NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	An Investigation of Tofacitinib PsA Initiators in the CorEvitas SpA Registry
Protocol number	A3921411
Protocol version identifier	3.0
Date	2 Oct 2023
Active substance	L04AA29
Medicinal product	Xeljanz® (tofacitinib IR/XR)
Research question and objectives	The objectives of this study are as follows: 1. To describe the effectiveness of all tofacitinib initiators at 6 months in psoriatic arthritis (PsA) patients. 2. To describe the effectiveness of all tofacitinib initiators at 6 months stratified by mono- and combination therapy of PsA.
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ACR 20/50/70	American College of Rheumatology 20/50/70
AE	adverse event
ANCOVA	Analysis of Covariance
AS	Ankylosing Spondylitis
bDMARD	biologic Disease Modifying Antirheumatic Drug
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CHF	Congestive Heart Failure
CI	Confidence Interval
CRP	C-reactive Protein
csDMARD	Conventional Synthetic Disease Modifying Antirheumatic Drug
CV	cardiovascular
DAPSA	Disease Activity in Psoriatic Arthritis
DMARD	Disease Modifying Antirheumatic Drug
EQ-5D-5L	European Quality of Life Five Dimension Five Level
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index
HAQ-S	Health Assessment Questionnaire Spine Flexibility

Abbreviation	Definition
HEOR	Health Economics and Outcomes Research
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus Kinase
mACR 20/50/70	Modified American College of Rheumatology 20/50/70
MDA	Minimal Disease Activity
MI	Myocardial Infarction
PASDAS	PsA Disease Activity Score
PASS	Post Authorization Safety Study
PCI	Percutaneous Coronary Intervention
PsA	Psoriatic Arthritis
PsO	Psoriasis
SAP	Statistical Analysis Plan
SM	Small Molecule
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada Enthesitis Index
TIA	Transient Ischemic Attack
TNFi	tumor necrosis factor inhibitor
tsDMARD	targeted synthetic Disease Modifying Antirheumatic Drug
US	United States

Abbreviation	Definition
VAS	Visual Analogue Scale
WPAI	Work Productivity Index

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not applicable.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	24May2023	9.3	Administrative change regarding CDAI and cDAPSA values	The values for CDAI and cDAPSA are being pulled from the database. Pfizer will not do any recalculation post-hoc
1	24May2023	9.5	Planned sample size reduced from 100 to 80 patients per group Substantial Amendment	Based on CorEvitas estimates and current enrollment pattern, it is estimated that it will take approximately 12 months to get to at least 80 patients per group.
1	24 May 2023	3	Adding Author (PPD) address and new PPD PPD	NY Pfizer offices changed
1	24 May 2023	6	Interim report 3, end of data collection, and final study report dates were updated	Update due to the amendment
2	02Oct2023	9.5	Planned sample size reduced from 80 to 73 patients per group Substantial Amendment	Based on CorEvitas estimates and current enrollment pattern, it is estimated that it will take approximately 12 months to get to at least 73 patients per group.

6. MILESTONES

Milestone	Planned date*
Start of data collection	15 November 2021
Interim Report 1	15 January 2022
Interim Report 2	19 December 2022
Interim Report 3	15 Sep 2023
End of data collection	29 March 2024
Final study report	28 June 2024

*The interim reports rely on reaching the appropriate number of patients for each analysis. These dates may change if there are delays in patient accrual within the registry.

7. RATIONALE AND BACKGROUND

Psoriatic arthritis (PsA) is an immune-mediated systemic inflammatory disease with multiple disease manifestations, including peripheral arthritis, enthesitis, dactylitis, and spondylitis, together with skin and nail psoriasis.[1] PsA may be associated with poor long-term outcomes and significantly diminished quality of life for patients.[2] PsA affects men and women equally with peak onset in adults between 30 to 50 years of age.[3] Prevalence estimates in the US range from 0.06% to 0.25%.[4] The incidence of PsA, ranges from 3.6 to 7.2 per 100,000 person-years.[4] PsA is reported to occur in up to 30% of patients with PsO.[5] Skin manifestations precede the PsA in 70% of patients.

According to evidence-based treatment recommendations by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the American College of Rheumatology (ACR), non-steroidal anti-inflammatory drugs and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) should be used in the early treatment of PsA. For patients in whom these are unsuccessful, biologic DMARDs (bDMARDs), such as tumor necrosis factor inhibitors, and targeted synthetic DMARDs (tsDMARDs), such as phosphodiesterase inhibitors are recommended.[1-6]

Tofacitinib is an oral Janus kinase (JAK) inhibitor approved in 2017 by the US Food and Drug Administration (FDA) for the treatment of adult patients with active PsA who have had an inadequate response or intolerance to methotrexate or other DMARDs. Tofacitinib is approved for use in combination with nonbiologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. Since approval, little is known about the patient profile of the PsA population treated with tofacitinib in clinical practice as well as the real-world effectiveness of tofacitinib in patients with psoriatic arthritis.

The purpose of this study is to provide a characterization of patients and effectiveness of tofacitinib in PsA patients newly initiating tofacitinib in the US CorEvitas PsA/spondyloarthritis (SpA) Registry. This study is not designed as a post authorization safety study (PASS) and is not a commitment or requirement to any regulatory authority.

8. RESEARCH QUESTION AND OBJECTIVES

There are two primary objectives for this study:

1. To describe the effectiveness of all tofacitinib initiators at 6 months in PsA patients.

2. To describe the effectiveness of all tofacitinib initiators at 6 months stratified by mono- and combination therapyof PsA.

9. RESEARCH METHODS

9.1. Study Design

To meet the study objectives, an observational retrospective cohort study will be conducted using patients enrolled in the CorEvitas PsA/SpA Registry initiating tofacitinib on or after 14 December 2017. Patients receiving tofacitinib will be included to assess the effectiveness of tofacitinib overall and stratified by key variables of interest. For further details, please refer to the detailed Statistical Analysis Plan (SAP) included as a stand-alone document.

9.2. Setting

The CorEvitas SpA Registry is a prospective, multicenter, observational disease-based registry launched in March 1st, 2013. This registry contains clinical data (eg, disease activity scores, laboratory results, comorbidities, imaging results, patient-reported outcomes data, etc.) that is not available in claims databases. As of August 1, 2020, the CorEvitas dataset includes 64 private and academic active clinical sites with over 66 providers throughout 30 states in the US. This registry collects data from both the providers and the patients at the time of a regularly-scheduled office visit. CorEvitas has enrolled over 4,000 patients with PsA or spondyloarthritis. The collection of data from CorEvitas represents over 9,800 patient years of data.

To be included in the CorEvitas PsA/SpA Registry, patients must be at least 18 years of age and have a diagnosis of PsA or AS by a rheumatologist. Patients are excluded from the registry if they are unable or unwilling to provide informed consent. The inclusion/exclusion criteria for this particular analysis are described in Section 9.2.1. and Section 9.2.2.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. PsA patients in CorEvitas initiating tofacitinib monotherapy or in combination with oral small molecules (eg methotrexate, leflunomide, sulfasalazine, apremilast) after 14 December 2017 (market approval of tofacitinib in the US) with no prior use of tofacitinib. Only the patient's first initiation after December 14, 2017 will be included in the analysis.

2. Have a 6 month follow-up visit (with ±3 month window).

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients taking tofacitinib in combination with any other bDMARD

9.3. Variables

Patient characteristics at baseline:

- Gender, age, race, and ethnicity;
- Duration of PsA (Age at onset);
- Time since PsA diagnosis
- Time since onset of PsO;
- Comorbidity history:
    - Cardiovascular disease: MI, stroke, TIA acute coronary syndrome, coronary artery disease, CHF, revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, other CV diseases, carotid artery disease, other coronary disease, peripheral arterial disease);
    - Hypertension;
    - Hyperlipidemia;
    - Serious infections;
    - Malignancy: lung cancer, breast cancer, lymphoma, skin cancer (melanoma and not melanoma), and other cancer;

- Thromboembolic events (Deep vein thrombosis, peripheral arterial thromboembolic and pulmonary embolism);
- Anxiety, depression, and other mood disorders;
- Crohn's Disease;
- Psoriasis;
- Diabetes;
- Ulcerative colitis;
- Uveitis;
- Metabolic Syndrome;
- Psoriatic Nail Dystrophy;
- Fibromyalgia.

- Smoking status;
- Alcohol use;
- Work status;
- Height and weight;
- Insurance (patient reported);
- Prior small molecule (SM) use;
- Prior biologic use:
  - Prior TNFi use;
  - Prior non-TNFi use.
- Current prednisone use (including dose).

Disease activity measures:

- Physician reported:
  - Tender Joint Count (28 and 68);

- Swollen Joint Count (28 and 66);
- SPARCC count;
- Enthesitis;
- Dactylitis;
- LEI count;
- Dactylitis count;
- MDA;
- DAPSA;
- PASDAS;
- ACR20/50/70;
- mACR20/50/70;
- Nail VAS;
- BSA;
- CRP;
- Spinal mobility measures (occiput to wall distance, left and right lateral lumbar flexion, modified Schober);
- Global assessment of PsO.

- Patient reported:
  - Pain (VAS);
  - Fatigue (VAS);
  - Global Skin Assessment;
  - HAQ-DI;
  - HAQ-S;
  - European Quality of Life-5 Dimensions (EQ-5D-5L);

- WPAI domains (4 categories).

9.4. Data Sources

Patients are enrolled in the CorEvitas PsA/SpA Registry during regularly-scheduled office visits. Upon enrollment, providers complete a set of Enrollment Questionnaires on PsA patients. Patients also complete an Enrollment Questionnaire, which captures several data elements, including the Health Assessment Questionnaire (HAQ) and the European Quality of Life-5 Dimensions (EQ-5D-5L). Both patient and provider reported disease activity measures obtained at each visit are captured in CorEvitas; this includes tender and swollen joint counts (28 and 66/68 joint counts), patient and physician global disease assessment, patient pain assessment and HAQ scores. Providers and patients complete Follow-Up Questionnaires approximately every 6 months. During the course of a regularly-scheduled office visit, the provider performs assessments as mandated on the CorEvitas Provider Questionnaires with recording of pertinent data. Results from certain laboratory tests are included, but not mandated. Likewise, during regularly-scheduled office visits, patients are asked to complete Questionnaires designed to capture information ranging from their general demographics and experience with prescription drug use to an overall global assessment of their disease. Early follow-up visits occur and questionnaires are completed whenever a registry patient is being prescribed or receiving a first dose of a new (different) eligible medication at a regularly-scheduled office visit. Eligible medications are biologics, biosimilars, and JAK inhibitors FDA-approved for the treatment of PsA. The next regularly-scheduled visit is calculated from the previous visit. Data are collected on patients for as long as they consent to remain in the registry.

9.5. Study Size

This is an estimation study and not hypothesis testing study. Precision estimates indicate that approximately ~~80~~ 73 patients with 12 months of follow-up are needed per group to achieve reasonably precise estimates for the outcomes of interest. For binomial proportions, a sample size of ~~80~~ 73 patients per group would yield a half width of the 2-sided 95% confidence interval (CI) to be less than 11 percentage points for the binomial proportions, and less than 16 percentage points for the difference in 2 binomial proportions.

As of October 1, 2020, there are 160 tofacitinib initiators within the CorEvitas registry of whom 93 have a 6 month follow-up visit. The first objective of the study will be assessed using the latest data cut available once the protocol is approved and will be reported in the first interim report. The stratifications by mono and combination therapylisted in the second objective will be reported in subsequent interim reports as sample sizes reach appropriate thresholds. For comparative analyses, this will be at least ~~80~~ 73 patients per arm. Precision estimates will be used to determine appropriate sample sizes for the descriptive analyses. The final report will be issued once all subgroups reach the minimal sample sizes to ensure sufficient precision in the estimates of the outcomes.

9.6. Data Management

All analyses will be carried out under the direction of biostatisticians of CorEvitas.

9.7. Data Analysis

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

In general, the data for all continuous endpoints will be summarized by timepoint and treatment group in tables containing descriptive statistics (N, mean, standard deviation, standard error of the mean, minimum, 1st, 2nd (ie, median) and 3rd quartiles and maximum) for baseline and change from baseline/percent change from baseline for those endpoints measured at baseline. The data for all categorical endpoints will be summarized by contingency tables that show the counts/frequency in the various categories by treatment group at each timepoint.

For binary endpoints, 95% CI using normal approximation to binomial proportions will be provided for each group. The 95% CI will also be provided for comparisons between groups using normal approximation for the difference in binomial proportions.

Continuous endpoints (eg, HAQ-DI) at month 6 will be analyzed as change from baseline with an analysis of covariance (ANCOVA) model that includes treatment and baseline value as covariates. Comparisons between groups will be performed using 95% CI.

9.8. Quality Control

CorEvitas or its designee monitors the conduct of the registry at each investigative site. Monitoring is primarily conducted remotely. Onsite monitoring visits are conducted once every 3 years, as needed, or as requested. A review of registry records including, but not limited to, the informed consent forms, Questionnaires, original source documents such as supporting medical records and office notes, patient study files, and any other registry documentation is conducted in accordance with applicable regulatory guidelines and the protocol. CorEvitas and its designees are required to maintain the confidentiality of all patients during and after an on-site monitoring visit.

Quality control checks are built into the on-screen data entry systems in an attempt to reduce queries and provide immediate feedback to the investigator regarding inadvertent omissions and out of range or noncompliant values. Changes made at any time are recorded in an audit trail that includes the date, time, and electronic ID of the person making the change.

CorEvitas will address and resolve discrepancies by requesting clarifications and/or missing data from the investigator as needed. Each investigator is expected to designate a point of contact to address such inquiries and to promptly address and resolve issues. Representatives or designees from CorEvitas reserve the right to perform random or systematic audits of CorEvitas Questionnaires at an investigator's site in order to assess the accuracy of the reported data compared to the information contained in the original medical records.

9.9. Limitations of the Research Methods

The CorEvitas PsA/SpA Registry includes a sample of adult patientswith PsA that are not necessarily representative of all adults with PsA in the US. In particular, these are PsA patients with regularly-scheduled visits with rheumatologists. Patients are recruited by rheumatologists who are required to indicate diagnosis upon enrollment of the patient into the CorEvitas PsA/SpA Registry. In addition, history of medication use prior to enrollment is derived from what is reported by patients and their current rheumatologist within the registry. Since registry reporting is not based on a fixed visit schedule, exact timing of visits to fit 6, 12, 24, or 36 months of post index data is not available for all patients so windows of time are used to determine eligible visits. The "cause" of visits is not captured, although the assumption can likely be made that the rheumatologist visit is "PsA-related." The registry captures provider reported prescribing; there are no measures of patient adherence.

As this is a real-world study, missing data could be expected for demographic characteristics (eg, age, etc.); however, the number of patients with missing data is expected to be very small. With multiple time points, some visits may have missing DAPSA (

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

This database does not contain any patient identification information (eg, name) and is exempt from IRB review.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in CT24-WI-GL02-RF02.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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 Corevitas 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.

13. REFERENCES

1. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016;68(5):1060-71.

2. Helliwell PS, Coates LC, Chandran V, et al. Qualifying unmet needs and improving standards of care in psoriatic arthritis. Arthritis Care Res. 2014;66:1759-66.

3. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64 Suppl 2:ii14-17.

4. Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. Rheum Dis Clin N Am. 2015 (41):545–68.

5. Gladman DD. Clinical features and diagnostic considerations in psoriatic arthritis. Rheum Dis Clin N Am. 2015;41:569–79.

6. Gossec L, Smolen JS, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016; 75: 499-510.

14. LIST OF TABLES

Table shells are included in the SAP.

15. LIST OF FIGURES

Figures are included in the SAP.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Date	Title
1	20 August 2021	Analysis of tofacitinib initiators with PsA SAP

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921411 Non Interventional Study Protocol Amendment 2_ v3_02Oct 2023_YL1.GV CLEAN
Document Title:	A3921411 Non Interventional Study Protocol Amendment 2_ v3_02Oct 2023_YL1.GV CLEAN

Signed By:	Date(GMT)	Signing Capacity
PPD	30-Sep-2024 16:30:43	Manager Approval