculosis, pneumocystis jiroveci pneumonia, and hepatitis B (nucleic acid analogs)

Information on patients in the control group should be collected until 12 months after the start of surveillance.

・Treatment start to Month 6: Malignant tumor and serious infection

*5: All adverse events in the Xeljanz group are subject to reporting.

In the control group, the following adverse events are subject to reporting.

・Serious infections: For 12 months from the start of surveillance

・Malignant tumor and adverse events leading to death: For 36 months from the start of surveillance

*6: For patients in the Xeljanz group (“1) Xeljanz group (2) in 6.5 observation period”) after the registration of patients in the control group is completed; only information until 6 months after the start of surveillance (Booklet 1) should be collected and no follow-up surveillance will be conducted.

7.1 Assessment variables

1) Registration items

For pre-treatment information (including the start date of the treatment), all items for the Xeljanz group and items [1] to [7] for the control group will be completed.

(1) Patient characteristics

[1] Confirmation of target patients

If the patient meets the conditions for target patients (answer “Yes”):

Timing of MTX treatment, weekly dosage at the prior treatment of MTX

If the patient does not meet the conditions for target patients (answer “No”):

[Only patients in the Xeljanz group] Reason for non-conformity with guidelines, reason for treatment of Xeljanz

[2] Drugs to be investigated

- Xeljanz group: Patient category :Newly prescribed, transferred from clinical study, or prescribed at other medical facility (name of the medical facility)

  Control group: Pharmacotherapy: whether of not MTX has been administered, whether or not biological preparations have been administered, whether or not disease-modifying antirheumatic drugs (DMARDs) or immunosuppressants have been administered

[3] ID number

[4] Patient's initials (as necessary)

[5] Gender

[6] Date of birth (Western calendar) or age at the treatment start

[7] Start date of treatment (surveillance)

- Xeljanz group: Since registration takes place before treatment, the scheduled date of treatment start should be recorded.
- Control group: For registration after surveillance start, write in “start date of surveillance.”

(2) Pre-treatment observation

[8] Contraindication (presence/absence of contraindication)

[9] Tuberculosis check (imaging diagnosis/tuberculin test/interferon γ measurement (Quantiferon test, T-SPOT test, etc.)/antituberculosis drug administration)

The results of tests within 3 months prior to the start of treatment should be recorded before the treatment.

*Patients with concurrent or suspected tuberculosis should be given appropriate antituberculosis drug.

[10] Hepatitis B virus test (HBs antigen, HBs antibody, and HBc antibody)

The results of tests within 3 months prior to the start of treatment should be recorded.

[11] Laboratory tests (peripheral leukocyte count, peripheral lymphocyte count, β-D-glucan)

2) Survey form

(1) Patient characteristics prior to and at the start of treatment

The following will be recorded for both treatment groups.

[1] Height/weight

[2] Inpatient/outpatient status

Indication (Patients with rheumatoid arthritis), stage and grade (Steinbrocker stage), and functional class (Steinbrocker functional class)

[3] Duration of disease

[4] Clinical history (past history and concurrent illness)

[5] History of smoking (history of smoking at treatment start)

[6] Family history of malignant tumor

(2) Previous treatment drugs for rheumatoid arthritis (3 months before treatment start)

The following will be recorded for both treatment groups.

[1] MTX

- Past use (presence/absence)
- Weekly dosage
- Duration of treatment

[2] Oral steroid use for rheumatoid arthritis

- Past use (presence/absence),period or treatment

[3] Tacrolimus

- Past use (presence/absence)
- Duration of treatment

(3) Dose record

[1] Xeljanz group

Number of doses per day, treatment period, reason for change (if there has been a change in administration)

[2] Control group

If there has been a switch to another type of pharmacotherapy, excluding Xeljanz, during the observation period, the case will be handled as a continued surveillance case, and the treatment record should be continuously entered.

In cases where Xeljanz has been administered, surveillance as a member of the control group will be handled as discontinued, and registration in the Xeljanz group will be necessary.

- MTX

Name of drug (name of product), weekly dosage, and duration of treatment

- Pharmacotherapy with drugs other than MTX (biological preparation, DMARDs, immunosuppressants, oral steroid preparations)

Name of drug (name of product), daily dosage (oral steroids), and duration of treatment

(4) Concomitant therapy (Xeljanz group)

For drug therapy, covering the period starting 3 months prior to the start of treatment in this Surveillance

and ending at the completion or discontinuation of the observation period will be completed. Medications used for the treatment of adverse events should also be recorded.

[Concomitant therapies coadministered with Xeljanz]

[1] MTX

[2] Biological preparations*

[3] DMARDS other than MTX and immunosuppressants*

[4] Oral steroid

[5] Other drugs

Name of drug (product name), dosage (MTX, Oral steroids), duration of treatment, and reason for treatment (Other drugs)

*Please do not coadminister biological preparations and immunosuppressants along with Xeljanz.

[Surgical treatment of rheumatoid arthritis]

Name of the surgical therapy for rheumatoid arthritis, the date of operation, and the reason for operation should be recorded.

(5) Whether or not pneumococcus vaccine has been administered (both groups). *Until 12 months after surveillance start in control group

(6) Prophylactic administration to prevent tuberculosis, pneumocystis jiroveci pneumonia, and hepatitis B (nucleic acid analogs) (both groups). *For control group, until 12 months after surveillance start

7.2 Tests/examinations

In Xeljanz group, enter results of tests performed from before treatment start to end of observation period or date of discontinuation.

For test/examination results, a copy of the original report may be attached; provided that personal information must be processed with masking (blackened) or other method to anonymize the data.

1) Clinical laboratory tests

The results of clinical laboratory to the start of treatment (within 1 month prior to the start of treatment including the date treatment is commenced) and during and until the completion/discontinuation of the observation period should be recorded. If the observation period is discontinued, the test results at the time of discontinuation should be recorded if at all possible.

[1] Hematological test: WBC, neutrophil, lymphocyte, RBC, platelets, and hemoglobin

*Results of tests performed prior to the start of treatment (within 1 month prior to the start of treatment including the date treatment is commenced) and at 1, 3, 6, 12, 24, and 36 months of treatment will be essential.

[2] Chemistry: AST (GOT), ALT (GPT), AL-P, LDH, HDL-C, LDL-C, γ-GTP, total bilirubin, triglyceride, serum creatinine and creatine kinase

*Results of tests performed prior to the start of treatment (within 1 month prior to the start of treatment including the date treatment is commenced) and at 1, 3, 6, 12, 24, and 36 months of treatment will be essential.

[3] Other tests: KL-6, β-D-glucan, and BUN

2) Chest X-ray or CT

Tests before treatment start and 12, 24, and 36 months after treatment start are considered essential.

3) Interferon γ (Quantiferon test, T-SPOT test, etc.)/tuberculin reaction

Tests before treatment start are considered essential.

4) Blood pressure (systolic/diastolic)

Tests before treatment start and 6, 12, 24, and 36 months after treatment start are considered essential.

5) Hepatitis B/C virus tests (HBs antigen, HBs antibody, HBc antibody, HBV-DNA, and HCV-antibody)

Tests before treatment start are considered essential. After treatment start, indicate whether HBV-DNA tests have been performed.

6) Assessment variables

The following assessment variables [1] to [6] will be evaluated.

The observation period will be as follows. If the observation period is discontinued, the test results at the time of discontinuation should be recorded if at all possible.

- Essential assessment timepoints: Assessment performed prior to the start of treatment (within 1 month prior to the start including the date treatment is commenced) and at 6, 12, 24, and 36 months of treatment (until completion of the observation period).

[Assessment variables]	
[1] Tender joint count (evaluation of 28 joints)	[2] Swollen joint count (evaluation of 28 joints)
[3] Patient-reported outcome (Patient VAS)	[4] Doctor-reported outcome (Doctor VAS)
[5] C-reactive protein (CRP)	[6] Erythrocyte sedimentation rate (ESR): 1-hour value

7.3 End-of-surveillance (discontinuation) record

Confirm whether or not treatment can be continued by Xeljanz or control group at end of observation period. If treatment by Xeljanz group or control group cannot be continued, write date of discontinuation and select item that corresponds to reason (multiple responses possible).

However, even if a switch to another type of pharmacotherapy, excluding Xeljanz, has been made in the control group after registration is complete, it will be handled as a continuing surveillance case, and if the pharmacotherapy has been discontinued, it will be handled as a surveillance discontinued case.

If adverse event or death is selected as the reason, the details thereof should be recorded in the adverse event section. [Also, for the control group, if the reason selected is associated with malignant tumor and death of patient (treatment start to 36 months) or serious infection (treatment start to Month 12 of treatment), the details thereof should be recorded].

[1] Remission
[2] Inadequate clinical response
[3] Adverse event

} [1]-[3]: Subject to follow-up survey e)

[4] Death (date of death)
[5] No revisit
[6] Transfer to another hospital/department (name of hospital/department)
[7] Treatment with Xeljanz tablets (*Only applicable for the survey form for the control group)

} [4]-[7]: End surveillance if any of the following apply

[8] Other

e) However, the observation period for subjects who correspond to “1) Xeljanz group (2) in 6.5 Observation period” will be only 6 months after the date of treatment start (Booklet 1) and no follow-up surveillance will be conducted.

7.4 Effectiveness evaluation

For the Xeljanz group, the following effectiveness evaluation will be performed.

Effectiveness will be evaluated based on the results of "7.2, 6) [Assessment variables] [1] to [6]."

(1) SDAI (Simplified Disease Activity Index)

Sponsor will calculate the values based on the results of [Assessment variables] [1] to [5], and based on which, disease activities will be evaluated.

Also, Sponsor will calculate the values for CDAI (Clinical Disease Activity Index) based on the results of [Assessment variables] [1] to [4], and based on which, disease activities will be evaluated.

(2) DAS28 and the changes thereof (rate)

Sponsor will calculate the values based on the results of [Assessment variables] [1], [2], [3], and [6], and based on which, disease activities will be evaluated. In addition, changes in DAS28 (rate) prior to the start of treatment and at each assessment timepoint will be computed to evaluate the increase and decrease at each timepoint.

7.5 Pregnancy status

For both treatment groups, female patients should be verified for presence/absence of pregnancy at the end of the observation period for each booklet.

7.6 Adverse events

Pertinent to safety assessment, the status of adverse events after the start of treatment should be verified and the following information should be recorded.

1) Xeljanz group

Upon occurrence of any adverse event, the investigator shall provide appropriate treatment, promptly report to Sponsor, and follow up on the progress and outcome in principle until the symptom disappears.

Also, occurrence of a serious adverse reaction or an adverse reaction identified as a key survey item should be separately investigated in detail if determined necessary by Sponsor.

[1] Presence/absence of adverse event

[2] Name of adverse event

[3] Diagnosis of malignant tumor (only if applicable)

[4] Date of occurrence

[5] Intervention

[6] Seriousness

[7] Outcome and date of outcome

[8] Causal relationship with Xeljanz

If the patient has died, describe the details in the course of death column.

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

Laboratory parameter

Site reference value

Unit

Date measured

Results

2) Control group

(1) Malignant tumors (including lymphomas) and/or serious infections (including herpes zoster and tuberculosis)

Upon occurrence of any malignant tumor and/or serious infection, the investigator shall promptly report to Sponsor, and follow up on the progress and outcome in principle until the symptom disappears. Moreover, if an adverse event has been found, the investigator will immediately contact the MR and/or others in charge of the company that sells the product utilized as control group.

[1] Presence/absence of malignant tumor and serious infection (For serious infections, from treatment start to 12 months after)

[2] Name of adverse event for malignant tumors and serious infections (for serious infections, from treatment start to 12 months after)

[3] Diagnosis of malignant tumor (only for malignant tumors)

[4] Date of occurrence

[5] Treatment

[6] Seriousness

[7] Outcome and date of outcome

[8] Causal relationship to the drug subject to surveillance

(2) Detailed information

If there has been a malignant tumor, serious infection, or death of the patient, write the details.

[1] Detailed information on malignant tumors (including lymphomas)

[2] Detailed information on serious infections (including herpes zoster and tuberculosis),

[3] Adverse events leading to death, course of death

Definition of [Malignant tumor]

An event to which definitive diagnosis of malignant tumor (including lymphoma) is given

*"Suspected malignant tumor (including lymphoma)" should also be reported as an adverse event.

Definition of [Serious infection]

Of the infections occurred during this Surveillance, a "serious infection" is defined as an event that;

[1] Results in or may result in death;

[2] Results in or may result in disability/incapacity;

[3] Requires hospitalization or prolongation of existing hospitalization; or

[4] Is another serious event equivalent to the above.

Note: Adverse events are any and all untoward events (including clinically significant abnormal changes in laboratory tests) occurred in subjects after starting Xeljanz treatment regardless of their causal relationship with Xeljanz. Serious adverse events are any untoward medical occurrences that result in death, are life-threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which represent significant health hazards.

7.7 Follow-up

In cases that discontinued (excluding those where the reason for discontinuation was “death of patient,” “did not return to hospital,” or “transferred to another hospital/department”), a follow-up survey will be conducted on information related to the drug administration conditions after discontinuation and adverse events (serious infections (12 months), malignant tumors, adverse events leading to death) for a period of 3 years after the date of treatment start, if possible[f]. If the subject is lost to follow up, follow-up survey will not be required.

f) However, the observation period for subjects who correspond to “1) Xeljanz group (2) in 6.5 Observation period” will be only 6 months after the date of treatment start (Booklet 1) and no follow-up survey will be conducted.

For cases that discontinued in the 24-month period following treatment start (booklets 1 to 3), information from the date of discontinuation onward should be written on the follow-up survey form issued by the sponsor. Cases discontinuing during the observation period from treatment start to the 25th month after (booklet 4) should be confirmed in the reinvestigation of information from the date of discontinuation onward for the period from treatment start to 36 months after.

7.8 Key survey items

The following events should be evaluated in this surveillance as key survey items; patients applicable to any of the key survey items in the Xeljanz group will be separately investigated in detail.

[1] Serious infection (including herpes zoster and tuberculosis)

[2] Neutrophil decreased and neutropenia

[3] Lymphocyte count decreased and lymphocytopenia

[4] Hemoglobin decreased and anemia

[5] Lipids increased and hyperlipemia

[6] Malignant tumor (including lymphoma)

[7] Gastrointestinal perforation

[8] Cardiovascular-related adverse events

[9] Impaired hepatic function

[10] Interstitial pneumonia

Priority survey items in the control group will be "serious infections (including herpes zoster and tuberculosis) and "malignant tumors (including lymphomas)."

8 Statistical analysis plan

8.1 Statistical analysis plan

The details of the analytical plan should be decided upon after consultation with experts on rheumatology.

8.2 Analysis set

The analysis sets for safety and effectiveness will consist of all evaluable cases in which there has been confirmed to be at least one administration of Xeljanz or the control drug. The details of the evaluable cases will be described in the statistical analysis plan. Both treatment groups will be included in the safety analysis set while only the Xeljanz group will be included in the effectiveness analysis set.

8.3 Analytical method

1) Safety analysis

The primary analysis on the safety analysis set will be performed on major adverse reactions, the proportion thereof, and the incidence of adverse reaction per exposure. Also, each factor that may affect the occurrence of adverse reactions will be evaluated, for instance, based on tabulation of factors such as patient characteristics.

2) Risk factor analysis for malignant tumors and serious infections

Proportion of malignant tumors and serious infections should be calculated along with incidence rates of adverse reactions per amount of exposure and their 95% confidence intervals. The hazard ratio adjusted by the proportional hazard model should be calculated along with its 95% confidence interval. In addition, comparison should also be made with the control group subset with patient background matched to that of the Xeljanz group.

3) Effectiveness analysis

The primary analysis on the effectiveness analysis set will be changes (rate) in SDAI and DAS28. CCI [redacted]

4) Based on the above analytical methods in (1) and (3), an interim analysis on the 6-month data of 4000 subjects of Xeljanz group will be performed and the results thereof will be submitted to regulatory authorities (see "5. Duration of surveillance" for submission").

9 Public release

The safety information accumulated and the progress of this Surveillance shall be publicly released as appropriate on the sponsor's website.

9.1 Public release by Pfizer Japan, Inc (hereinafter Pfizer).

Pfizer by posting the results of this Surveillance in ClinicalStudyResults.org, shall fulfill its obligations concerning public release of medical information. The results of surveillance to be released by Pfizer. shall be either of the

following. In addition, as required, the results may be presented at academic conferences or in medical journals for the purpose of providing proper-use information.

- Surveillance registered to www.clinicaltrials.gov (ClinicalTrials.gov) by Pfizer, regardless of the reason for such registration.
- Surveillances other than above with the results that are of scientific and medical importance as determined by Pfizer.

The timing of public release will be dependent on the presence of any country in which the product has been approved at the completion of surveillance using the Pfizer product.

Any surveillance involving an already-approved Pfizer product in any country will require Pfizer to publicly release the results within 1 year of the finalization of last-patient last-visit data.

The information to be posted by Pfizer in ClinicalStudyResults.org. shall include; "The title of the implementation guideline for post-marketing surveillance, and study phase and indication," "Labeling of the product approved," "Summary of findings," "Citation of literature references," and "Disclaimer."

Literature references used by Pfizer are limited to those widely recognized and accessible through searchable literature databases.

10 Reference

・Package Insert of Xeljanz Tablets 5 mg

Appendix

"3. Target sample size"

A list of combinations for "certain sample size" in the Xeljanz and control groups

Sample size for safety analysis in "3. Target sample size" [g]			
"Certain sample size [h]" that requires 3-year observation		6-month observation	
(1) Sample size in the control group	(2) Sample size in the Xeljanz group	(3) Sample size in the Xeljanz group	(4) Sample size in the Xeljanz group Total [(2)+(3)]
2000	4000	0	4000
2050	3814	186	4000
2100	3653	347	4000
2150	3511	489	4000
2200	3385	615	4000
2250	3273	727	4000
2300	3173	827	4000
2350	3082	918	4000
2400	3000	1000	4000

g) Subjects who meet the conditions described in "2. Subjects".

h) A "certain sample size" will be reached when both the sample size in the control group and the sample size in the Xeljanz group exceed the number of subjects in any line of the combination of (1) and (2).

References

1. Staging of rheumatoid arthritis and classification of progress (Steinbrocker staging system)

Stage I (Initial stage)	○1. No radiological finding of osteolysis 2. Radiological finding of osteoporosis (bone atrophy) may be present.
Stage II (Medium stage)	○1. Radiological finding of osteoporosis (bone atrophy) with or without mild fracture of subchondral bone. There may be mild cartilage destruction. ○2. Articular movement may be restricted, but no joint deformity 3. Muscle atrophy around the joint 4. Lesions in the extracapsular soft tissue such as subcutaneous nodule and peritendinitis may be present.
Stage III (Progressive stage)	○1. Osteoporosis (bone atrophy) and radiological finding of bone and cartilage destruction ○2. Joint deformity such as subluxation, ulnar malposition or extension is present. There is no fibrous or osseous ankylosis. 3. Severe muscle atrophy 4. Lesions in the extracapsular soft tissue such as subcutaneous nodule and peritendinitis may be present.
Stage IV (Terminal)	○1. Fibrous or osseous ankylosis is present. 2. Meet all criteria applicable to Stage III

○: Essential criteria required for categorizing patients based on disease stage and progress.

<Excerpt: Steinbrocker O. et al. therapeutic criteria in rheumatoid arthritis. JAMA 140:659,1949>

2. Steinbrocker functional classification of rheumatoid arthritis

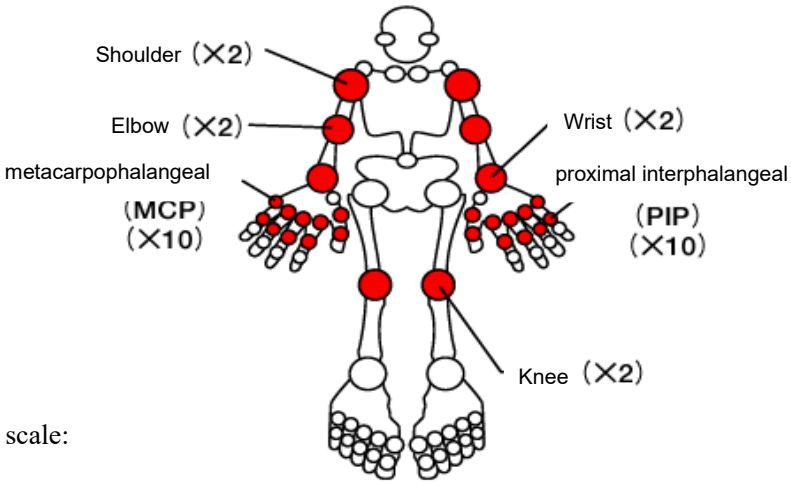
Class 1	Complete ability to carry out all the usual duties without handicaps
Class 2	Adequate for normal activities despite handicap of discomfort or limited motion of one of the joints
Class 3	Limited to little or none of the duties of usual occupation or self-care
Class 4	Incapacitated, largely or wholly bed-ridden or confined to a wheelchair with little or no self-care

<Excerpt: Steinbrocker O. et al. therapeutic criteria in rheumatoid arthritis. JAMA 140:659,1949>

3. SDAI / CDAI / DAS28

[Joints subject to assessment]

Right and left shoulders, elbows, wrists, and PIP (proximal interphalangeal joints), MCP (metacarpophalangeal joints) and knees; 28 joints in total.



[Assessment variables]

ESR (mm/hr)
CRP (mg/dL)
Tender joint count: TJC
Swollen joint count: SJC
Patient/doctor-reported outcome [visual analog scale: VAS (0 to 100 mm)]

- SDAI (Simplified Disease Activity Index)
  TJC (28 joints) + SJC (28 joints) + Patient VAS + Doctor VAS + CRP (mg/dL)
- CDAI (Clinical Disease Activity Index)
  TJC (28 joints) + SJC (28 joints) + Patient VAS + Doctor VAS

- DAS28 (Disease Activity Score in 28 joints)
  ・With measurement of ESR:
  $DAS28(4/ESR) = 0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.70\times\ln(ESR)+0.014\times(VAS)$
  $DAS28(3/ESR) = [0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.70\times\ln(ESR)]\times1.08+0.16$
  ・With measurement of CRP:
  $DAS28(4/CRP) = 0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.36\times\ln(CRP+1)+0.014\times(VAS)+0.96$
  $DAS28(3/CRP) = [0.56\times\sqrt{(TJC)}+0.28\times\sqrt{(SJC)}+0.36\times\ln(CRP+1)]\times1.10+1.15$

Note) DAS28 (3/ESR) and DAS28 (3/CRP) will be in place only if VAS is not performed. "ln" stands for natural logarithm.

<Source: DAS Website (http://www.das-score.nl)>

[Assessment criteria]

Assessment criteria	Criteria for disease activities			
	Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28	＜2.6	≧2.6～＜3.2	≧3.2～≦5.1	＞5.1
SDAI	≦3.3	>3.3～≦11	>11～≦26	＞26
CDAI	≦2.8	>2.8～≦10	>10～≦22	＞22

<Source: 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis>

4. Tuberculosis tests

【Tuberculin reaction】Criteria for interpretation

Determination		Code	Reaction
Negative		-	Diameter of reddening 9mm or less
Positive	Weakly positive	1+	Diameter of reddening 10 mm or more
	Moderately positive	2+	Diameter of reddening 10mm or more, accompanied by induration
	Strongly positive	3+	Diameter of reddening 10mm or more with induration accompanied by double redness, blisters, or necrosis

(Excerpted from package insert of Purified Protein Derivative (PPD) Tuberculin (revised September 2013 (Ver. 6))

【Quantiferon ®TB Gold】Interpretation of results

Measured value for M (IU/mL)	Measured value for A (IU/mL)	Result	Interpretation
Irrelevant	0.35 or more	Positive	Tuberculosis infection suspected
0.5 or more	0.1 or more < 0.35	Indeterminate	Make a comprehensive determination, taking into account the degree of infection risk
	< 0.1	Negative	Not infected with tuberculosis
< 0.5	< 0.35	Indeterminable	Not determined because immunodeficiency etc. is suspected

(Cite from Quantiferon®TB Gold package insert (revised September 2016 (Ver. 10))

【T-SPOT®.TB】Assessment criteria

1. With the use of the following formulas, calculate (1) and (2).

[(spot count in wells of panel A)(- spot count in wells of negative control)]…(1)

[(spot count in wells of panel B)(- spot count in wells of negative control)]…(2)

2. With the use of figures (1) and (2) calculated in 1, assess the results according to the following assessment criteria.

Positive: If spot count for both (1) and (2) or one of them is 6 or more

Negative: If spot count for both (1) and (2) is 5 or less.

Indeterminate: If the count for both (1) and (2) or the maximum of the value for both is 5 to 7

*If the result is "indeterminate," the result of a determination of "positive" or "negative" is itself valid, but it is possible that the reliability will be somewhat less than in cases where the figure is 8 or higher or 4 or lower. For this reason, it is recommended that the test be repeated in cases where the result is "indeterminate."

(Cited from home page for T-SPOT®.TB product information)