NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Characteristics and 6-month Outcomes Among Real-World Rheumatoid Arthritis Patients Initiating Inflectra
Protocol number	C1231007
Protocol version identifier	3.0
Date	24 July 2023
Research question and objectives	The objectives of this study are as follows: 1. To describe the characteristics of patients newly initiated on Inflectra. 2. To describe 6-month outcomes after initiating Inflectra, among patients who have 6-months follow-up information in CorEvitas' RA Registry.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CABG	coronary artery bypass grafting
CDAI	Clinical Disease Activity Index
CHF	congestive heart failure
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CV	cardiovascular
CVD	cardiovascular disease
DAS	Disease Activity Score
DVT	deep venous thrombosis
EQ-5D-3L	3-Level version of EuroQoL-5 Dimensions
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HAQ	health assessment questionnaire
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Board Review
JAK	Janus Kinase
LDA	low disease activity
mACR	modified American College of Rheumatology
MI	myocardial infarction

Abbreviation	Definition
MTX	methotrexate
PCI	percutaneous coronary intervention
PRO	patient reported outcome
RA	rheumatoid arthritis
SAP	Statistical Analysis Plan
SJC	swollen joint count
TIA	transient ischemic attack
TJC	tender joint count
US	United States
VAS	visual analogue scale

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

N/A.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 administrative	18-Jul-2022	Study Information	Deleted medicinal product and active substance and updated author name to new NIS Lead.	Medicinal product and active substance are not applicable for this study type. The study was handed over to a new NIS Lead, therefore author information was updated.
		Section 3	Updated respsonsible parties.	Section 3 was updated due to changes in the study team.
		Section 6	Updated study timelines	Study timelines were updated to reflect the current status.
		Section 10.3	Corrected template wording.	This section was corrected as there is no IRB approval required for these types of studies.
		Section 9.6.1 and 9.6.2	These sections were deleted according to template instructions.	This is a secondary structured data analysis study. Following instructions on the protocol template section 9.6.1 and 9.6.2 were deleted.
		Section 10.3	Section 10.3 was updated to reflect the local requirements for his study.	Wording in section 10.3 was updated, because this secondary structured data collection does not need to apply for IRB approval according to local requirements.
2 administrative	24 July 2023	Section 3.	Address change	Pfizer New York headquaerters address change
		Section 6.	Milestones section Planned Dates changed	It is changed to match with Registry
		Protocol template	Protocol template is updated	It is updated to the latest protocol template for Secondary Data Collection studies.

6. MILESTONES

Milestone	Planned date
Start of data collection	09 December 2022
End of data collection	03 February 2023
Final study report	11 October 2023

7. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, immune-mediated, inflammatory disease affecting many joints, including those in the hands and feet. RA has a wide global presence and is estimated to affect 0.5 to 1% of the general population. Inflectra is 1 of 4 currently approved biosimilars for infliximab, approved in April 2016.[1] There is a need to understand how biosimilars are used in the real world for rheumatoid arthritis patients (eg, attitudes/hesitancy about biosimilars, sequencing, issues with payers). There are also questions about how Inflectra is being used in the real world (eg, line of therapy, how many patients use originators first versus those who do not). This study will examine treatment patterns and effectiveness of real-world Inflectra initiators in the CorEvitas' RA Registry.

8. RESEARCH QUESTION AND OBJECTIVES

There are 2 objectives for this study:

1. To describe the characteristics of patients newly initiated on Inflectra.
2. To describe 6-month outcomes after initiating Inflectra, among patients who have 6-months follow-up information in the CorEvitas' RA Registry.

9. RESEARCH METHODS

9.1. Study Design

This is a descriptive retrospective study of RA patients initiating Inflectra from the CorEvitas' Registry. Primary outcome of this study will be the achievement of low disease activity (LDA) (Clinical Disease Activity Index [CDAI] $\leq$10) at 6 months. Secondary outcomes will be the achievement of remission (CDAI $\leq$2.8), Δ CDAI, Δ health assessment questionnaire (HAQ), Δ patient pain, Δ patient fatigue, and achievements of modified American College of Rheumatology (mACR)20/50/70.

For further details, please refer to the detailed Statistical Analysis Plan (SAP) included as a stand-alone document.

9.2. Setting

CorEvitas' RA Registry is an ongoing longitudinal clinical registry that was established in 2001. Longitudinal follow-up data is collected from both patients and their treating rheumatologist during routine clinical encounters using RA Registry questionnaires. The RA Registry has enrolled over 56,090 patients with RA. The collection of data from the RA Registry represents over 210,949.53 patient years of data. Structured clinical data is available in this Registry (eg, disease activity scores, comorbidities, imaging results, patient-reported outcomes data, etc) that is not available in claims databases.

9.2.1. Inclusion Criteria

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

1. Be at least 18 years of age.
2. Have been diagnosed with RA by a rheumatologist.
3. Have initiated treatment with Inflectra.
4. Had assessment of effectiveness in patients who have at least 1 follow up visit.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

Patient characteristics at baseline:

- Age, sex, race, and ethnicity
- Education
- Work status
- Insurance type
- Smoking status and alcohol use
- Body mass index
- Medication use
    - Prior Medication use

        - Number of prior conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (not including at the time of the Inflectra initiation)
        - Concomitant therapy (none, methotrexate [MTX] only, nonMTX csDMARD only, MTX & nonMTX csDMARD)
        - Number of prior biologics
        - Prednisone use (History, Current, dose in current users)
        - Last therapy prior to Inflectra
    - Reason for Inflectra initiation
        - Number of patients with at least 1 initiation reported
        - Total number of reasons
        - %Safety, %Efficacy, %Cost/Insurance, %Other reasons

- History of Comorbidities
    - Cardiovascular disease [CVD] (myocardial infarction [MI], stroke, acute coronary syndrome, coronary artery disease, congestive heart failure [CHF], revascularization procedure including percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, other cardiovascular [CV], deep venous thrombosis [DVT], and transient ischemic attack [TIA])
    - History of malignancy (lung cancer, breast cancer, lymphoma, skin cancer [melanoma and squamous], and other cancer)
    - Hypertension
    - Diabetes
    - Depression
    - Fibromyalgia

Disease activity measures:

- Clinical Characteristics and Assessments

- Disease duration
- Age of onset
- Composite disease activity measures (physician derived elements)
  - Clinical Disease Activity Index (CDAI)
  - Disease Activity Score ([DAS]28, erythrocyte sedimentation rate [ESR])
  - Physician global assessment of 28 joint count (tender joint count [TJC], swollen joint count [SJC])
- Patient reported outcome (PRO) measures
  - Health Assessment Questionnaire (HAQ)
  - Pain visual analogue scale (VAS) (0-100)
  - Patient global assessment VAS (0-100)
  - Fatigue VAS (0-100)
  - Stiffness VAS (0-100)
  - 3-Level version of EuroQol-5 Dimensions (EQ-5D-3L)

9.4. Data Sources

This is a retrospective analysis of an existing database of patient encounters from the CorEvitas RA Registry.

Providers and patients complete follow-up questionnaires approximately every 6 months. Eligible medications are biologics, biosimilars, and Janus Kinase (JAK) inhibitors that are Food and Drug Administration (FDA) approved for the treatment of RA.

9.5. Study Size

This is a descriptive, exploratory study; therefore, power calculations were not considered. Sample size calculations are not applicable.

As of 21 July 2021, there were approximately 235 Inflectra initiators.

9.6. Data Management

Stata Release 16 (StataCorp LLC, College Station TX), R Version 4.0.3 (The R Foundation for Statistical Computing, Vienna Austria), or SAS Version 9.4 (SAS Institute, Cary NC) will be used for analyses. Refer to the SAP.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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 primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality Control

Detailed quality control of the analyses will be documented in the SAP.

9.9. Limitations of the Research Methods

The following items could potentially limit the generalizability of the results.

The RA Registry used in this research includes a sample of adults with RA that are not necessarily representative of all adults with RA in the United States (US) and Canada. In particular, these are patients with RA with clinical visits with rheumatologists. In addition, history of medication use prior to enrollment is derived from what is reported by patients and their current rheumatologist within the registry. The "cause" of visits is not captured, although the assumption can likely be made that the rheumatology visit is "RA related." The Registry captures physician-reported prescribing, and there are no measures of patient adherence. Additional possible study limitations are variables with small cell counts (n<5) which will be suppressed to protect patient confidentiality, and 6-month outcome analyses will be unadjusted.

Given that this is a retrospective analysis, there are no risks in what is planned to be carried out in the protocol.

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 is a retrospective study for which IRB approval is not required according to local regulations.

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 the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practice (GPP)[2]

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 party responsible for collecting data from the participant 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. U.S. Food & Drug Administration. Biosimilar Product Information. Updated December 27, 2021. Accessed January 10, 2022. https://www.fda.gov/drugs/biosimilars/biosimilar-product-information.

2. Battisti WP, Wager E, Baltzer D, et al. Good Publication Practice for Communicating Company Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163(6):461-4.

14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

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