Study Information

Title	Compare Effectiveness of Tofacitinib 11 mg QD to Tofacitinib 5 mg BID
Protocol number	A3921359
Protocol version identifier	1.0
Date	10 December 2019
Active substance	Tofacitinib citrate
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	Main objective is to compare effectiveness of tofacitinib 11 mg once daily (QD) initiators to tofacitinib 5 mg twice daily (BID) initiators
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
BID	Twice daily
CDAI	Clinical Disease activity index
CRP	C- reactive protein
csDMARD	Conventional Disease modifying anti-rheumatic drug
DAS	Disease activity score
mDAS	Modified Disease Activity Score
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EQ-5D	Euro Qol 5D
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GEP	Good Epidemiology Practices
mHAQ	modified Health Assessment questionnaire
HAQ	Health Assessment questionnaire
IEA	International Epidemiology Association
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
JAK	Janus kinase
LDA	Low Disease Activity
LTE	Long Term Extension
MCID	Minimally clinically important difference
MR	Modified release
MTX	methotrexate
NI	Non Interventional
PD	Pharmacodynamic
PK	Pharmacokinetic
PS	Propensity Score
QD	Once daily
RA	Rheumatoid arthritis
SAP	Statistical analysis plan
SAS	Statistical Analysis System
TyK2	Tyrosine kinase 2
US	United States

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Not Applicable.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Final approved protocol*	December 2019
Start of analysis/data collection	30 September 2018
Approved SAP	20 March 2018
End of data collection	30 August 2019
Final study report	11 October 2019

** This protocol was created retrospective from start of data collection and is part of an Significant Qulaity Event (SQE).*

7. RATIONALE AND BACKGROUND.

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. The efficacy and safety of tofacitinib 5 mg twice daily (BID) administered as monotherapy or in combination with conventional disease modifying anti rheumatic drugs (csDMARDs), mainly methotrexate (MTX), in patients with moderately to severely active rheumatoid arthritis (RA), have been demonstrated in Phase 2,[1-5] Phase 3,[6-11] and Phase 3b/4[12] studies of up to 24 months' duration, and in long-term extension (LTE) studies with up to 9.5 years of observation.[13-15]

The immediate release (IR) formulation of tofacitinib was approved in November 2012 in the US for the treatment of moderate to severe rheumatoid arthritis (RA) as a twice daily (BID) regimen. It was followed by Food and Drug Administration (FDA) approval of 11 mg modified release once daily (QD) dose in February of 2016.

The modified release (MR) QD regimen has the potential to improve drug compliance of patients, patient convenience, and to offer additional dosing options for patients. Data from completed pharmacokinetic (PK) studies demonstrated that the desired pharmacokinetic and pharmacodynamic (PK-PD) profile was achieved by the MR dose. Overall similarity of PK parameters between IR and MR formulations were found Phase 1 PK studies comparing MR and IR formulations. Therefore, based on the pharmacokinetic (PK) profile for the 2 formulations (IR and MR) and from the information obtained from IR BID programs, FDA approved MR based on clinical pharmacology studies.

It is hypothesized that patients prescribed tofacitinib 11 mg MR formulation once daily (QD) will achieve similar benefit to those prescribed tofacitinib 5 mg BID dosage in real world use. This study will therefore seek to compare the effectiveness of the MR 11 mg QD regimen to the IR 5 mg BID regimen for the treatment of RA in a real-world registry of RA patients.

8. RESEARCH QUESTION AND OBJECTIVES

Primary Objective:

The overall aim of this study is to the compare clinical effectiveness of tofacitinib in patients initiating tofacitinib 11 mg QD or 5 mg BID identified from the Corrona US RA Registry.

Secondary Objective:

The study also aims to descriptively assess effectiveness in patients that switched from tofacitinib 5 mg BID to tofacitinib 11 mg QD after February 2016.

9. RESEARCH METHODS

9.1. Study Design

This is an observational study conducted in a cohort of tofacitinib-exposed patients to evaluate effectiveness of tofacitinib MR 11 mg QD tablet compared to IR 5 mg BID tablet. In this secondary data collection study of structured data, patient therapeutic strategies are not determined by this protocol.

9.2. Setting

Using the United States (US) Corrona RA Registry database,[16] patients with RA who have been exposed to tofacitinib IR or MR on or after February 2016 will be included in this study. In order to adequately measure the outcome, the initiators will also be required to have a follow-up visit at 6 months (+/- 3 months) after tofacitinib initiation.

For the primary analysis comparing QD to BID patients, we will consider those patients who initiated tofacitinib 5 mg BID on or after February 2016 and those that initiated tofacitinib 11 mg QD after it became available in February 2016. Although the sample size will be smaller than if all tofacitinib 5 mg BID patients were considered, the inclusion of those patients may introduce noise since there is the possibility that they could differ from the more recent initiators. Therefore, we will consider the cleaner cohort of all patients initiating tofacitinib on or after February 2016.

For the secondary aim, patients that switched from tofacitinib 5 mg BID to tofacitinib 11 mg QD ("switchers") will be considered. Patients will be considered to have switched from 5 mg BID to 11 mg QD if they initiated 5 mg BID after February 2016 and subsequently changed their dose to 11 mg QD.

9.2.1. Inclusion Criteria

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

1. All US Corrona RA Registry patients who initiated tofacitinib 5 mg BID or tofacitinib 11 mg QD after it became available in February 2016.

2. Patients must have a follow-up visit at 6 months (+/- 3 months) after tofacitinib initiation. These 6 month visits are part of routine practice and is not associated with this protocol.

3. Patients must have a valid clinical disease activity index (CDAI) at initiation and at 6-month follow-up visit.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

The US Corrona RA Registry is an efficient data collection system for evaluating a range of efficacy outcomes associated with therapies used to treat RA. The endpoints chosen for this study will be extracted from patient and physician questionnaires. Demographic data collected includes age, gender, race and ethnicity. In addition, baseline disease characteristics like disease duration and severity etc. will be captured for both the IR and MR cohorts under study to evaluate disease characteristics.

Primary outcome: Minimally clinically important difference (MCID) improvement as defined by difference in Clinical Disease activity index (CDAI) from initiation to 6 month visit. MCID is dependent on baseline disease activity (at initiation); MCID≥2 if CDAI at initiation of Low CDAI ≤10, MCID≥6 if CDAI at initiation Moderate of 10<CDAI≤22 and MCID≥11 if CDAI at initiation high of >22.

Secondary Outcomes:

- Change in CDAI from baseline to 6 month follow-up (as a continuous variable).
- Achievement of Remission (CDAI≤2.8) at 6 month follow-up (among all).
- Achievement of Remission (CDAI≤2.8) at 6 month follow-up (among those that were not in remission at initiation).
- Achievement of Low Disease Activity (LDA) (CDAI≤10) at 6 month follow-up (among all).
- Achievement of Low Disease Activity (LDA) (CDAI≤10) at 6 month follow-up (among those that were not in remission or LDA at initiation).
- Achievement of improvement from baseline to 6 month follow-up in modified Health Assessment Questionnaire (mHAQ) of at least 0.25 (as a dichotomous variable).
- Achievement of improvement from baseline to 6 month follow-up in Health assessment questionnaire (HAQ) of at least 0.22.

- Change from baseline to 6 month follow-up HAQ (HAQ as a dichotomous variable).
- Change from baseline to 6 month follow-up modified HAQ (mHAQ as a continuous variable).
- Change from baseline to 6 month follow-up HAQ (HAQ as a continuous variable).
- Change from baseline to 6 month follow-up modified Disease activity Score (mDAS as a continuous variable).
- Change from baseline to 6 month follow-up Disease activity score- erythrocyte sedimentation rate (DAS ESR) (as a continuous variable).
- Change from baseline to 6 month follow-up DAS- C- reactive protein (DAS CRP) (as a continuous variable).
- Change from baseline to 6 month follow-up patient pain (as a continuous variable).
- Change from baseline to 6 month follow-up patient fatigue (as a continuous variable).
- Change from baseline to 6 month follow-up Euro-Qol (EQ-5D) index (as a continuous variable).
- Modified American College of Rheumatology (ACR) ACR20, ACR50, ACR70.

Detailed definitions for the original analysis as well as all subsequent analyses will be included in respective statistical analysis plans (SAPs).

9.4. Data Sources

The US Corrona RA Registry is the data source for this study. It is an independent, prospective, national, observational cohort. Patients are recruited from 187 private and academic sites across 43 states, with 799 providers participating. Providers and subjects complete study questionnaires approximately every 6 months at routine clinic encounters. As of September 2019, the Corrona database included information on 53,438 patients with RA. Data on 403,679 patient visits and 192,141 patient-years of follow-up observation time have been collected, with a mean patient follow-up of 4.48 (median 3.24) years. Data are collected on subjects for as long as they consent to remain in the study.

9.5. Study Size

Power calculations (below) indicate that to detect a reasonable difference of 15% in the percentage meeting MCID in CDAI, about 300-500 patients per group would be needed.

With the following assumptions:

- Consider the dichotomous outcome of meeting MCID in CDAI.
- We would like to have 90% power to detect a difference between the 2 groups in percentage meeting MCID in CDAI.
- We would like to have a low chance (alpha of 5%) of declaring that there is a difference in the outcomes between the 2 groups when in actuality there is not (type I error).

The following Table 1, gives the number needed per group and total number needed for different scenarios of meeting MCID for CDAI and percent of patients who are available under common support (eg, percent of patients in the control group that are similar enough to the treatment group so that we are comfortable that the 2 cohorts are similar). If we assume that the percentage meeting MCID in CDAI is 50%, the following sample sizes are required.

Table 1. Sample Size Determination

Difference between the 2 groups in percentage meeting MCID in CDAI that can be detected	Analyzable Data Set, N per group	% under common support	N per group required to recruit	Total N required to recruit
10%	535	50%	1070	2140
10%	535	75%	713	1426
15%	**237**	**50%**	**474**	**948**
15%	**237**	**75%**	**316**	**632**
20%	131	50%	262	524
20%	131	75%	175	350
25%	84	50%	168	336
25%	84	75%	112	224

Under different scenarios for projections of the total number of tofacitinib 11 mg QD initiators over time, it was estimated that there would be about 180-220 tofacitinib 11 mg QD initiators with 6 month follow-up visits by the end of 2018.

9.6. Data Management

Statistical analyses will be performed using Statistical Analysis System (SAS) Version 9.4 (SAS Institute, Cary, NC) and STATA Version 15 (StataCorp, LP, College Station, TX).

9.7. Data Analysis

Patients initiating tofacitinib during or after February 2016 with a six-month follow-up visit (+/- 3 months) will be considered for analysis. Patient and disease characteristics at initiation for the two cohorts of 11 mg QD and 5 mg BID will be considered. Propensity score matching and adjustment for covariates will be used to identify a balanced, matched subset of patients to use in final analyses.

The primary outcome will be minimum clinically important difference (MCID) improvement as defined by difference in CDAI from initiation to 6 month visit (dichotomous variable). Secondary outcomes at the 6 month visit (follow-up): change in CDAI from initiation to follow-up, achievement of remission (CDAI≤2.8) and achievement of low disease activity (LDA) (CDAI≤10), achievement of improvement from baseline to follow-up in HAQ of 0.22 and change from baseline to 6 month follow-up HAQ, modified DAS, DAS ESR, DAS CRP, patient pain, patient fatigue, EQ5D index, modified ACR20/50/70. Sensitivity analysis, will be performed if needed.

Detailed methodology for the original analysis as well as all subsequent analyses is documented in respective SAPs, which are 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 would be reflected in a protocol amendment.

9.8. Quality Control

The Corrona registry has standard operating procedures in place to monitor, perform edit and logic checks, and make corrections to the data, as necessary. Specifically, the data for each site is reviewed by the Quality Department or other delegated Corrona representative for completeness and internal consistency at regular intervals. The Quality Department generates a list of queries for each site, sends to the clinical site coordinator, and requests verification or correction for each query within 14 days. The Quality Department or other designated Corrona representative enters corrected data onto the Corrona database. An audit trail of all corrections to the data, and the personnel making and date of corrections, is stored with the data in the Corrona database.

9.9. Limitations of the Research Methods

This study has a number of limitations. Patient characteristics and access to medications can vary substantially between countries, due to payer and regulatory differences, thus these results may be less applicable outside of the US. Propensity score (PS) methods are intended to adjust for non-random treatment assignment, however, the possibility of bias and endpoint misclassification remains for observational studies. Furthermore, while we accounted for the most clinically significant variables, unmeasured residual confounding is a possibility.

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)

IRB/IEC approvals/waivers not required.

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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practices (GEP) guidelines issued by the International Epidemiological Association (IEA).

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

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 Corrona becomes aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

The protocol will be disclosed at clinical trials.gov website along with the final study results. In addition, the study results will be submitted to national and international medical conferences and a final publication will be developed and submitted to an indexed, peer-reviewed medical journal in the area of rheumatology. Results from the interim/full analysis may also be reported to European Medicines Agency (EMA) to support MR submission.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.