NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Title	Comparative Analysis of Adherence and Effectiveness Outcomes Between Rheumatoid Arthritis (RA) Patients Treated with Tofacitinib Modified Release (MR) Formulation 11mg Once Daily (QD) and Tofacitinib Immediate Release (IR) Formulation 5 mg Twice Daily (BID) within a United States (US) Healthcare Claims Database
Protocol number	A3921349
Protocol version identifier	Version 1
Date	27 March 2019
Active substance	L04AA29 (tofacitinib)
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	Primary Objectives: To compare two proxies of medication effectiveness (a validated criteria-based algorithm and a persistence-based measure) over 12 months of follow-up among RA patients treated with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily. Compare 12-month proportion of RA patients who are persistent and adherent with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily. Secondary Objectives: To compare a persistence-based measure of effectiveness over 6 months of follow-up among RA patients treated with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily. Compare 6-month proportion of RA patients

	who are persistent and adherent with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily. CCI [redacted]
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
bDMARD	Biologic disease-modifying antirheumatic drug
BID	Twice daily (bis in die)
CIRAS	Claims-based index for RA severity
COB	Coordination of Benefits
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
CPT	Current Procedural Terminology
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DAS	Disease Activity Score
ED	Emergency department
ER	Emergency room
FDA	Food and Drug Administration
GLM	Generalized linear model
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10 CM	International Classification of Diseases, 10th Revision, Clinical Modification
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IEC	Independent Ethics Committee
IR	Immediate release
IRB	Institutional review board
IV	Intravenous
JAK	Janus Kinase inhibitor
MPR	Medication Possession Ratio
MR	Modified release
MTX	Methotrexate
nbDMARD	Non-biologic disease-modifying antirheumatic drug
NDC	National Drug Code
NIS	Non-interventional study
NSAID	Non-steroidal anti-inflammatory drug
PDC	Proportion of Days Covered
PMDA	Pharmaceutical and Medical Devices Agency

Abbreviation	Definition
QD	Once daily (quaque die)
RA	Rheumatoid Arthritis
RCT	Randomized controlled trial
RX	Outpatient pharmacy prescription
TNFi	Tumor-Necrosis Factor-alpha inhibitor
US	United States

2. RESPONSIBLE PARTIES

Principle Investigator(s) of the Protocol

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3. ABSTRACT

Not applicable.

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned date
Start of data collection (programming start)	27 March 2019
End of data collection (draft tables)	16 April 2019
Interim study report	1 May 2019
Final study report	31 Jan 2020

6. RATIONALE AND BACKGROUND

Tofacitinib 5 mg immediate release formulation (IR) was approved for twice daily (BID) dosing schedule by the Food and Drug Administration (FDA) in November 2012 for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. In February 2016, an 11 mg once a day (QD) modified release (MR) tablet for treatment of rheumatoid arthritis was approved in the United States. It may be used as monotherapy or in combination with methotrexate (MTX) or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Biologic disease-modifying antirheumatic drugs s (bDMARDs) have been used for many years to treat RA with varying levels of success; however, no study has compared the effectiveness and treatment patterns of tofacitinib to bDMARDs in a real-world setting.

In study A3921215, a randomised controlled direct comparative clinical study conducted in Japan, the MR formulation did not meet the non-inferiority criteria based on the stringent criteria requested by the Pharmaceutical and Medical Devices Agency (PMDA), the Regulatory Agency in Japan. However, the point estimate of the difference in efficacy between the MR and IR formulations, based on the primary endpoint of Disease Activity Score (DAS)28, was within the pre-specified margin. Nonetheless, the data from this study are not sufficient to conclude statistical similarity between the clinical efficacy of MR and IR formulations. While randomised controlled trials (RCT) are considered high in the hierarchy of medical evidence for a conventional treatment comparison, the A3921215 results may not be applicable to clinical practice due to many factors including reduced adherence. Patients tend to demonstrate worse adherence when they know their medication is being monitored. For example, in a metanalysis of RCTs that used electronic pill count monitors, patients had lower adherence in studies where they were blinded to the fact of monitoring than in studies where they were aware of the monitoring.[2] Since once daily dosing is associated with significantly improved adherence,[2] the double-dummy nature of A3921215 and high levels of patient monitoring may have masked the benefit of the MR 11 mg QD formulation relative to IR 5 mg BID by minimizing the variation in adherence across the two study arms.

Increasingly, there is a recognition that patients' use of medicines in regular clinical practice or in settings better reflecting the reality of healthcare delivery can explain differences between expected efficacy based on RCT outcomes and actual effectiveness in real world.[1] Evidence from medication use in the real-world setting can help to extrapolate and/or augment data obtained in randomised controlled trials and establishes a broad picture of a medication's place in everyday clinical practice.[6]

A study comparing MR 11 mg QD and IR 5 mg BID within the Corrona RA registry demonstrated that 6 months post initiation, tofacitinib MR 11 mg QD is effective in managing signs and symptoms of RA in real world clinical use; and that it does so to a similar degree as tofacitinib IR 5 mg BID formulation (Pfizer, data on file). However, adherence information is not collected in the register and could not be evaluated.

This study is designed to compare the RA patient adherence between patients initiating tofacitinib MR 11 mg QD to those starting IR 5 mg BID, and to compare two proxy measures of effectiveness in an insurance claims-based real-world data setting.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objectives:

To compare, through multivariate regression analyses:

- Two proxies of medication effectiveness (a validated criteria-based algorithm and a persistence-based measure)[3] over 12 months of follow-up among RA patients treated with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily.

- 12-month proportion of RA patients who are persistent and adherent with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily.

Secondary Objectives:

To compare, through multivariate regression analyses:

- A persistence-based measure of effectiveness over 6 months of follow-up among RA patients treated with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily.

- A 6-month proportion of RA patients who are persistent and adherent with tofacitinib MR 11 mg once daily and tofacitinib IR 5 mg twice daily.

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8. RESEARCH METHODS

8.1. Study Design

To address the objectives, a retrospective cohort design will be employed to evaluate patient characteristics, proportion persistent and adherent, and effectiveness proxies in RA patients newly initiating tofacitinib within the Truven Health MarketScan Research Databases, CCI [redacted]

8.2. Setting

This study will utilize the de-identified claims data in the Truven Health MarketScan Research Databases.

8.2.1. Inclusion Criteria

This study will include individuals with RA who are commercially insured (commercial claims and encounters database) or Medicare-eligible retirees with employer sponsored Medicare Supplemental coverage (Medicare database) who are treated with tofacitinib.

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

1. First pharmacy claim for tofacitinib is a 30-day supply (index event).

2. Index prescription is for labelled dosing for tofacitinib MR 11 mg QD or IR 5 mg BID between 01 March 2016 and 31 October 2018 (the identification period) (See Annex 2 for operationalization). Since the specific dose frequency, ie, twice daily or once daily is not available, for those initiating a 30 days supply of tofacitinib MR 11 mg, a quantity of 30 pills is required (ie, 1x11 mg per day) and for those starting a 30 days supply of tofacitinib 5 mg, 60 pills (2x5 mg per day) will be required. Patients from the overall cohort will be further assigned into MR 11 mg QD and IR 5 mg BID subcohorts based on their assignment at index.

3. Continuously enrolled in a commercial or Medicare Supplemental insurance plan for at least one year before the index date through at least 1 year after the index date. Note: Patients will have a variable length baseline of at least a year long. The baseline period will be censored at January 1, 2013 based on licensed data availability. The majority of baseline measures will use data from the 12 months immediately prior to the index date. Select measures will use data during the entire variable length baseline.

4. Presence of The International Classification of Diseases, 9th Revision or 10th Revision, Clinical Modification (ICD-9 CM or ICD-10 CM) code for RA (in any position) during the one-year pre-index period or on the index date.
ICD-9 = 714.0x-714.4x & 714.81 or ICD10 = M05.* & M06.0*-M06.3* or M06.8*-M06.9*.

5. At least 18 years old as of the index date.

6. At least one claim for methotrexate anytime pre-index.

8.2.2. Exclusion Criteria

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

1. Patients with claims for other conditions for which advanced therapies (bDMARD or Janus Kinase inhibitor (JAK)) are used during the one-year pre-index period or on the index date: ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, juvenile idiopathic arthritis or ulcerative colitis will be excluded from the study.

Table 1. Exclusionary Diagnosis

Disease	ICD-9 diagnosis code	ICD10 diagnosis code
Ankylosing Spondylitis	720.0x	M45.*
Crohn's Disease	555.xx	K50.*
Psoriasis	696.1x	L40.0*-L40.4*, L40.8*- L40.9*
Psoriatic Arthritis	696.0x	L40.5*
Ulcerative Colitis	556.xx	K51.*
Juvenile RA	714.3*	M08.*

ICD: International classification of diseases; RA = rheumatoid arthritis

2. Patients with evidence of the index medication during the one-year pre-index period. Patients will be allowed to have been treated with other advanced therapies defined as other bDMARDs or other JAK inhibitors (not tofacitinib) during the one-year pre-index period.

3. Patients with more than one advanced therapy prescription fill on the index date will be removed from the study, ie, a bDMARD and JAK inhibitor or more than one JAK inhibitor or two different tofacitinib formulations (ie, IR and MR), filled on the index date will be removed from the study.

8.3. Cohort Assignment

Patients will be assigned to a tofacitinib study cohort based on the first tofacitinib claim and formulation observed and for which the patient meets the other inclusion/exclusion criteria While patients may have multiple eligible treatment episodes, only the first will be evaluated. Patients whose first tofacitinib prescription reflects a 11 mg formulation and day supply consistent with daily dose equal to 11 mg will be assigned to MR 11 mg QD. Patients whose first tofacitinib prescription reflects 5 mg formulation with a daily dose equal to 10 mg will be assigned to IR 5 mg BID. Patients are only eligible for inclusion in one cohort.

8.4. Period of Observation

All patients will be required to have been continuously enrolled in the health plan for at least 24 months (12 months prior to index, and 12 months post index, at minimum). Patients will have a variable length pre-index baseline period of at least 12 months. The 12 months prior to the index date will be used to assess the majority of pre-index characteristics. However, for select measures, eg, use of methotrexate, number of prior advanced therapies, and years since first RA diagnosis, the entire variable length baseline period will be utilized. The twelve months following the index date will be used to assess outcomes including adherence, persistence, and medication effectiveness.

8.5. Variables

Adherence is defined as percentage of time with medication on hand and will be assessed with the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC). Both measures have been evaluated in numerous publications for rheumatoid arthritis and other conditions and will be reported in current study for 6 and 12-month follow-up periods. Both

adherence measures will leverage tofacitinib medication days supply in the numerator, for which PDC adjusts for overlap in prescriptions while MPR does not. Further, the PDC is a more conservation measure of adherence as the denominator includes all pre-defined follow-up (360 days for the 12-month period; 180 days for the 6-month period), which may include time after stopping a medication in the calculation, while MPR only includes time between first and last prescription (plus last prescription days supply) in the denominator. Patients with an MPR or PDC ≥0.8 are typically characterized as adherent. The Pharmacy Quality Alliance recommends use of PDCs for adherence measurements.[8]

The proportion of patients who are persistent with treatment is also commonly evaluated in similar published studies and will be reported for 6 and 12-month follow-up periods. Prior studies have indicated at least 1/3rd of patients are not persistent with TNFi therapy, which is consistent with proportion of patients with inadequate response in clinical trials.[5] This measure takes into account patients who have not discontinued (gap of 60 days between refills) or switched medications; however, it may underestimate the proportion who are persistent depending on the duration of gap (ie, 60 vs. 90 days) for patients that may appear to discontinue and resume treatment for multiple reasons including hospitalization, drug samples not recorded in claims, use of stockpile, etc. Hence sensitivity analyses with different gaps are often employed.

Two measures of effectiveness will be used in this study: 1) a validated algorithm-based, dichotomous measure (over the 12 month follow up period) and 2) a duration of therapy based continuous measure of medication persistence (over 6 and 12 month follow up periods).

Among patients with at least one year of follow up, medication effectiveness at one year after the index date will be determined using an algorithm-based proxy measure of effectiveness based on the following six criteria.[3,7] This measure was shown to have good sensitivity, specificity, positive and negative predictive values ranging from 75% to 90% using a gold standard of low disease activity (DAS28 ≤3.2) or improvement in DAS28 by >1.2 units, which the authors suggested was consistent with but not identical to European League Against Rheumatoid Arthritis (EULAR) responder definition.[3]

The second effectiveness proxy is length of treatment duration which captures both the sustained positive treatment effect as well as inefficacy, loss of efficacy and adverse events as well as any discontinuations unrelated to treatment effect, such as costs and adherence.[11] Note that the MR and IR tofacitinib formulations have same costs. Duration of therapy has been used as an endpoint to demonstrate the improved effectiveness of methotrexate relative to other csDMARDs despite similar efficacy in RCT.[11] In this study, treatment duration was defined as the number of days between index date to the first of the following: the date of last prescription that is followed by a gap of 60 days without evidence of another advanced therapy prior to expiration of gap; the day before receipt of another advanced therapy; or the end of follow up period.

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
Index date	Baseline Patient Characteristics	Month and year of the patient's treatment index date (see Section 8.2.1, 8.2.2).
Age	Baseline Patient Characteristics	Patient age as of the index date.
Age group	Baseline Patient Characteristics	Age categorized into: 18–44, 45–64, and 65+.
Sex	Baseline Patient Characteristics	Male or female.
Geographic region	Baseline Patient Characteristics	Region in which the study patient is enrolled in a health plan will be categorized into five geographic regions: Northeast, North Central, South, West, and Unknown.
Insurance type	Baseline Patient Characteristics	Insurance type (commercial or Medicare) of index claim.
bDMARD use, 12 month pre-index, categorical	Baseline Clinical Characteristics	The count of unique bDMARDs with at least one prescription (Annex 2) received during the 12 month pre-index period. Will characterize use of 0, 1, 2 or more bDMARDs.
bDMARD use, 12 month pre-index, continuous	Baseline Clinical Characteristics	Number of unique bDMARD medications and claims during 12 months pre-index.
bDMARD use, variable pre-index, categorical	Baseline Clinical Characteristics	The count of unique bDMARDs with at least one prescription (Annex 2) received during the entire variable length pre-index period. No use will be classified as bDMARD naïve. Use of 1, 2 or more will be classified as bDMARD experienced.
TNFi use, 12 month pre-index, categorical	Baseline Clinical Characteristics	The count of unique TNFi with at least one prescription (Annex 2) received during the 12 month pre-index period. Will characterize use of 0, 1, 2 or more TNFi's.
TNFi use, 12 month pre-index, continuous	Baseline Clinical Characteristics	Number of unique TNFi claims during 12 months pre-index.
TNFi use, variable pre-index, categorical	Baseline Clinical Characteristics	The count of unique TNFi with at least one prescription (Annex 2) received during the entire variable length pre-index period. No use will be classified as TNFi naïve. Use of 1, 2 or more will be classified as TNFI experienced.

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
Advanced therapy use 12 month pre-index, categorical	Baseline Clinical Characteristics	Use of bDMARDs or JAK inhibitors (Annex 2) during 12 months pre-index. Will characterize use of 0,1, 2 or more advanced therapies.
Advanced therapy use 12 month pre-index, continuous	Baseline Clinical Characteristics	Number of unique medications and claims during 12 months pre-index.
Advanced therapy use, variable length pre-index, categorical	Baseline Clinical Characteristics	Use of any bDMARDs or JAK inhibitors (Annex 2) during variable length pre-index period. No use will be classified as advanced therapy naïve. Use of 1, 2 or more will be classified as advanced therapy experienced.
csDMARD use, 12 month pre-index, categorical	Baseline Clinical Characteristics	The count of unique csDMARDs with at least one prescription (see Annex 2) during the 12 month pre-index period as 0,1,2 or more.
csDMARD use, 12-month pre-index, continuous	Baseline Clinical Characteristics	The count of unique csDMARD medications and claims (see Annex 2) during 12-month pre-index period.
csDMARD use, 90 days pre-index, dichotomous	Baseline Clinical Characteristics	Presence of csDMARD in 90 days pre-index.
Combination therapy, 90 days post-index (including index)	Baseline Clinical Characteristics	Combination therapy defined as first comedication with any csDMARD (Annex 2) within 90 days on or after the index date. Classify first csDMARD as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine or other. If more than 1 csDMARD on same day, note methotrexate plus other or if not with methotrexate, just classify as >1 csDMARD other than methotrexate. Monotherapy defined as the complement to combination therapy.
Quan-Charlson comorbidity score, continuous, 12-month pre-index	Baseline Clinical Characteristics	A weighted scale of 17 co-morbidities (based on associated diagnosis codes on medical claims in the 12-months pre-index) presented as a summative score to evaluate co-morbid chronic illness burden.
Quan-Charlson comorbidity score, categorical 12-month pre-index	Baseline Clinical Characteristics	The continuous Quan-Charlson comorbidity score categorized into: 0, 1-2, 3-4, 5+ QCCI comorbidities (Annex 3).[4,9]
Opioid, non-steroidal anti-inflammatory drug (NSAID) use, dichotomous, 12-month pre-index	Baseline Clinical Characteristics	The use of weak and/or strong opioids and/or non-steroidal anti-inflammatory drug (NSAID) (Annex 2) during the 12-month pre-index periods.
Opioid, non-steroidal anti-inflammatory drug (NSAID) use, continuous 12 month pre-index	Baseline Clinical Characteristics	The number of pharmacy claims for weak and/or strong opioids and/or non-steroidal anti-inflammatory drug (NSAID) (Annex 2) during the 12-month pre-index periods.

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
Pre-index corticosteroids, dichotomous	Baseline Clinical Characteristics	The use of oral corticosteroids (Annex 2) during the 12-month pre-index.
Pre-index corticosteroid total exposure/dose, continuous, 12-month pre-index	Baseline Clinical Characteristics	The total prednisone-equivalent dose of oral corticosteroids in the 12 months prior to index, defined as: the sum of prednisone equivalent dose (Strength*quantity/equivalence factor) of a filled corticosteroid. (Dose equivalent factors: Betamethasone=0.6, Dexamethasone=0.75; Methylprednisolone, Triamcinolone=4, Prednisone, Prednisolone=5; Hydrocortisone=20, Cortisone=25; Fludrocortisone=n/a).
Visit with a rheumatologist in 90 days prior to index, dichotomous	Baseline Clinical Characteristics	At least one ambulatory visits (office visit or outpatient visit) in which the physician was a rheumatologist in the 90 days before or on the index date.
Visit with a rheumatologist in 12 months prior to index, dichotomous	Baseline Clinical Characteristics	At least one ambulatory visits (office visit or outpatient visit) in which the physician was a rheumatologist in the 12 months before or on the index date.
Visit with a rheumatologist in 12 months prior to index, continuous	Baseline Clinical Characteristics	Count of Ambulatory visits (office visit or outpatient visit) in which the physician was a rheumatologist in the 12 months before or on the index date.
Disease duration	Baseline Clinical Characteristics	The number of days from the earliest claim with a diagnosis of RA in the variable length baseline until the index date.
Total all-cause costs, 12-month pre-index, continuous	Baseline Clinical Characteristics	Sum of patient and plan paid costs for all healthcare resource use in 12 month pre-index period. CPI adjusted to 2018 dollars (http://data.bls.gov/cgi-bin/surveymost?cu U.S. Medical Care, 1982-84=100 - CUUR0000SAM).
Comorbidities, 12 month pre-index, dichotomous Cardiovascular diseases Chronic obstructive pulmonary disease (COPD) Asthma Kidney disease Diabetes Depression Anxiety Liver disease Sleep disorders Hypertension Hyperlipidemia	Baseline clinical characteristics	Presence or absence of codes for the comorbidities of interest during the 12-months prior to index (Annex 2).

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
Pre-index Claims-based index for RA severity (CIRAS), 12 month pre-index, continuous	Baseline clinical characteristic	The Claims-based Index for RA Severity will be implemented. CIRAS provides a single value of severity using the following 9 measures: age, gender, inflammatory marker tests, rehabilitation visits, Felty Syndrome, platelet orders, rheumatoid factor tests, chemistry panels, and rheumatologist visits. Scores range from 0 (low) to 10 (high)(Annex 4).[10]
Length of variable length pre-index period, continuous	Baseline characteristic	The period from start of continuous enrollment through index without gaps in coverage.
Length of variable length pre-index period, categorical	Baseline characteristic	Continuous variable length duration categorized into <13, 13-18, 19-24, 25-30,31-36 and >36 months.
CCI		
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CCI		

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
CCI [redacted]	[redacted]	[redacted]
Treatment Persistent, 6 and 12 months post-index, dichotomous	Outcome (persistence)	Patients who do not have a switch to another advanced therapy or discontinue tofacitinib (ie, 60-day gap between the run out of prior tofacitinib prescription and subsequent fill) over 6 and 12 month follow-up periods are characterized as persistent. The run out date is the prescription fill date + day supply – 1. For retail outpatient pharmacy prescription (RX) claims, the day supply will be utilized. There are no null tofacitinib days supply in dataset; however, claims with negative days supply or zero days supply will be excluded. Most tofacitinib prescriptions are for 30 days supply (86%) followed by 90 (12%) and 60 (~1%) days. Patients with early refills will be allowed to accumulate a stockpile of the index medication of up to 14 days for later use. A change in the formulation of active ingredient prescribed, eg, 5 mg BID vs 11 mg QD is not considered a switch for persistence endpoints in primary analyses.
Medication Possession Ratio (MPR), 6 and 12 months post-index, continuous	Outcome (adherence)	The total days supply between the first and including the last tofacitinib prescription divided by the time between the first through and including last index therapy prescription days supply. Multiple prescriptions for the same treatment with the same fill date will be treated as one prescription with longest days supply; and for all prescriptions days supply will be capped at end of follow-up. MPR will be capped at 1.0 and will be reported at 6 months and 12 months.
Medication Possession Ratio (MPR), 6 and 12 months post-index, dichotomous	Outcome (adherence)	High adherence (MPR≥0.8) vs. Low Adherence (MPR <0.8).
Proportion of Days Covered (PDC), 6 and 12 months post-index, continuous	Outcome (adherence)	The PDC was defined as number of days covered by arrays for each fill or administration during the denominator periods of 180 and 360 days post-index. Patients with early refills will be allowed to stockpile medications up to a maximum of 14 days total for later use. PDC is capped at 1.0.
Proportion of Days Covered (PDC), 6 and 12 months post-index, dichotomous	Outcome (adherence)	High adherence (PDC≥0.8) vs. Low Adherence (PDC <0.8).

Table 2. Variables Used in Analyses

Variable	Role	Operational definition
Medication Effectiveness, algorithm defined, 12 months post-index, dichotomous	Outcome (effectiveness)	Patients who meet all 6 effectiveness criteria will be considered effectively treated. Patients who fail any one of the 6 criteria are considered not effectively treated.
High adherence criterion	Effectiveness criterion 1	High adherence criterion met if PDC >=0.8 during the 12 month follow-up period.
Dose escalation criterion	Effectiveness criterion 2	No dose escalation criterion is met if no increases in index medication dose between index and 12 months after index. Dose increase threshold defined per Table 3.
No treatment switch criterion	Effectiveness criterion 3	No treatment switch criterion is met if there is no use of an advanced therapy (Annex 2) other than index therapy during the 12 month follow-up period.
Addition of csDMARD criterion	Effectiveness criterion 4	No addition of csDMARD criterion is met if there are no claims for any csDMARD during the 1-year post-index for which there was not a claim during 1-year pre-index and/or 90 days post-index.
Oral glucocorticoids criterion	Effectiveness criterion 5	The oral glucocorticoids criterion is met if a) For patients with no oral glucocorticoid prescriptions in the 6 months prior to index date, there is not more than 30 total days supply of oral glucocorticoids between 3-12 months post index; b) For patients with at least one claim for oral glucocorticoids during 6 months pre-index, oral glucocorticoid dose does not increase during months 6-12 post-index compared to the 6 months before the index date. Dose increase is **defined as ≥20% increase** in prednisone equivalent dose (per above) for all glucocorticoid claims filled during the respective time periods. Note: Patients with more than one glucocorticoid injection during months 3-12 after index will be evaluated per the injection glucocorticoid criterion.
Injection glucocorticoid criterion	Effectiveness criterion 6	The injectable glucocorticoids criterion is met if patients have one or fewer glucocorticoid injections during months 3-12 after index date. Patients having one or more glucocorticoid injections on a single day are not considered to have failed the criterion.
Medication effectiveness, Duration of therapy (persistence), continuous, 12 month post-index	Outcome (effectiveness proxy)	The number of days between index date to the first of the following: the date of last prescription that is followed by a gap of 60 days without evidence of another advanced therapy prior to expiration of gap; the day before receipt of another advanced therapy; or the end of follow up period. A sensitivity analysis will be conducted for the Tofacitinib MR and IR comparison to include a switch in formulation as a criterion for discontinuation.

Table 3. Dose Escalation Criteria

Generic Name	Standard dosing schedule	Criteria for dose escalation for medication effectiveness
Tofacitinib (tofacitinib IR)	5 mg twice daily	At least 1 claim in the follow-up period with an average daily dose of at least 20 mg/day.
tofacitinib (tofacitinib MR)	11 mg once daily	At least 1 claim in the follow-up period with an average daily dose of at least 22 mg/day.

CCI

[redacted]

[redacted]

CCI [redacted]

8.7. Study Size

The sample size for this study is fixed by the number of people meeting the inclusion criteria during the observation period. No formal sample size computation was performed. All patients who meet inclusion/exclusion criteria will be included in the analyses.

8.8. Data Management

The MarketScan Research Databases comply with both the spirit and the letter of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The MarketScan Databases meet the criteria for a limited-use dataset and contain none of the data elements prohibited by HIPAA for limited-use datasets.

8.9. Data Analysis

8.9.1. Primary and Secondary Analyses

Descriptive and multivariate regression analyses will be performed to satisfy the primary and secondary analyses as described in Table 4. Details on the descriptive and multivariate methods follow in Section 8.9.2 and Section 8.9.3 respectively.

Table 4. Primary and Secondary Objectives for Comparison Between MR 11 mg QD and IR 5 mg BID.

Endpoint	Objective	Type	Post Index Duration	Analysis[a]
Effectiveness[b] (algorithm defined)	Primary	Dichotomous	12 months	Generalized linear model
Effectiveness[c] (duration of persistence)	Primary	Continuous	12 months	Cox regression
Adherence (MPR)	Primary	Continuous	12 months	Generalized linear model
Adherence (MPR ≥80%)	Primary	Dichotomous	12 months	Logistic regression
Adherence (PDC)	Primary	Continuous	12 months	Generalized linear model
Adherence (PDC ≥80%)	Primary	Dichotomous	12 months	Logistic regression
Effectiveness (duration of persistence)	Secondary	Continuous	6 months	Cox regression
Adherence (MPR)	Secondary	Continuous	6 months	Generalized linear model
Adherence (MPR ≥80%)	Secondary	Dichotomous	6 months	Logistic regression

Table 4. Primary and Secondary Objectives for Comparison Between MR 11 mg QD and IR 5 mg BID.

Endpoint	Objective	Type	Post Index Duration	Analysis[a]
Adherence (PDC)	Secondary	Continuous	6 months	Generalized linear model
Adherence (PDC ≥80%)	Secondary	Dichotomous	6 months	Logistic regression

a. Analyses will be repeated stratifying by number of previous advanced treatments (0, 1, and 2+ prior) if feasible.
b. The proportions of patients not meeting each of the 6 criteria separately will be described.
CCI [redacted]

8.9.2. Descriptive Analysis

All study variables, including pre- and post-index measures, will initially summarized descriptively. In general, numbers and percentages will be provided for dichotomous and polytomous variables, while means, medians, and standard deviations will be provided for continuous variables. Missing or unavailable data will not be imputed.

Results will be stratified by treatment cohort, bivariate comparisons of pre- and post-index measures will be provided, and appropriate tests (eg, t-test, Mann Whitney-U test, chi-square test) will be used based on the distribution of the measure. The analysis that is performed (ie, the methods that are used and the patients who are included) will be specific the objective being examined. Descriptive techniques will be implemented for each objective.

8.9.3. Multivariate Analysis

To control for possible confounding of the relationship between the outcomes and independent variable of interest multivariable (logistic, generalized linear, and Cox) regression models will be evaluated as described in Table 4.

The models will include insurance type, region, age, sex, prior advance therapies in variable length period (None, 1 and 2+) as covariates. The following variables will be evaluated for inclusion as a covariate and be included if differences between MR 11 mg QD and IR 5 mg BID at baseline with p <0.10: 12-month pre-index use (% and means) of csDMARD, opioids, corticosteroids and presence of comorbidities including, cardiovascular disease, chronic obstructive pulmonary disease (COPD), asthma, kidney disease, depression, anxiety, liver disease, sleep disorders, hypertension, hyperlipidemia, Quan-Charlson comorbidity index and CIRAS scores, rheumatologist visit count during 1-year pre-index, disease duration, pre-index total costs, length of pre-index period, use of advanced therapy in 12 month pre-index and presence of csDMARD in 90 days post-index.

Generalized linear models (GLM) will be fit, using appropriate distributions and links for the nature of the data (eg, normally-distributed data with identity link, binary data and logit link). Point estimates, 95 percent confidence intervals, and p-values will be presented for contrasts; analysis of variance table will be presented to display the strength of the independent

variables, including point estimates and p-values. If there are problems with model fit, for example, failure to converge, transformation of data may be used in order to try a different distribution and link.

CCI [redacted]

8.10. Quality Control

This is a retrospective study, so issues of quality control at study sites, eg, data queries, do not apply. Analyses are programmed according to the specifications in the protocol, and if applicable, the statistical analysis plan, and documented in a programming plan. Final deliverables are reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks are documented in the programming plan.

8.11. Limitations of the Research Methods

Limitations that are general to claims database analyses and specific to this study should be noted. First, diagnosis of autoimmune conditions will be identified using ICD-10-CM diagnosis codes, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes. Second, the baseline period for this study will generally be 12 months long. Therefore, patients treated with a bDMARD or tofacitinib in the baseline can be considered to be prior users of therapy; however, patients with no bDMARD or tofacitinib use in the baseline may have just been off therapy for the 12 months prior. Lastly, this study will include an examination of medication effectiveness at 1 year among all bDMARD and tofacitinib users. Effectiveness (yes/no) will be measured using a validated algorithm; however, the algorithm was not validated for all medications being included. Specifically, tofacitinib was approved for treatment of RA after the algorithm was developed. This study will include consultation with physicians to determine if the algorithm is valid for all study medications or if modifications need to be implemented.

8.12. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws.

9.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

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

IRB is not required for this study as it uses commercially available de-identified secondary data sources and is considered exempt from the requirements for "human subjects research" in the US.

9.4. 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-RF04 and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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.

11. 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.

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14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. DRUG AND DIAGNOSIS CODE LISTS

The drug and diagnosis codes corresponding to the variables in this protocol will be found in the study folder.

ANNEX 3. CCI CODE LIST

The CCI Code list will be maintained in the study folder. QCCI is a weighted sum of 0/1 indicator variables for 17 disease categories. The weights are:

1*(cci01+cci02+cci03+cci04+cci05+ cci06+cci07+cci08+cci09+cci10)

2*(cci11+cci12+cci13+cci14)

3*(cci15)

6*(cci16+cci17)

cci01 = 'Myocardial infarction (MI)'
cci02 = 'Congestive heart failure (CHF)'
cci03 = 'Peripheral vascular disease (PVD)'
cci04 = 'Cerebrovascular disease (CD)'
cci05 = 'Dementia'
cci06 = 'Chronic pulmonary disease (CPD)'
cci07 = 'Rheumatologic disease (RD)'
cci08 = 'Peptic ulcer disease (PUD)'
cci09 = 'Mild liver disease (MLD)'
cci10 = 'Diabetes without chronic complication'
cci11 = 'Diabetes with chronic complications'
cci12 = 'Hemiplegia or paraplegia'
cci13 = 'Renal disease'

cci14 = 'Any malignancy, including leukemia and lymphoma'
cci15 = 'Moderate or severe liver disease'
cci16 = 'Metastatic solid tumor'
cci17 = 'AIDS/HIV'

ANNEX 4. CLAIMS-BASED INDEX OF RA SEVERITY (CIRAS)

Measure[10]	Score
Age (continuous)	-0.066
Gender 0: male 1: female	-0.092
Inflammatory marker test ordered 0: no 1: yes	0.60
Rehabilitation visit 0: no 1: yes	0.69
Rheumatoid factor test 0: no 1: yes	2.1
Felty's syndrome 0: no 1: yes	2.3
Number of platelet counts ordered 0 = 0 visits 1 = 1 visit 2 = 2 visits 3 = 3 visits 4 = 4+ visits	0.42
Number of chemistry panels ordered 0 = 0 panels 1 = 1 panel 2 = 2 panels 3 = 3 panels 4 = 4 panels 5 = 5+ panels	-0.14
Rheumatologist visit count 1 = 0 visits 2 = 1-4 visits 3 = 5+ visits	0.52
Intercept	6.5

Number of platelet counts, chemistry panels, and rheumatologist visits are counted 1 per person per day.

Codes for CIRAS Calculation

	Codes	**Visits/Tests**
Inflammatory Markers	85651, 85652 86140, 86141	ESR CRP
Rehabilitation	OT/PT Codes: G0151,G0152,G0157,G0158, G0159,G0160,S9129,S9131,97001,97002,97003,97004	Occupational therapy/physical therapy visits
Rheumatoid Factor	CPT 86430,86431	Rheumatoid Factor Test Qual, Rheumatoid Factor Test Quant
Felty's syndrome	ICD-9/10: 714.1, M05.0x	
Platelet counts	CPT: 85049	Automated platelet count
Chemistry panels	CPT: 80053, 82248, 82465, 82977, 83540, 83615, 84100, 84478, 84550	A/G Ratio, Albumin, Alkaline Phosphatase, Alanine Aminotransferase, Asparate Aminotransferase, Direct and Total Bilirubin, BUN/Creatinine Ratio, Calcium, Carbon Dioxide, Chloride, Cholesterol, Creatinine, Gamma Glutamyltransferase, Globulin, Glucose, Iron, Lactate Dehydrogenase, Phosphate, Potassium, Total Protein, Sodium, Triglycerides, Urea Nitrogen (BUN), Uric Acid

Document Approval Record

Document Name:	A3921349 Final NIS Protocol, 27 March 2019
Document Title:	A3921349 Final NIS Protocol, 27 March 2019

Signed By:	Date(GMT)	Signing Capacity
PPD	09-Apr-2019 15:27:20	Manager Approval
PPD	09-Apr-2019 17:10:54	Final Approval
PPD	09-Apr-2019 17:29:37	Manager Approval
PPD	10-Apr-2019 00:19:25	Final Approval