NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Title	Comparative Analysis of Outcomes among Rheumatoid Arthritis Patients Treated with Xeljanz Versus Biologic DMARDs using a United States Healthcare Claims Database
Protocol number	A3921305
Protocol version identifier	1.2
Date	6 December 2019
Active substance	L04AA29 (tofacitinib)
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	**Primary Objective:** To compare rheumatoid arthritis (RA)-related costs among patients treated with tofacitinib (Immediate-Release formulation (IR); Modified-Release formulation (XR) and combined) to patients treated with each of the biologic DMARDS (bDMARDs), individually, as well as to TNFi and to non-TNFi each combined as groups. **Secondary Objectives:** Explore the differences in demographic and clinical characteristics between patients treated with tofacitinib vs. each individual bDMARD. Compare treatment patterns including dosing, concomitant medication use, adherence, persistence, and switching with tofacitinib vs. each individual bDMARD. Compare all-cause and RA-related health care utilization of patients treated with tofacitinib vs. each individual bDMARD.

	Compare all-cause healthcare costs for patients treated with tofacitinib vs. each individual bDMARD. Compare medication effectiveness among patients treated with tofacitinib vs. each individual bDMARD.
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TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
bDMARD	Biologic disease-modifying antirheumatic drug
CCAE	Truven MarketScan Commercial Claims and Encounters
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
ED	Emergency department
ER	Emergency room
FDA	Food and Drug Administration
CCI	[redacted]
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
IRB	Institutional review board
IR	Immediate-Release formulation of tofacitinib (5 mg)
IV	Intravenous
MPR	Medication Possession Ratio
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
RA	Rheumatoid Arthritis
RX	Outpatient pharmacy prescription
SC	Subcutaneous
TNFi	Tumor-Necrosis Factor-alpha inhibitor
UHC	Urgent Health Care
US	United States
XR	Modified-Release formulation of tofacitinib (11 mg)

2. RESPONSIBLE PARTIES

Name, degree(s)	Job Title	Affiliation	Address
PPD	PPD	PPD	PPD
PPD, PhD	PPD	PPD	PPD
PPD, PharmD, MS	PPD	PPD	PPD
PPD, PharmD, MS	PPD	PPD	PPD
PPD, PhD	PPD	PPD	PPD

3. ABSTRACT

Not applicable.

4. AMENDMENTS AND UPDATES

Amend-ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Substantial or Administrative	Reason
1.2	6 December 2019	CCI			
		CCI			

Amend-ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Substantial or Administrative	Reason
		Section 2	Replace "PPD " with "PPD "	Administrative	Change in team membership.
		Section 5	Dates updated to include additional data and updated data availability	Administrative	Update milestone dates.
		Section 8.1, and related references	Changing the identification-period dates	Administrative	Updated dates are more relevant for the current usage of tofacitinib
		CCI	[redacted]	[redacted]	[redacted]
		CCI	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		CCI	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]

Amend-ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Substantial or Administrative	Reason
		CCI [redacted]	[redacted]	[redacted]	[redacted]
		Annex 3, Annex 4	Added, "Drug codes will be refreshed based on latest data. That is, use the dictionaries to obtain the most comprehensive lists. Examples are displayed below."	Administrative	To ensure that the most up-to-date codes are used and hence most correct extraction is performed.
		Annex 5 and related references	Change the display dates of the Consumer-Price Index.	Administrative	To make consistent with the updated identification-period dates.
1.1	20 December 2018	Global	Tofacitinib IR versus Tofacitinib XR distinctions made and analyses added.	Substantial	It is felt that a sufficient number of Tofacitinib XR patients have accrued to allow for a set of analyses that could yield meaningful results.
		Global	Changed NBDMARD to csDMARD.	Administrative	"Conventional synthetic" DMARD (csDMARD) is more correct.
		Global	Changed biologics to biologic DMARD (bDMARD).	Administrative	"biologic DMARD" (bDMARD) is more correct.
		5	Milestone Dates updated.	Administrative	Updated to correct schedule of work.
		7, 8, title page, Table 2	Added IR and XR to objectives, specified analyses.	Administrative	XR formulation now substantially used to warrant investigating it.
		8	Changed "Number of prior bDMARDs" to 0, 1, 2+.	Administrative	Originally 0, 1, 2, 3+, was felt that 3+ is too diluted as a category.
		8 8.2.1	Changed dates of initiation to January 2014 to July 2018.	Substantial	two years of tofacitinib RA prescribing; less likely that patients in later-line treatment.
			Changed definition of combination therapy.	Administrative	To bring into alignment the definition with other projects.
			CCI [redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]

Amend-ment number	Date	Protocol section(s) changed	Summary of amendment(s)	Substantial or Administrative	Reason
			Added reference to ICD-10	Administrative	ICD-10 will be utilized.
		8.4, 8.5	Deleted.	Administrative	Text redundant; details found later in protocol.
		8.2.1, 8.7 (now 8.3)	Changed baseline censoring from 2011 to 2012.	Administrative	Change corresponding to changed of dates of initiation to January 2014 to July 2018.
		8.8.2 (now 8.6.2)	Clarified the calculation of the total daily dose of corticosteroids.	Administrative	Clarification needed.
		8.8.3 (now 8.6.3)	Proportion of Days covered definition clarified.	Administrative	Clarification needed.
		8.8.5 (now 8.6.5)	Untitled Figure added with notes, explaining the summation of costs.	Administrative	Clarification needed.
		8.12.5 (now 8.10.5)	Updated methodology for analysis of cost data.	Substantial	Previous text was outdated.
		CC	[redacted]	[redacted]	[redacted]
		9, 10, 11	Added up-to-date text, per SOP.	Administrative	Updated SOP released 15-Aug-2018.
		References	Added References.	Administrative	Citations added are associated with new text; adding citations for older text for completeness.
		Annex 2	Replace table with a statement that dictionaries will be used instead.	Administrative	Less error prone to use existing dictionaries.
		Annex 3	Changed to “List of conventional synthetic DMARDS”.	Administrative	To document the csDMARDs used.
		Annex 4	Annex 3 from previous version moved to Annex 4.	Administrative	More logical flow of the information presented.
		Annex 5	Consumer Price Index Values.	Administrative	To document the Consumer Price Index for cost-of-living adjustments.

5. MILESTONES

Milestone	Planned date
Start of data collection	16 Dec 2019
End of data collection	15 March 2020
Final study report	15 July 2020

6. RATIONALE AND BACKGROUND

Tofacitinib 5 mg immediate release formulation (IR) was approved for a 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 tablet (XR) 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). Since approval, little is known about the effect of tofacitinib on patient outcomes relative to biologic disease-modifying antirheumatic drugs (bDMARDs) among rheumatoid arthritis (RA) patients in the real world. Biologic DMARDs currently approved for RA include: 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)]. Biologic DMARDs 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.

A similar comparative analysis focusing on the early experience with tofacitinib was previously conducted. This analysis is designed to provide an updated characterization of medication effectiveness and health care cost and utilization in RA patients treated with tofacitinib vs. bDMARDs in the period following the initial introduction of tofacitinib, as well as a comparison of the tofacitinib 11 mg QD and tofacitinib 5 mg BID formulations.

7. RESEARCH QUESTION AND OBJECTIVES

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

7.1. Primary Objective

To compare RA-related costs among patients treated with tofacitinib (IR, XR and combined groups) to patients treated with each of the bDMARDs (individually, as well as to TNFi and to non-TNFi each combined as groups).

7.2. Secondary Objectives

- Explore the differences in demographic and clinical characteristics between patients treated with tofacitinib vs. each individual bDMARD.

- Compare treatment patterns including dosing, concomitant medication use, adherence, persistence, and switching with tofacitinib vs. each individual bDMARD.

- Compare all-cause and RA-related health care utilization of patients treated with tofacitinib vs. each individual bDMARD.

- Compare all-cause healthcare costs for patients treated with tofacitinib vs. each individual bDMARD.

- Compare medication effectiveness among patients treated with tofacitinib vs. each individual bDMARD.

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 or bDMARDs between 01 February 2016 and 31 July 2019 utilizing the Truven Health MarketScan Research Database, see Section 8.7 below.

In choosing the January 2014, there will have been potentially two years of tofacitinib RA prescribing, and it is less likely that patients in later-line treatment will predominate.

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 (Truven MarketScan Commercial Claims and Encounters (CCAE) database) and with Medicare Supplemental insurance paid for by their employers and treated with tofacitinib or bDMARDs for RA between 01 February 2016 and 31 July 2019. To be included in the final study sample, patients must meet the following inclusion criteria:

1. At least one claim for methotrexate during the variable-length pre-index period.

2. At least one claim for tofacitinib or bDMARDs between 01 February 2016 and 31 July 2019 (the identification period).

   Medication index date: For patients treated with bDMARDs or tofacitinib, the index date will be the date of the first claim for bDMARDs or tofacitinib during the identification period.

3. Continuously enrolled in a commercial (CCAE) 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, 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.

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.

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 bDMARDs 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 RA	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) bDMARDs during the one-year pre-index period.

3. Patients with more than 1 bDMARD or bDMARD with tofacitinib filled on the index date will be removed from the study.

8.3. Cohort Assignment

Patients will be assigned to a study cohort based on the medication received on the index date. The tofacitinib cohort will include patients with a pharmacy claim for tofacitinib on the index date. The bDMARD cohort will include patients with pharmacy or medical claims for a bDMARD on the index date. Patients will be further classified by the tofacitinib

preparation received (IR or XR) or bDMARD received (TNFI or non-TNFi) on the index date.

CCI

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

- **Pre-index csDMARD use:** The use of csDMARDs (methotrexate, sulfasalazine, hydroxychloroquine, etc., other csDMARDs) 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 csDMARDs received during the baseline. These measures will be created during the 12 month baseline and during the entire variable length baseline period.

- **Combination vs. monotherapy:** whether the patient is treated with combination therapy (ie, treated with any csDMARDs) or monotherapy at index will be determined. Patients with a use of at least one of four specific csDMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide) within 90 days on or after the index date will be considered as being treated with combination therapy.

- **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.[2,3] The Quan-Charlson comorbidity score will also be categorized into the following groups: zero, one to two, three to four, and five or more.

- **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.

- **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.

Note: The total dose for corticosteroids is calculated as the sum(prednisone equivalent dose of administered corticosteroids) divided by the maximum of days supplied for medication given on the same date, and then averaged over all dates on which patient was given corticosteroids.

- **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 their index bDMARD 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 bDMARD.

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. Please see Section 8.11, for additional details on gap and variables needed.

- **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 bDMARD 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 bDMARD (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 bDMARD 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):** The MPR will be evaluated 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 bDMARD prescription or administration days supply. For infusible products (except rituximab), the presumed days supply is in Table 2. 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.

- Proportion of Days Covered (PDC):

  - For all medications (except rituximab) 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 infused and subcutaneous (SC) versions of medications, a presumed days supply will be attributed to each infusion claim based on the product label Table 2. Patients with early refills will be allowed to stockpile medications up to a maximum of 14 days total for later use.

  - For rituximab, because of the dosing schedule PDC is not easily interpretable and may not be relevant. For purposes of inclusion, if there are 3 or more rituximab administrations, the patient will be considered adherent.

- **csDMARD adherence/addition.** Adherence with or addition of a csDMARD during the 12 month follow-up will be identified.

  - **Combination therapy patients**. For patients who initiate combination therapy with csDMARDs a single measure of adherence will be created using all claims for csDMARDs 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.

  - **Monotherapy patients.** For those who initiated monotherapy, addition of a csDMARD 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.[4,5] 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. Some of the 6 criteria cannot be measured for all of the index medications. For example, adherence cannot be calculated for patients treated with rituximab; therefore, medication effectiveness will not be calculated for patients treated with rituximab at index.

- High adherence to index agent will be determined based on PDC >=0.8 during the 12 month follow-up period. (Sensitivity analysis will be conducted to determine the effect of different adherence threshholds, eg, 0.7, 0.9).

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

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

- No adding of a new csDMARD to the index therapy. Adding a new bDMARD will be considered as having at least 1 claim for any csDMARDs during follow-up and not having a claim for the same csDMARD during the baseline. Changing from 1 csDMARD at baseline to a different csDMARD at follow-up will be considered as adding a new csDMARD, ie, failing the algorithm. (That is, any csDMARD present during the 1-year post-index and not present during 1-year pre-index results in the patient not meeting csDMARD effectiveness criterion).

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

    - 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 + 365). 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 + 365).

    - 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 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.

    - At most one parenteral or intra-articular glucocorticoid joint injection on unique days after the patient had been on bDMARD treatment for more than three months between (index date + 91) to (index date + 365).

      NOTE: Patients having more than one glucocorticoid injection code on a single day are considered to have failed to meet the glucocorticoid injection criteria.

Table 2. Adherence and Dose Escalation Criteria

Generic Name	Standard dosing schedule	(Presumed) day supply	Criteria for dose escalation for medication effectiveness
subcutaneous/oral only			
adalimumab	40 mg every other week. Some patients may benefit from increasing the frequency to 40 mg every week.	Day supply rounded to the nearest 28 day period. Day supplies less than 14 days will be rounded to 28 days.	At least 1 claim in the follow-up period with an average weekly dose of at least 40mg/week.
certolizumab pegol	400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; For maintenance dosing, 400 mg every 4 weeks can be considered.	Day supply rounded to the nearest 28 day period. Day supplies less than 14 days will be rounded to 28 days.	At least 1 claim from index date+56 days to the end date with an average weekly dose greater than or equal to 200mg/week.
etanercept	50 mg once weekly.	Day supply rounded to the nearest 28 day period. Day supplies less than 14 days will be rounded to 28 days.	At least 1 claim in the follow-up period with an average weekly dose of at least 100mg/week.
tofacitinib (tofacitinib IR)	5 mg twice 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.
tofacitinib (tofacitinib XR)	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 22 mg/day.
IV only			
infliximab	3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may increase to 10 mg/kg or treat every 4 weeks.	56 days for all claims (for discontinuation)	Any of the following 3 criteria: 1. The dose of last Rx claim (rounded up to next 100 mg) is at least 100 mg greater than the first dose (rounded up to the next 100). OR 2. There are ≥11 infusion dates during the follow-up period. OR 3. There fewer than 7 weeks

Generic Name	Standard dosing schedule	(Presumed) day supply	Criteria for dose escalation for medication effectiveness
			(49 days), between any 2 consecutive infliximab infusions not including the time between the first and second, or second and third infusions.
rituximab	N/A	N/A	N/A
IV and subcutaneous			
tocilizumab	IV: 4 mg/kg every 4 weeks then 8 mg/kg every 4 weeks. SC <100 kg: 162 mg every other week. Then increase to weekly per response SC ≥100 kg: 162 mg every week.	SC: Day supply from claim rounded to the nearest 28 day period. Day supplies less than 14 days will be rounded to 28 days. IV: 28 days	SC claims: At least 1 SC claim with an average weekly dose greater than 324mg/week OR IV claims: identify the dose of the first IV Rx claim and the dose of the last IV claim. If the dose of the last IV claim is >2.2 times the dose of the first IV claim then the patient dose escalated.
golimumab	SC: 50 mg /month. IV: 2 mg/kg at weeks 0 and 4, then every 8 weeks.	SC: Day supply from claim rounded to the nearest 28 day. Day supplies less than 14 days will be rounded to 28 days. IV: 28 days	SC claims: At least 1 SC claim with an average weekly dose greater than 25 mg/week OR IV claims: identify the dose of the first IV claim and the dose of the last IV claim. If the dose of the last IV claim is at least 50 mg greater than the dose of the first IV claim then the patient dose escalated.
abatacept	SC: 125 mg once weekly with or without an IV loading dose (see IV criteria). IV: weeks 0, 2, 4, and then every 4 weeks, dose determined by weight. <60 kg: 500 mg. 60-100 kg: 750 mg. 100 kg+: 1000 mg.	SC: day supply from claim rounded to the nearest 28 day. Day supplies less than 14 days will be rounded to 28 days. IV: 28 days	SC claims: At least 1 SC claim with an average weekly dose greater than 250 mg/week IV claims: identify initial dose and last dose. If last dose is greater than first dose +100 mg then the patient dose escalated.

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 bDMARD or csDMARD.

- **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. See figure below. (Medical costs may be further broken down into ambulatory costs, emergency services costs, inpatient costs, and other costs).

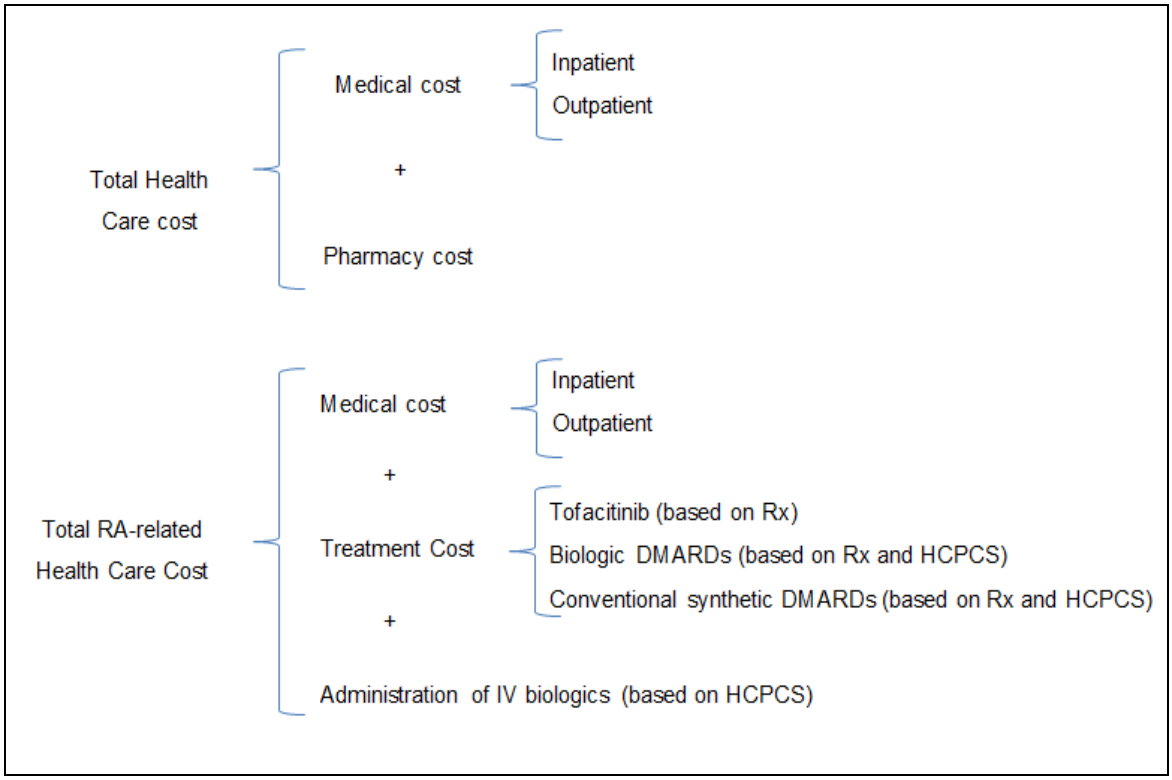
- Costs will be adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between 2016 (the earliest start of the pre-index period) and 2018 (the cost of claims occurring in 2019 will not be adjusted).[6] See Annex 5.

- 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.[7]

- **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, bDMARDs, csDMARDs, and administration of intravenous (IV) bDMARDs (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.

- **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.



NOTES:

- Outpatient includes:
  - ER;
  - Outpatient hospital Office visits;
  - Home health care;
  - Urgent care (see note below);
  - Other medical services.

- Urgent Health Care (UHC) visits are stored differently in the Truven Marketscan database (not in the variable "SVCSCAT", another variable in Truven Marketscan) and so any visit listed above can have UHC at the same time. That is UHC cost is not mutually exclusive from the other visit types for cost.

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. 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* 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

8.10.1. Primary Objective

- To compare RA-related costs among patients treated with tofacitinib (IR, XR and combined groups) to patients treated with each of the bDMARDs (individually, as well as to TNFi and to non-TNFi each combined as groups).

CCI [redacted] 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. CCI [redacted]

8.10.2. Secondary Objectives

- Explore the differences in demographic and clinical characteristics between patients treated with tofacitinib vs. each individual bDMARD.

For this objective descriptive analysis will be conducted. CCI [redacted]

- Compare treatment patterns including dosing, concomitant medication use, adherence, persistence and switching with tofacitinib vs. each individual bDMARD.

For this objective, treatment patterns will be summarized across the cohorts of interest. CCI [redacted]

- Compare all-cause and RA-related health care utilization of patients treated with tofacitinib vs. each individual bDMARD.

For this objective descriptive analysis will be conducted. [redacted]

- Compare all-cause healthcare costs for patients treated with tofacitinib vs. each individual bDMARD.

For this objective descriptive analysis will be conducted [redacted]

- Compare medication effectiveness among patients treated with tofacitinib vs. each individual bDMARD.

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 descriptive analysis will be used, [redacted]

8.10.3. 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.

CCI

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- CCI [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

8.12. 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.

8.13. Limitations of the Research Methods

8.13.1. 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 bDMARD in the baseline can be considered to be continuing users of bDMARD therapy; however, patients with no bDMARD 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 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.

8.14. 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 Truven Marketscan 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.

12. REFERENCES

[redacted]

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13. LIST OF TABLES

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. LIST OF RA TREATMENTS

Drug codes will be refreshed based on latest data. That is, use the dictionaries to obtain the most comprehensive lists of NDC and HCPCS codes.

ANNEX 3. LIST OF CONVENTIONAL SYNTHETIC DMARDS

Drug codes will be refreshed based on latest data. That is, use the dictionaries to obtain the most comprehensive lists. Examples are displayed below.

Generic Names	J-codes	NDC
Hydroxychloroquine	n/a	Please look-up in "redbook."
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	

ANNEX 4. LIST OF OTHER MEDICATIONS

Drug codes will be refreshed based on latest data. That is, use the dictionaries to obtain the most comprehensive lists. Examples are displayed below.

Medication	**HCPCS, if applicable**
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, J7510
prednisone	J1690, J7506, K0125
triamcinolone	J3300, J3301, J3302, J3303
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	

ANNEX 5. CONSUMER PRICE INDEX VALUES

Use the following values of yearly averaged CPI (source: http://data.bls.gov/cgi-bin/surveymost?cu U.S. Medical Care, 1982-84=100 - CUUR0000SAM)

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	AVERAGE
2016	454.175	458.295	458.620	459.994	461.230	462.075	464.164	468.379	469.154	469.230	469.333	469.447	463.675
2017	471.700	474.546	474.561	473.582	473.512	474.360	476.126	476.869	476.485	477.121	477.198	477.802	475.322
2018	481.060	482.897	483.984	484.034	484.853	486.019	485.193	484.172	484.708	485.269	486.886	487.409	484.707
2019	490.204	491.227	492.306	493.331	494.928	495.563	497.687	500.916	501.468	506.100			496.373

Data extracted on: November 17, 2019 (10:56:00 PM)

CPI for All Urban Consumers (CPI-U)

Series Id: CUUR0000SAM
Not Seasonally Adjusted
Series Title: Medical care in U.S. city average, all urban consumers, not seasonally adjusted
Area: U.S. city average
Item: Medical care
Base Period: 1982-84=100

Download: xlsx

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	HALF1	HALF2
2009	369.830	372.405	373.189	374.170	375.026	375.093	375.739	376.537	377.727	378.552	379.575	379.516	373.286	377.941
2010	382.688	385.907	387.142	387.703	387.762	388.199	387.898	388.467	390.616	391.240	391.660	391.946	386.567	390.305
2011	393.858	397.065	397.726	398.813	399.375	399.552	400.305	400.874	401.605	403.430	404.858	405.629	397.732	402.784
2012	408.056	410.466	411.498	412.480	413.655	415.345	416.759	417.123	418.039	418.359	418.653	418.654	411.917	417.931
2013	420.687	423.221	424.154	423.815	422.834	424.264	424.836	426.866	428.026	428.082	427.740	427.089	423.162	427.107
2014	429.621	432.769	433.369	434.054	434.874	435.352	435.924	435.777	436.575	437.027	438.445	439.720	433.340	437.245
2015	440.969	442.783	444.020	446.663	447.213	446.271	446.773	446.536	447.289	450.065	451.371	451.072	444.653	448.851
2016	454.175	458.295	458.620	459.994	461.230	462.075	464.164	468.379	469.154	469.230	469.333	469.447	459.065	468.285
2017	471.700	474.546	474.561	473.582	473.512	474.360	476.126	476.869	476.485	477.121	477.198	477.802	473.710	476.934
2018	481.060	482.897	483.984	484.034	484.853	486.019	485.193	484.172	484.708	485.269	486.886	487.409	483.808	485.606
2019	490.204	491.227	492.306	493.331	494.928	495.563	497.687	500.916	501.468	506.100			492.927	