Study information

Title	Comparative Analysis of Outcomes among Patients Initiating Xeljanz in Combination with Oral MTX Who Withdraw MTX Versus Continue MTX Using a United States Healthcare Claims Database
Protocol number	A3921336
Protocol version identifier	Version 1
Date of last version of protocol	01 May 2018
Active substance	L04AA29 (tofacitinib)
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	**Primary Objective:** Compare treatment patterns including dosing, concomitant medication use, adherence, persistence, and switching among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX. **Secondary Objectives:** Explore the differences in demographic and clinical characteristics among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX. Compare rheumatoid arthritis (RA)-related costs among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX. Compare medication effectiveness among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX. Compare all-cause and RA-related health care utilization among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX. Compare all-cause healthcare costs among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ARRA	American Recovery and Reinvestment Act
CIRAS	Claims-based index for RA severity
CMS	Centers for Medicare & Medicaid Services
COB	Coordination of benefits
COPD	Chronic obstructive pulmonary disease
CPI	Consumer price index
CPT	Current Procedural Terminology
ED	Emergency department
ER	Emergency room
FDA	Food and Drug Administration
GLM	Generalized linear model
HCFA	Care Financing Administration
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	The International Classification of Diseases, 9th Revision, Clinical Modification
IEC	Independent Ethics Committee
IRB	Institutional review board
ISPOR	International society for pharmacoeconomics and outcomes research
IV	Intravenous
MTX	Methotrexate
NB-DMARD	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
RA	Rheumatoid Arthritis
RAPID3	Routine assessment of patient index data
RX	Outpatient pharmacy
TNFi	Tumor-Necrosis Factor-alpha inhibitor
UB	Uniform Bill
US	United States

2. RESPONSIBLE PARTIES

Principal 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	1 May 2018
End of data collection	31 May 2018
Final study report	30 September 2018

6. RATIONALE AND BACKGROUND

Tofacitinib was approved 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. It may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiologic disease-modifying antirheumatic drugs (NB-DMARDs).

Pfizer is currently conducting a phase 3b/4 study (A3921192) which was designed to evaluate the sustained efficacy and safety of tofacitinib modified release formulation (11 mg QD) after withdrawal of MTX versus tofacitinib modified release formulation plus continued MTX treatment in subjects with moderate to severe rheumatoid arthritis who are insufficiently responding to their stable dose of methotrexate treatment. This retrospective claims analysis is designed to compare the effectiveness and treatment patterns among tofacitinb+MTX patients who withdraw MTX vs. continue MTX in a real world setting.

7. RESEARCH OBJECTIVES

The primary and secondary objectives will be conducted among patients who are identified from the Truven Health MarketScan Research Database.

Primary Objective

- Compare treatment patterns including dosing, concomitant medication use, adherence, persistence, and switching among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

Secondary Objectives

1. Explore the differences in demographic and clinical characteristics among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

2. To compare RA-related costs among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

3. Compare medication effectiveness among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

4. Compare all-cause and RA-related health care utilization among tofacitinib+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

5. Compare all-cause healthcare costs among tofacitinb+MTX patients who withdraw MTX vs. persist with MTX or experience interrupted MTX.

8. RESEARCH METHODS

8.1. Study Design

To address the objectives, a retrospective cohort design will be employed to evaluate patient characteristics, treatment patterns, medication effectiveness, and health care cost and utilization in RA patients newly initiating tofacitinib in combination with oral MTX between January of 2014 and January 2017 utilizing the Truven Health MarketScan Research Database, see Section 8.7 below.

8.2. Setting

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

8.2.1. Inclusion Criteria

This study will include individuals who are privately insured and with Medicare Supplemental insurance paid for by their employers and initiating tofacitinib in combination with MTX for RA between 01 January 2014 and 31 January 2017. To be included in the final study sample, patients must meet the following inclusion criteria:

1. At least one claim for tofacitinib between 01 January 2014 and 31 January 2017 (the identification period).

    a. **Medication index date**. The index date will be the date of the first claim for tofacitinib during the identification period.

    Note: Patients will have a variable length baseline of at least a year long. The baseline period will be censored at January 1, 2012 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.

    b. Tofacitinb initiation. Patients must have a 2nd claim for tofacitinib within 60 days of the end of the days supplied from their index claim (at least two claims with no 60 day gap).

    c. Oral MTX initiation. Patients must have an initial prescription for oral MTX in the period between 30 days prior to index date and 30 days following index date followed by a 2nd prescription for oral MTX within 60 days of the end of the days supplied from their initial MTX claim (at least two claims/administrations with no 60 day gap).

2. Presence of The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 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*.

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

8.2.2. Exclusion Criteria

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

1. Patients with claims for other conditions for which biologics are used during the one-year pre-index period or on the index date: ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, or ulcerative colitis will be excluded from the study.

Table 1. Exclusionary Diagnoses

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 Rheumatoid Arthritis	714.3*	M08.*

2. Patients with evidence of the index medication during the one-year pre-index period will be removed from the analysis. Patients will be allowed to have been treated with other biologics approved for RA (Tumor-Necrosis Factor-alpha inhibitors (TNFi) [adalimumab (Humira), etanercept (Enbrel), certolizumab pegol (Cimzia), golimumab (Simponi), infliximab (Remicade)] and non-TNFi's with alternative mechanisms of action [abatacept (Orencia), and rituximab (Rituxan), anakinra (Kineret), tocilizumab (Actemra)]) during the one-year pre-index period.

3. Patients with 1 or more biologics on the index date will be removed from the study.

4. Patients with tofacitinib therapy prior to index.

5. Patients with 1 or more claims for injectable MTX (see Jcodes in Annex 2.B.) in combination with tofacitinib.

8.3. Cohort Assignment

Patients will be assigned to a study cohort based on MTX status following initiation of combination therapy with tofacitinib and MTX. The "MTX discontinued" cohort will contain patients who experience a gap in MTX therapy of >60 days within 12 months post-index. The "MTX interrupted" cohort will contain patients who experience a gap in MTX therapy of >60 days with 1 or more subsequent fills within 12 months post-index. The "MTX persistent" cohort will contain patients with no gap >60 days within 12 months post-index. If sample size is insufficient, the MTX "discontinued" and "MTX interrupted" cohorts may be combined.

8.4. Sample Subsets

The following sample subsets will be identified and included in the analysis of select outcomes.

- **Commercial vs. Medicare Supplemental-** Patients who meet all selection criteria and have Medicare Supplemental insurance at index will be classified as such.

- **Number of prior Biologics:** 0, 1, 2, 3+ at any time prior to index.

- **Pre-index MTX therapy**: Treatment with MTX prior to index medication.

8.5. Period of Observation

All patients will be required to be continuously enrolled in the health plan for at least 24 months. Patients will have a variable length 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, number of prior biologic therapies, and years since first RA diagnosis, the entire variable length baseline period will be utilized.

Measures utilizing the variable length baseline are noted. All baseline periods will be censored at January 1, 2012. The twelve months following the index date will be used to assess outcomes including treatment patterns, and health care costs, utilization and medication effectiveness.

8.6. Variables

8.6.1. Patient Characteristics

- **Index month/year**-The month and year of the patient's index date will be identified.

- **Age**-Age will be defined as of the index year.

- **Age groups**-Patients will be assigned to one of the following age groups: 18–44, 45-64, and 65+.

- **Sex**-sex will be captured from enrollment data; patients with undefined gender will be removed from the study sample.

- **Insurance type**-Whether the patient was covered under a commercial or Medicare Supplemental insurance plan will be captured.

- **Geographic region**-The United States (U.S.) region in which the study patient is enrolled in a health plan will be determined and reported and states will be categorized into five geographic regions: Northeast, North Central, South, West, Unknown.

8.6.2. Clinical Characteristics

- **Pre-index biologic use**-The use of biologics during the pre-index period will be identified. In addition, indicator variables will identify the specific biologic(s) used during the pre-index period. A count will be created to identify the number of different biologics received during the baseline. These measures will be created during the 12 month baseline and during the entire variable length baseline period.

- **Pre-index NB-DMARD use:** The use of the 4 main NB- DMARDS (methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide), and the other NB-DMARDS will be identified during the pre-index period. In addition, indicator variables will identify the specific medications used during the pre-index period. A count will be created to identify the number of different NB-DMARDS received during the baseline. These measures will be created during the 12 month baseline and during the entire variable length baseline period.

- **Pre-index Quan-Charlson comorbidity score**-A comorbidity score will be calculated based on the presence of diagnosis codes on medical claims in the 12-months pre-index period.[1,2] The Quan-Charlson comorbidity score will also be categorized into the following groups: zero, one to two, three to four, and five or more.

- **Comorbid conditions**—General comorbid conditions will be defined using the Clinical Classifications Software managed by the Agency for Healthcare Research and Quality (AHRQ).[3] This measure generates indicator variables for specific disease conditions based on ICD-9-CM diagnoses. The top 25 comorbid conditions identified during the pre- and post-index period will be presented.

- **Pre-index claims based index of RA severity (CIRAS):** The claims-based index for RA severity will be implemented. CIRAS provides a single value of severity using the following 9 measures.

[1] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173(6):676-82.

[2] Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, Steiner JF. Association of patient-centered outcomes with patient-reported and ICD-9-based morbidity measures. Ann Fam Med 2012;10(2):126-33.

[3] Clinical Classification Software (CCS) for ICD-9-CM. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp

Measure[4]	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

- **Pre-index medications**-The most common medications used during the 12-month pre- and post-index periods will be identified. The most common 25 medications received will be identified.

- **Opioid, non-steroidal anti-inflammatory drug (NSAID) use**-The use of weak and/or strong opioids and/or non-steroidal anti-inflammatory drug (NSAID) during the 12-month pre- and 12-month post-index periods will be identified. The number of pharmacy claims for opioids and/or NSAIDs and the number of days from the index date to the first opioid and/or NSAIDs claim will be identified.

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

- **Opioid, NSAID use while persistent.** In addition to opioid/NSAID use during the follow-up, use of opioids/NSAIDs while persistent and after persistence will be identified in the 12-month follow-up period.

- **Corticosteroid use.** The use of oral corticosteroids during the 12-month pre- and 12-month post-index periods will be identified. In addition, the total prednisone-equivalent dose of oral corticosteroids will be calculated.

- **Pre-index visit with a rheumatologist.** A 0/1 flag will be created to determine if the patient had an ambulatory visits (office visit or outpatient visit) in which the physician was a rheumatologist in the 90 days before or on the index date. A separate variable will be created identifying the number of visits with a rheumatologist during the entire 12-month baseline. A flag will also be created identifying the presence of a rheumatologist visit in the entire variable length baseline and the number of visits in the variable length baseline.

- **Disease duration.** The number of days from the earliest claim with a diagnosis of RA in the variable length baseline until the index date will be identified. Disease duration will only be created during the variable length baseline.

- **Pre-index Out-of-pocket expenses.** The patient's total all-cause and RA-related out of pocket healthcare cost for healthcare services in the one year before the index date and during the entire variable length baseline period will be calculated.

- **Comorbidities of interest.** 0/1 flags will be created to identify the presence of the following comorbidities during the 12-month baseline period.

    - Cardiovascular diseases;
    - Chronic obstructive pulmonary disease (COPD);
    - Asthma;
    - Kidney disease;
    - Diabetes;
    - Depression;
    - Anxiety;
    - Liver disease;
    - Sleep disorders;
    - Hypertension;
    - Hyperlipidemia.

8.6.3. Treatment Patterns

- **Non-persistence.** A 0/1 flag will be created to identify if the patient is not persistent with tofacitinib before the end of the 12 month follow-up period.

  Non-persistence will be identified based on a gap in treatment with the index medication or switching to another biologic.

  Among patients with 1 year of follow-up, persistence through the end of the 1 year follow-up will be identified. Persistence will be identified based on the day supply (or presumed day supply) and fill dates of claims for the index medication (see Table 2 for a listing of presumed day supplies). Persistence with the index medication will be defined as not having a gap in therapy of at least 60 days between fills/infusions. For retail pharmacy (RX) claims the day supply will be utilized. For Healthcare Common Procedure Coding System (HCPCS) claims a presumed day supply derived from the product label will be utilized. A gap of at least 60 days between the run-out date (service date + day supply-1) and the next service date will be considered non-persistence. Patients with early refills will be allowed to accumulate a stockpile of the index medication of up to 14 days for later use.

- **Post persistence treatment patterns.** Patients who are not persistent for the entire follow-up period will be classified into the following mutually exclusive categories based on the first occurrence of non-persistence: switch immediately, discontinue then restart, discontinue then switch, discontinue and never switch or restart.

  - **Switch immediately.** Patients will be classified as switching immediately if they initiate a non-index biologic before a 60-day gap in treatment is observed for the index medication.

  - **Discontinue then restart.** Patients will be classified as discontinuing and then restarting if there is a gap in the index therapy of at least 60 days and the first medication observed after the gap is the index medication.

  - **Discontinue then switch.** Patients will be classified as discontinuing and then switching if there is a gap in the index therapy of at least 60 days and the first medication observed after the gap is a biologic (including Tofacitinib) different from index medication.

  - **Discontinue without switch or restart.** Patients will be classified as discontinuing without switch or restart if they have a gap in therapy of at least 60 days and there are no claims for either the index med or a different biologic for the remainder of the follow-up period.

- **Switch any time**. In addition to the 4 mutually exclusive treatment patterns, patients with a switch medication any time during the 12-month follow-up period will be identified.

- **Restart any time**. In addition to the 4 mutually exclusive treatment patterns, patients who have a claim for the index medication any time after they are considered non-persistent with the index treatment (ie, including after switching) during the 12-month follow-up, will be identified.

- **Medication Possession Ratio (MPR):** In addition to the adherence measure in the medication effectiveness assessment (see Section 8.6.4), the MPR will be evaluated for persistent patients as the total days supply between the first and including the last prescription/administration divided by the time between the first through and including last biologic prescription/administration days supply. Adherent patients will be considered those with MPR ≥0.8. For MPR calculations, multiple prescriptions having 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. Also, the MPR will be capped at 1.0.

- **NB-DMARD adherence/addition.** Adherence with MTX and addition of a non-biologic DMARD other than MTX (sulfasalazine, hydroxychloroquine, leflunomide) during the 12 month follow-up will be identified.

    - **MTX adherence.** A single measure of adherence (PDC) will be created using all claims for MTX during the 12-month follow-up period. Adherence will be calculated as the total day supply divided by the number of days from the first claim during the follow-up until the end of the follow-up.

    - **NB-DMARD addition**. Addition of a NB-DMARD will be evaluated.

8.6.4. Medication Effectiveness

Among patients with at least one year of follow up, medication effectiveness at one year after the index date will be determined using the following six criteria.[5],[6] For each of the 6 criteria, a 0/1 flag will be created. Patients who are effectively treated for each of the 6 criteria will be considered effectively treated. Patients who fail any of the 6 criteria are therefore not effectively treated.

1. High adherence to index agent: a proportion of days covered (PDC) will be calculated based on total days supply over the 1 year follow-up. The PDC will be calculated by using the date of service and the day supply for each fill of the index medication. For patients that receive both 5mg and 11mg tofacitinb, both configurations will be treated interchangeably. Patients with early refills will be allowed to stockpile medications up to a maximum of 14 days total for later use.

[5] Curtis, J.R., et al., *Derivation and preliminary validation of an administrative claims-based algorithm for the effectiveness of medications for rheumatoid arthritis.* Arthritis Res Ther, 2011. **13**(5): p. R155.

[6] Oladapo, et. al. *Medication Effectiveness with the Use of Tumor Necrosis Factor Inhibitors Among Texas Medicaid Patients Diagnosed with Rheumatoid Arthritis*. Journal of Managed Care Pharmacy. 657 – 67. Vol. 20, No. 7. July 2014

2. No increase in dose for index medication compared to the starting dose. Dose escalation will be identified per the criteria listed in Table 2.

3. No switching from the index medication to a (different) biologic agent or tofacitinib. A switch will be defined as use of a different biologic or tofacitinib any time during the follow-up period.

4. No adding of a new non-biologic DMARD to the index therapy. Adding a new non-biologic will be considered as having at least 1 claim for one of the 3 main:

    1. NB-DMARDs during follow-up and not having a claim for the same NB-DMARD during the baseline. Changing from 1 NB-DMARD at baseline to a different.

    2. NB-DMARD at follow-up will be considered as adding a new NB-DMARD, ie, failing the algorithm.

5. Oral glucocorticoids. Only National Drug Code (NDC) codes for oral glucocorticoids will be included:

    a. For patients with no claims for oral glucocorticoid prescriptions in the six months prior to the index date: cannot receive more than 30 days of oral glucocorticoids between (index date +91) to (index date + 359). 30 days of oral glucocorticoids will be determined by summing up the day supply of all glucocorticoids claims with a fill date between (index date +91) to (index date +359).

    b. For patients with claims for oral glucocorticoids during the six months prior to the index date: No increase in oral glucocorticoid dose during months 6-12 after:

        a. Index compared to the 6 months before the index date. Increase in oral glucocorticoids will be determined from the prednisone equivalent dose for all glucocorticoid claims filled during the respective time periods.

6. At most one parenteral or intra-articular glucocorticoid joint injection on unique days after the patient had been on biologic treatment for more than three months between (index date +91) to (index date +359).

Table 2. Adherence and Dose Escalation Criteria

Generic Name	Standard dosing schedule	(Presumed) day supply	Criteria for dose escalation for medication effectiveness
SC/oral only			
tofacitinib	5 mg twice daily or 11 mg once daily	Day supply rounded to the nearest 30 day period. Day supplies less than 15 days will be rounded to 30 days.	At least 1 claim in the follow-up period with an average daily dose of at least 15 mg/day for both 5 mg and 11 mg doses.

8.6.5. Health Care Cost and Utilization

All cost and utilization measures will be identified in the 12-month pre-index period and the 12-month post-index period. Claims occurring on the index date will be considered part of the post-index period. Baseline and follow-up costs and the change in 12-month costs from baseline to follow-up will then be examined. Cost measures will comprise the total amount paid by the health plan and patient.

- **Health care resource utilization**-Health care resource utilization will be calculated for ambulatory visits (office and outpatient), emergency department (ED) visits, and inpatient admissions.

- **RA-related resource health care utilization**-Health care resource utilization related to RA will be calculated for ambulatory visits, emergency room (ER) visits, and inpatient admissions Utilization will be defined as RA-related if the claim had a diagnosis for RA in any position and/or is for the administration of a biologic or NB-DMARD.

- **Health care costs**-Health care costs will be computed as the combined health plan and patient paid amounts. Costs will be calculated as total costs, pharmacy costs, and medical costs, Medical costs will be further broken down into ambulatory costs, emergency services costs, inpatient costs, and other costs. Costs will be adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2013 (the earliest start of the pre-index period) and 2015 (the cost of claims occurring in 2016 will not be adjusted).[7]

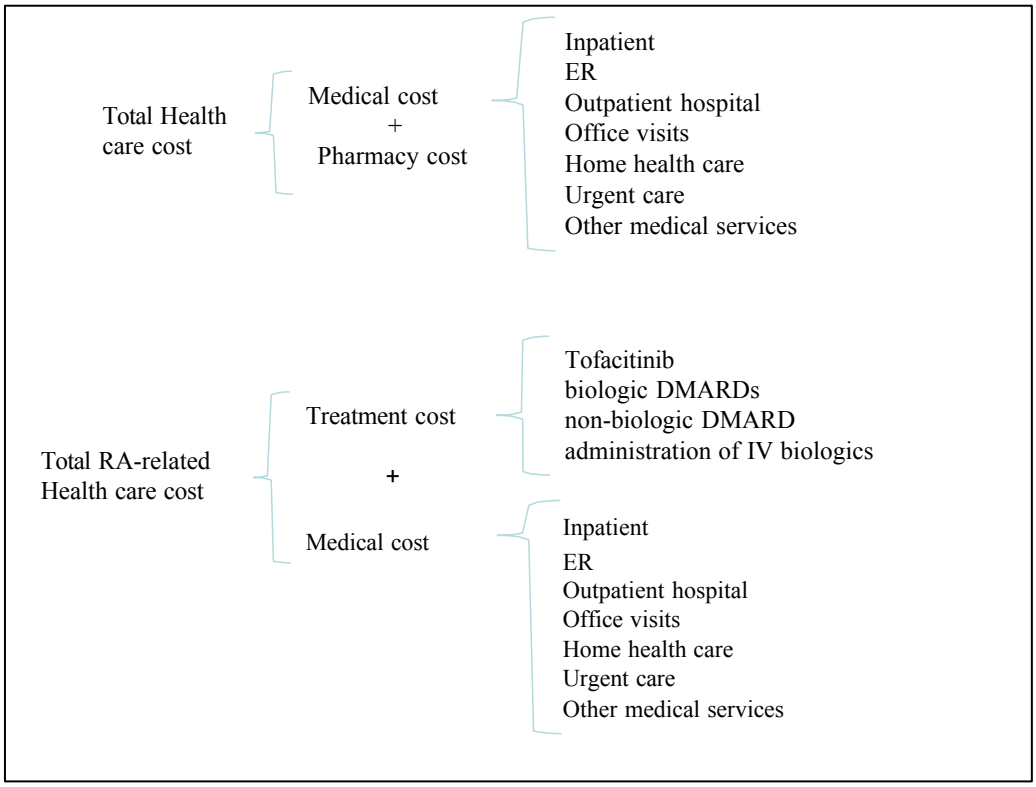
  Costs from other payers are of importance for older patients dually eligible for commercial and Medicare coverage. Payments from Medicare (and other payers) will be estimated based on coordination of benefits information obtained by the health plan in its usual course of business. This study will incorporate the amounts estimated to be paid by other payers for a total paid or allowable amount.[8]

- **RA-related health care costs**-CPI- and coordination of benefits (COB)-adjusted RA-related health care costs will be calculated as total costs related to RA (treatment and other medical claims with a diagnosis of RA). RA-related treatment costs will include the cost of tofacitinib, biologic DMARDs, non-biologic DMARDs, and administration of intravenous (IV) biologics (CPT = 96413 or 96415). Medical costs will include all utilization with a diagnosis of RA and are also not treatment claims. Medical costs will comprise: inpatient costs, ambulatory costs, emergency services costs, administration, and other costs.

[7] US Department of Labor, Bureau of Labor Statistics. *Consumer Price Index. Medical Care*. Series ID: CUUR0000SAM. Washington, DC: U.S. Dept. of Labor, Bureau of Labor Statistics. http://data.bls.gov/cgi-bin/surveymost?cu

[8] Frytak JF, Henk JH, et al. Health Services Utilization Among Alzheimer's Patients: Evidence from Managed Care. Alzheimer's and Dementia. 2008; 4(5):361-67.

- **Monthly costs**-Total all-cause and RA-related health care cost will be identified during each month (30-day period) of the patient's 12-month baseline and the 12-month follow-up period.



8.7. Data Sources

8.7.1. Truven

The Truven Health MarketScan Research Databases reflects the combined healthcare service use of individuals covered by Truven Health clients (including employers, health plans, and hospitals) nationwide in the US. Truven Health builds databases comprise the healthcare experience of the clients' covered populations, as well as information about the populations themselves and the providers that serve them. MarketScan Research Databases provide detailed cost, utilization, and outcomes data for healthcare services performed in both inpatient and outpatient settings. In the claims databases, the medical services are linked to outpatient prescription drug claims and person-level enrollment data using unique enrollee identifiers.

The MarketScan Commercial Database contains the healthcare experience of privately insured individuals. Coverage is provided under a variety of fee-for-service, fully capitated, and partially capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations.

The data that make up the Commercial Database are stored in the following tables:

- *The Inpatient Admissions Table* contains records that summarize information about a hospital admission. Truven Health constructs this table after identifying all of the service records associated with an admission (eg, the hospital claims, physician claims, surgeon claims, and claims from independent labs). Similar information (such as payments for professional services) is then summed across the claims. The admission record includes the principal procedure and diagnosis, Major Diagnostic Category, and Diagnosis-Related Group. It also includes all diagnoses and procedures (up to 14 each) found on the service records.

- *The Inpatient Services Table* contains the individual claims that are summed to create the inpatient admission records. An admission identifier on both the Inpatient Admissions and the Inpatient Services Tables identifies the claims that make up each admission record.

- *The Outpatient Services Table* comprises services that were rendered in a doctor's office, hospital outpatient facility, or other outpatient facility.

- *The Facility Header Table* contains the header records from facility claims for inpatient and outpatient services, including full diagnosis information.

- *The Outpatient Pharmaceutical Claims Table* contains outpatient prescription drug data from multiple sources, including mail-order data. Each record includes National Drug Code (NDC), therapeutic class, ingredient cost, dispensing fee, copayment, deductible, total gross payment, and other data elements.

- *The RED BOOK™ Supplement Table* contains *RED BOOK* variables that enhance prescription drug analyses. These variables are linked to the Outpatient Pharmaceutical Claims Table by NDC.

- *The Annual Enrollment Summary Table* provides a single record per year for each enrollee, showing enrollment start and end dates and, for some demographic variables, the most prevalent demographic and plan information; for other variables, monthly values are included.

- *The Enrollment Detail Table* provides a single record per month of enrollment for each enrollee, with detailed demographic information.

- *The Population Aggregate Table* provides average counts of the covered (insured) population to use for rate-supported analysis. The counts are recorded by several demographic variables (eg, age group, gender, region, etc.).

The MarketScan Medicare Supplemental Database contains the healthcare experience of individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as Coordination of Benefits Amount, or

COB) and the employer-paid portion are included in this database. The tables that make up the Medicare Supplemental Database are the same as those that make up the Commercial Database.

Claims are not included in the database until they have been adjudicated; there is a lag of approximately six months after the close of a calendar year or a quarter between services provided and their inclusion in the Research Databases. However, the Early View Database has a 90-day lag that includes paid amounts for 100 percent of prescription drugs, approximately 85 percent of physician office visits, and approximately 70 percent of hospital claims. The MarketScan Early View Database includes all of the components found in the standard MarketScan Commercial and Medicare Supplemental Databases. It includes standardized inpatient, outpatient, pharmaceutical, and health-plan enrollment data. The MarketScan Early View Database captures healthcare services incurred up to 90 days before data release and includes only adjudicated claims. However, the medical component of care for some patients will not be complete, since some claims (particularly inpatient claims) take longer to be adjudicated. Because this study is examining only comorbidities prior to and treatments during or prior to tofacitinib initiation fully adjudicated claims are not required and all available data will be used including Commercial, Medicare Supplemental, and Early View Databases.

8.8. Study Size

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

8.9. 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.

8.10. Data Analysis

Primary Objective

- **To compare treatment patterns including dosing, concomitant medication use, adherence, persistence and switching** among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.

For this objective, treatment patterns will be summarized across the cohorts of interest. Specific treatment patterns include non-persistence with the index medication, receipt of an opioid, receipt of an NSAID, adherence with the index medication, adherence with MTX.

Secondary Objectives

- **Explore the differences in demographic and clinical characteristics among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.**

For this objective descriptive analysis will be conducted. The goal of this objective will be to describe the respective populations and explore the presence of demographic differences between the cohorts. Known demographic characteristics (eg, age, gender geographic location, pre-index cost and utilization) will be summarized. In addition, other patient characteristics (eg, most common comorbid diagnoses and most common medications received) will be summarized.

- **To compare RA-related costs among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.**

For this objective both descriptive and multivariable analysis will be conducted. For the descriptive analysis, 12-month RA-related cost measures will be presented per patient during the baseline and follow-up periods. The change in health care cost from baseline to follow-up will be identified. In addition, total RA-related health care cost will be presented in each of the months of the baseline and follow-up. The mean cost in each month will be included on a figure demonstrating the trend in costs over time. Multivariable analysis of cost will also be conducted using generalized linear models (see Section 8.10.3).

- **Compare medication effectiveness using a validated claims-based algorithm among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.**

Medication effectiveness at one year will be examined by the medication cohorts of interest using patients who have at least 1 year of follow-up. For this objective both descriptive analysis and multivariable analysis will be used. Descriptive analysis will focus on quantifying the percentage of patients who are effectively treated at one year. Analysis of this objective may also include multivariable analysis (eg, logistic regression). Specifically, the dependent variable will be effectively treated at one year (yes/no) and the independent variables will be study cohort, demographic characteristics, characteristics of interest, and other characteristics identified from previous objectives (see Section 8.10.4).

- **Compare all-cause and RA-related health care utilization among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.**

For this objective descriptive analysis will be conducted. Utilization measures (flags and 12-month counts) will be presented per patient during the baseline and follow-up periods. In addition, for counts the change from baseline to follow-up will be calculated.

- **Compare all-cause healthcare costs among tofacitinb+MTX patients who discontinue MTX vs. persist with MTX or experience interrupted MTX.**

For this objective descriptive and multivariable analysis will be conducted. For the descriptive analysis, 12-month cost measures will be presented per patient during the baseline and follow-up. The change in 12-month costs from the baseline to the follow-up will also be calculated. In addition, total all-cause cost will be presented in each of the months of the baseline and follow-up. The mean cost in each month will be included on a figure demonstrating the trend in costs over time. Multivariable analysis of follow-up health care cost will also be conducted using generalized linear models (see Section 8.10.3).

- **Evaluate the primary and secondary objectives in cohorts of interest.**

All objectives will be evaluated for Commercial and Medicare Supplemental lives separately as well as by Monotherapy vs. Combination regimens as identified in Section 8.10.2 and by prior biologic experience (0, 1, 2, 3+ at any time prior to index).

8.10.1. Descriptive Analysis

All study variables, including pre- and post-index measures, will initially be analyzed descriptively. In general, numbers and percents 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.

Multivariable techniques (including effect decomposition) will be used when comparing outcomes and controlling for differences in patient characteristics between study cohorts.

8.10.2. Multivariate Analysis

To control for possible confounding of the relationship between the outcomes and independent variable of interest, select objectives will be conducted utilizing multivariable methods as described above.

Final outcomes for multivariate analysis will be selected after review of descriptive results. Possible outcomes of interest include: total all-cause health care cost, total RA-related health care cost, cost of biologics/tofacitinib/administration/nb-DMARDS, medication effectiveness (yes vs. no).

For each model, specific predictors to be included will be determined based upon clinical rationale and statistical significance. Variables listed in Section 8.6.1 and 8.6.2 will be considered for inclusion in the multivariable models. Additional variables identified throughout the course of the study will also be considered. Following standard procedure,

regression diagnostics will be performed for each model to assess goodness of fit and violations of model assumptions (eg, multicollinearity, heteroskedasticity). When there are violations of the model, programmers will note them and make appropriate corrections to the data (ie, typically through transformation of either the independent or dependent variables) or in the method of estimation.

8.10.3. Cost Data

Because health care costs are often skewed, estimated cost measures will be modeled using Manning and Mullahy's formulation.[9] This method avoids potential difficulties introduced by transformation and retransformation of the dependent variable.[10] Coefficients from a generalized linear model (GLM) are estimated cost ratios. Cost ratios, 95 percent confidence intervals, and p-values will be presented for each categorical covariate included in the model. For ease of interpretation and comparison with the bivariate results, the average cost will be predicted for each cohort and may also be predicted for pre-determined levels of other patient characteristics (eg, combination vs. monotherapy, gender).

If a significant number of patients have zero values for costs (eg, more than 5% in one of tofacitinb+MTX patients who withdraw MTX or continue MTX groups), estimated cost measures will be compared using Blough et al.'s formulation of the traditional two-part model (ie, one equation estimating the probability of any cost and a GLM with a gamma distribution and log link estimating the level of cost).[11] This method avoids potential difficulties introduced by transformation and retransformation of the dependent variable.

Odds ratios, 95 percent confidence intervals, and p-values will be presented for each categorical covariate included in the logistic model estimating the probability of non-zero costs, if any. Cost ratios, 95 percent confidence intervals, and p-values will be presented for each categorical covariate included in the GLM model estimating the level on costs. For continuous covariables of both models, estimates and their 95 percent confidence intervals, and p-values will be presented.

8.10.4. Dichotomous Data

For binary variables, the probability of achievement (eg, being effectively treated at one year) will be modeled using logistic regression. For ease of interpretation, the results of logistic regression will be presented as odds ratios, 95 percent confidence intervals, and p-values for each categorical covariate included in the model, and for continuous covariables, estimates and their 95 percent confidence intervals, and p-values will be presented.

[9] Manning WG, Mullahy J. Estimating log models: to transform or not to transform. J Health Econ. 2001

[10] Manning WG. The logged dependent variable, heteroskedasticity, and the retransformation problem. J Health Econ. 1998;17(3):283-295.

[11] Blough DK, Madden CW, Hornbrook MC. Modeling risk using generalized linear models. J Health Econ. 1999;18(2):153–171.

8.10.5. Other Continous Data

For continuous variables, mean values will be modeled using a normal model. The results will be presented as mean differences, 95 percent confidence intervals, and p-values for each categorical covariate included in the model, and for continuous covariables, estimates and their 95 percent confidence intervals, and p-values will be presented.

8.10.6. Decomposition

Given that the sample size for this study will be relatively small and the comparator populations will be noticeably different, implementing propensity score matching may reduce the available sample below what is needed for a meaningful study. One possible solution would be to implement a method known as decomposition [Blinder (1973), Oaxaca (1973)] Decomposition splits out the treatment effect into two parts, the effect of the actual treatment and the effect of the other differences between the treatment groups. Presumably, if the treatment groups were randomly assigned, then the effect of the treatment would be the entire effect and the effect of all other differences would be negligible. However, since biologic treatment choice is not randomly assigned, the decomposition method would determine how much of the treatment effect is due to the medication and how much is due to the difference in characteristics between the two tofacitinib cohorts (tofacitinb+MTX patients who withdraw MTX or continue MTX).

8.11. 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 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.

8.12. Limitations of the Research Methods

8.12.1. Claims

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. Second, the baseline period for this study will be 12 months long. Therefore, patients treated with a biologic in the baseline can be considered to be continuing users of biologic therapy; however, patients with no biologic 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 biologic users. Effectiveness 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.

8.13. Other Aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

As this is a retrospective non-interventional study using fully anonymized secondary data, no additional informed consent is required.

9.2. Patient Withdrawal

Not applicable.

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 Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, 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 (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual Adverse Event (AE) reports.

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.

COMMUNICATION OF ISSUES

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 investigator 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.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this non-interventional (NI) study protocol that the investigator becomes aware of.

12. REFERENCES

None.

13. LIST OF TABLES

14. LIST OF FIGURES

None.

15. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. ANNEX 2. LIST OF RA TREATMENTS

a. Biologics/JAK inhibitor

NDC codes will be refreshed based on latest data.

Generic Name	Brand Name	Route of Administration	TNF or Non-TNF	NDC	HCPCS
tofacitinib	Xeljanz	Oral	Non-TNF	00069100103 00069100101 00069100102	
adalimumab	Humira	SC	TNF	00074937402 00074379902 00074433902 00074433906 00074433907 54569552400 54868482200	
anakinra	Kineret	SC	Non-TNF	55513017701 55513017707 55513017728 66658023401 66658023407 66658023428	
certolizumab pegol	Cimzia	SC	TNF	50474070062 50474071079 50474071081	
etanercept	Enbrel	SC	TNF	54868478200 58406044501 58406044504 54868544400 58406043501 58406043504 58406044501 58406044504 58406045501 58406045504 58406042534 58406042541	
abatacept	Orencia	IV	Non-TNF		C9230 J0129
abatacept	Orencia	SC	Non-TNF	00003218811 00003218831	
golimumab	Simponi	SC	TNF	57894007001 57894007002 57894007101 57894007102	
golimumab	Aria	IV	TNF		J1602
tocilizumab	Actemra	IV	Non-TNF		C9264 J3262
tocilizumab	Actemra	SC	Non-TNF	50242013801	
Infliximab Infliximab-dyyb Infliximab-abda	Remicade Inflectra Renflexis	IV	TNF		J1745 Q5102
rituximab	Rituxan	IV	Non-TNF		J9310

b. Non-Biologic (Traditional) DMARDs

Generic Names	J-codes	NDC
Hydroxychloroquine	n/a	See attached Excel Sheet
Methotrexate	J8610, J9250, J9260	
Leflunomide	n/a	
Sulfasalazine	n/a	
Other Medications:		
Chloroquine	J0390	Proprietary codes (based on groupings of NDC codes by generic name) will be used to identify these drugs from pharmacy claims
Combos	n/a	
Cyclosporine	J7502, J7515, J7516, C9438, J7503, K0121, K0122, K0418	
Thalidomide	n/a	
Azathioprine	J7500, J7501, C9436, K0119, K0120	
Cyclophosphamide	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097, C9420, C9421	
Auranofin	n/a	
Aurothioglucose	J2910	
Gold Sodium Thiomalate	J1600	
Penicillamine	n/a	
Tacrolimus	J7507, J7525, C9006, J7508	
Minocycline	J2265	

17. ANNEX 3. LIST OF OTHER MEDICATIONS

GLUCOCORTICOIDS^	
betamethasone	J7624
Budesonide	
cortisone	J0810
dexamethasone	J1094, J1095, J1100, J8540, Q0137, Q0138, S0173
Fludrocortisone	
hydrocortisone	
methylprednisolone	J1020, J1030, J1040, J2920, J2930, J7509
prednisolone	J1680, J2640, J2650,
prednisone	J1690, J7506, K0125
triamcinolone	J3300, J3301, J3302,
NSAID	
	J1885
Opioids	
^Proprietary codes (based on groupings of NDC codes by generic name) will also be used to identify these drugs from pharmacy claims	