NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Malignancy and Cardiovascular Risk Assessment Using the Consortium of Rheumatology Researchers of North America Registry (Corrona) as an External Comparator for Tofacitinib-Exposed Patients within the Rheumatoid Arthritis BID Clinical Trial Program: A Comparative Post-Approval Safety Study
Protocol number	A3921204
Protocol version identifier	2.0
Date of last version of protocol	09 November 2017
EU Post Authorisation Study (PAS) register number	To be determined
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Country(-ies) of study	United States of America
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
Apo-B	Apolipoprotein B
BMI	Body Mass Index
BID	Bis in die (Twice a day)
CABG	Coronary artery bypass grafting
CDAI	Clinical Disease Activity Index
CHF	Congestive Heart Failure
Corrona	Consortium of Rheumatology Researchers of North America
CRP	C-Reactive Protein
CV	Cardiovascular
CVD	Cardiovascular Disease
DAS-28	Disease Activity Score 28
DMARD	Disease Modifying Antirheumatic Drug
EBV	Epstein Barr Virus
e-HRD	Electronic Health Record Data
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
GI	Gastrointestinal
HDL-c	High Density Cholesterol
HR	Hazards ratio
IL	Interleukin
INFγ	Interferon-γ
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
JAK	Janus Kinase
LDL-c	Low Density Cholesterol
LOCF	Last observation carried forward
LTE	Long Term Extension
MACE	Major Adverse Cardiovascular Events
mHAQ/HAQ	Modified Health Assessment Questionnaire
MI	Myocardial Infarction
MTX	Methotrexate
NDA	New Drug Application
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal antiinflammatory drug

P2	Phase 2
P3	Phase 3
P2P3LTE	Phase 2, Phase 3, Long Term Extension Population
PASS	Post-Approval Safety Study
PML	Progressive multifocal leukoencephalopathy
RA	Rheumatoid Arthritis
RF+	Risk Factor Positive
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEER	Surveillance and Epidemiology End Results
SIAC	Site Investigator Advisory Committee
SOP	Standard Operating Procedure
Sr	Senior
TAE	Targeted Adverse Event
t-Chol	Total Cholesterol
TIA	Transient Ischemic Attack
TG	Triglycerides
TNF	Tumor Necrosis Factor
TyK2	Tyrosine Kinase 2
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Tofacitinib (Xeljanz®) is an oral Janus kinase inhibitor for treatment of RA in patients with inadequate response to methotrexate (MTX-IR). The clinical development program included approximately 4,800 patients with 7,000 patient-years (pt-yr) of exposure at the time of submission to the United States (US) Food and Drug Administration (FDA) in 2011 (Pfizer, 2014). Due to the design of the Phase 3 trials, limited patient numbers and exposure are available for the comparators in these trials. As such, external data sources (i.e., published and public-domain literature sources) have been used to provide background rates for qualitative comparison to the clinical program safety events. The proposed study seeks to supplement those data by performing a formal comparison of malignancy and cardiovascular event rates from the tofacitinib clinical trial program with event rates from the Consortium of Rheumatology Researchers of North America (Corrona) registry. The primary analysis will be on a cohort of RA patients within Corrona initiating a biologic that overlap the tofacitinib trial population characteristics based on prior disease modifying antirheumatic drug use and patient clinical and demographic characteristics. A propensity score will be used to determine patients in the two cohorts (Corrona biologic initiators [unexposed to tofacitinib] and tofacitinib trial patients) with common support (a similar range of scores). Multivariable adjusted hazard ratios (HRs) will be estimated to compare the risk of malignancy and cardiovascular events in the two populations. A series of secondary Corrona RA cohorts will be compared to the tofacitinib clinical trial population for sensitivity analyses to evaluate the robustness of the estimated effects in the primary analysis. Secondary cohorts include, but are not limited to, direct propensity score matched population, RA initiators restricted to 'tofacitinib trial eligible' biologic initiators, and a comparison to rates in the full RA population. A final report describing the statistical analyses and presenting the estimated effects and conclusions will be delivered by Corrona.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer as a commitment to the US FDA.

4. AMENDMENTS AND UPDATES

- The tofacitinib population for analysis was updated to focus on the totality of data from the RA clinical trial program. The cohort of interest includes data from the Phase 1, Phase 2, Phase 3 and long-term extension (P123LTE) rheumatoid arthritis clinical trial program.
- The data-cut for both the tofacitinib cohort and Corrona patient cohorts has been updated to May 2016 to provide more current data from the tofacitinib clinical trial program. Power estimates have been updated to reflect the associated person-years of tofacitinib exposure.
- Secondary analyses focused on drug dosing have been removed to focus on the totality of data within the clinical trial program. A US-only cohort clinical trial population has been added.
- The endpoints of interest have been refined to focus on 4 key events: all malignancies (excluding NMSC), major adverse cardiovascular events (MACE), non-fatal myocardial infarction (MI) and non-fatal stroke.
- Exposure time definitions in the Corrona cohort have been updated to include censoring at the time of specified serious adverse events that is not the event of interest (in order to parallel a resulting exit for indicated events in the tofacitinib trial).
- A comparative analysis to the full Corrona population will not be made. Rates of events using all follow-up time in Corrona will be estimated for contextualization.
- Safety endpoints of lymphoma, lung and breast cancer have been removed (all malignancies [excluding non-melanoma skin cancer (NMSC)] is the malignancy endpoint).
- Due to the timing of the tofacitinib CV adjudication procedures, CV analyses will be restricted to patients enrolled from February 2009 and onward. This adjustment will improve comparability between the tofacitinib and Corrona databases, methodologically.

5. MILESTONES*

	Milestone	Planned date
1.	Protocol and Statistical Analysis Finalization	November 2017
2.	Database Structure Alignment	February 2018
3.	First draft of population characteristics tables	March 2018
4.	Preliminary Analysis Report	April 2018
5.	Revised Preliminary Report for Pfizer Review	June 2018
6.	Final study report	July 2018

*Each milestone is dependent on the one prior happening according to schedule

Milestone 2. Corrona, with assistance from the Pfizer data services and biostatistical teams, will complete harmonization and finalize the dataset.

Milestone 3. Corrona will provide a draft table (characteristics and comparison of the populations – primary propensity trimmed population) which will provide a working document for the Corrona and Pfizer data and biostatistical teams to decide upon factors for the propensity scoring.

Milestone 4. Corrona will deliver a draft report of the primary analysis.

Milestone 5. After Corrona and Pfizer review the draft preliminary report, comments will be addressed and a second draft of the preliminary report (including initial secondary analyses) will be delivered.

Milestone 6. Corrona will finalize all analyses as outlined in this protocol and deliver a final report.

6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations (Alamanos, 2005). RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities. Compared with the general population, RA patients are at a higher risk for cardiovascular disease (CVD) and malignancies (including lymphoma). These patients are also treated with multiple classes of agents, including nonsteroidal antiinflammatory drugs (NSAIDs), glucocorticoids, and disease modifying antirheumatic drugs (DMARDs) including biologicals, each of which carry significant risks as well as benefits.

Tofacitinib is the first oral JAK inhibitor to show clinical efficacy in the management of RA. Many of the cytokines that are dysregulated in RA signal through JAKs (Walker et al, 2005; McInnes et al, 2007; McInnes et al, 2011). Tofacitinib reduces the production of proinflammatory mediators (Meyer et al, 2010) by inhibiting the signaling of multiple cytokines important in the pathogenesis of RA. Unlike biological therapies, such as TNF inhibitors and anti-IL-6 receptor monoclonal antibodies that markedly inhibit one cytokine pathway over an extended period of time, JAK inhibition by tofacitinib results in a pattern of partial and reversible inhibition of the intracellular effects from several inflammatory cytokines.

As of May 10, 2016, 6300 patients were treated with tofacitinib for RA BID in clinical trials. Due to the design of the Phase 3 (P3) and long-term extension (LTE) studies, there are limited patient numbers and patient-years of exposure for comparators. Further, duration of placebo exposure before mandatory rescue was limited for ethical reasons. Thus, external data sources (i.e., published and public-domain literature sources) were used to provide background rates for qualitative comparison to the clinical program safety data. Multiple data sources were searched to ensure that the full range of published and public domain event rates in the RA patient population were obtained.

The proposed study seeks to supplement those data by performing a formal comparison of malignancy and cardiovascular (CV) safety from the tofacitinib clinical trial program with data from the Corrona registry. With over 40,000 RA patients enrolled to date, the Corrona registry is equipped to evaluate comparative safety utilizing matching and statistical adjustments for potential confounders.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer as a commitment to the US FDA.

6.1. Malignancies

Certain types of cancers may occur in higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer (Khurana, 2008). In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

Due to the immunosuppressive properties of approved RA therapies, researchers have investigated the risk of lymphopoietic and hematopoietic cancers in men and women with RA. Collectively these data suggest an increased risk, most commonly for lymphomas. Persons with RA are 2 to 3-times more likely to develop lymphoma compared with the general population; risk may be related to both therapy and RA severity (Askling, 2005; Ekstrom, 2003; Franklin, 2006; Geborek, 2005; Gridley, 1993; Smitten, 2008; Wolfe, 2007). Some of these lymphomas arise in B cells, in association with latent Epstein Barr Virus (EBV) infection, and some regress with reduction in immunosuppressive therapy. It is not clear whether the risk of lymphoma in RA patients is increased further by methotrexate or TNF inhibitor agents.

At the time of the new drug application (NDA) submission, the incidence rate for all malignancies (excluding NMSC), in RA patients treated with tofacitinib in the Phase 2, 3 and long-term extension (LTE) studies was 0.939 events per 100 PYO, reported in 65 out of a total of 4,791 tofacitinib treated patients. The most common malignancies were lung cancer (16 patients) and breast cancer (11 patients). When compared with the Surveillance Epidemiology and End Result (SEER) database, the standardized incidence ratios (SIRs) for all malignancies (excluding NMSC), lung cancer, breast cancer and lymphoma were consistent with estimates within the RA population in patients treated with nonbiologic and biologic DMARDs (Howlader, 2011; Smitten, 2008).

6.2. Cardiovascular Disease

Patients with RA are at increased risk of cardiovascular disease (CVD); the risk has been reported as being approximately 2 to 3-fold greater than the general population (Kremers, 2008). The body of published evidence for increased risk of serious CV events among RA patients is more extensive than the published information on lipid patterns. The extent to which adverse lipid profiles contribute to increased CV risk in patients with RA is unclear.

Data have shown that traditional risk factors do not appear to confer the same cardiovascular risk in RA patients as the general population (Gonzalez, 2008). Lipids, for example, have been proposed as inverse acute phase reactants known to be affected by inflammatory states and an inverse relationship of lipid levels with RA disease activity has been observed (Bismuth, 2002; Myasoedova, 2010; Choy, 2009). Recently, an apparent paradox regarding lipid measures and the risk of CV disease among persons with RA has been noted (Myasoedova, 2011).

In their study of 651 patients with RA, Myasoedova and colleagues found that inflammatory measures (i.e. ESR) were significantly associated with the risk of CV disease in RA (Myasoedova, 2011). However, the data showed a significant nonlinear association for total cholesterol and CV risk: an increased risk of CV disease was noted for total cholesterol <150 mg/dL while there was no apparent increase in CV risk for total cholesterol (t-Chol) ≥150 mg/dL. A similar association was found for low density lipoprotein cholesterol (LDL-c) with marginally increased risk of CV disease for LDL-c <100 mg/dL and no apparent increase in CV risk for LDL-c ≥100.

Tam (Tam, 2007) and others have demonstrated that t-Chol, high density lipoprotein cholesterol (total, HDL-c), LDL-c, triglycerides (TG) and apoprotein (Apo) B levels all increased significantly in RA patients treated with tumor necrosis factor (TNF) inhibitors. These findings may suggest normalization of lipid levels suppressed by inflammation; however, additional studies are needed before lipid metabolism and its interaction with inflammatory disease is clearly understood.

Administration of tofacitinib in patients with RA is associated with a dose dependent increase in LDL-c, as well as HDL-c and t-Chol. The increase in LDL-c occurs rapidly and plateaus within approximately 3 months of initiation of tofacitinib. The mean percent increase in LDL-c is approximately 14 to 20% at 12 months; HDL-c showed a slightly lower magnitude mean increase (approximately 15 to 18% at 12 months). Increases in triglycerides

also are observed in tofacitinib treated patients, although a slower more gradual mean increase was seen compared to the changes in cholesterol.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to estimate the incidence rates and corresponding hazard rate ratios of malignancy and cardiovascular endpoints comparing patients from the tofacitinib RA BID clinical program to patients initiating a biologic DMARD and never exposed to tofacitinib (unexposed) in the Corrona registry.

7.1. Endpoints

The proposed study will evaluate incidence rates and corresponding hazard rate ratios of the following outcomes among persons exposed to tofacitinib versus comparator. All outcomes described in this section are primary:

1. All malignancies (excluding NMSC);

2. Major adverse cardiovascular events (MACE) (a composite measure comprised of cardiovascular death, death due to acute myocardial infarction [MI], sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, death due to other cardiovascular causes [i.e., peripheral artery disease], non-fatal myocardial infarction [MI], and non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage);

3. Non-fatal MI; and

4. Non-fatal stroke.

8. RESEARCH METHODS

8.1. Study design

To meet the study objective, an external comparison retrospective cohort study will be conducted. Exposed (patients exposed to tofacitinib as part of the RA BID clinical trial program) and unexposed (patients from Corrona prescribed biologic therapies other than tofacitinib and never exposed to tofacitinib) will be compared adjusting for key clinical and demographic characteristics expected to confound the relationship between tofacitinib and malignancies and tofacitinib and CV disease. Other potential confounding variables (i.e. those that may confound the malignancy effect but not CV effect and vice versa) will be

controlled as appropriate in the analysis. Operational definitions of criteria for development of the propensity score are described in the statistical analysis plan (SAP).

8.2. Setting

8.2.1. Tofacitinib Clinical Trial Database

The tofacitinib clinical dataset of the RA BID program used for this analysis will be based on data cutoff as of May 2016. The analysis population will be all patients who received at least 1 dose of tofacitinib in completed Phase 1, Phase 2, Phase 3 and the LTE RA studies (P123LTE), comprised of 6,300 patients exposed to tofacitinib, with a total of approximately 21,886 patient years of drug exposure. Cumulative patient exposure was counted from the first dose of tofacitinib in the Phase 1, Phase 2 and Phase 3 studies to the last dose of tofacitinib plus 28 days, regardless of whether this occurred in the Phases 1-3 or in the LTE studies. Exposure time was summed across the Phases 1-3 and LTE studies. LTE exposures are limited to dosing within the LTE studies. The protocols included for the analysis include: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year data), A3921073, A3921109, A3921129, A3921130, A3921152 and A3921237.

8.2.2. Corrona

The Corrona RA Registry was founded in 2000. Corrona is an independent registry run by a group of experienced academic and clinical rheumatologists throughout the US. Data on Rheumatoid Arthritis, Psoriatic Arthritis, Osteoarthritis, Osteoporosis, and Osteoporosis Risk derived from rheumatologists and patients are entered from the site where the physician saw the patient.

The Corrona registry includes a network of 686 academic and community rheumatologists at 174 sites in 41 states within the US. Corrona is a disease-based registry. RA-related treatments include any DMARD treatments, prednisone use, NSAID use etc. Access to and use of biological DMARDs (bDMARDs) in the US varies depending on patient insurance and study period. In the Corrona database, approximately 35% of the contemporary RA study population is prescribed tumor necrosis factor (TNF) antagonists (based on last visit in 2011 or later) and 15% are prescribed a non-TNF biologic. All patients with a diagnosis of RA treated by participating rheumatologists are eligible to be included in Corrona. Treatment decisions are at the discretion of the physician. At enrollment, patient and current treating rheumatologist-reported past drug use is obtained; current drug utilization is captured by both patient and physician report, and drug discontinuation and new drug start data are gathered by physician report during follow-up. Both patient and physician reported disease activity measures obtained at each visit are captured in Corrona; this includes tender and swollen joint counts (28 joint counts), patient and physician global disease assessment, patient pain assessment and mHAQ scores (full HAQ since 10/2010). Corrona visits for RA patients follow standard of care which is approximately every 4-6 months (Corrona median time between visits for RA patients is 5 months). Median total follow up on patients with at least one follow up visit is 3.3 years.

8.2.2.1. Corrona Governance and Oversight

Corrona, LLC is a Delaware Corporation with Corporate Headquarters in Waltham, Massachusetts. Corrona is in compliance with State of Delaware regulations and maintains a formal Board of Directors and Executive Committee that oversee the operations of the company. The Board of Directors and Executive Committee must report any financial conflicts to the Corrona Ethics Subcommittee of the Board. Science and publication matters are reviewed by the Scientific Advisory Committee (SAC) and site issues are addressed by the Site Investigator Advisory Committee (SIAC).

Corrona, LLC Leadership

Name	Title
Joel Kremer, MD	Founder and Chief Medical Officer
Jeffrey Greenberg, MD, MPH	VP, Chief Scientific Officer
Raymond Hill	Executive Chairman of the Board
Jessica Eisenhaure	VP and General Counsel
DB Kartik	Chief Operating Officer
Bryon Cail	Chief Financial Officer

8.2.3. Study Population

8.2.3.1. Subject Selection

The study population will consist of patients diagnosed with RA.

- Tofacitinib Exposed
    - Patients enrolled within the P123LTE tofacitinib RA BID clinical development program as of May 10 2016 for the malignancy analyses; For the CV analyses patients from studies A3921019, A3921025, A3921035, and A3921039 will be excluded since initiations started prior to CV adjudication (February 2009)
    - With at least one documented exposure to tofacitinib.
- Tofacitinib Unexposed (Corrona primary comparator population)

- Patients diagnosed with RA by their treating rheumatologist, enrolled within the Corrona registry from 1 October 2001 through 10 May 2016;
- With a minimum of 1 follow-up visit;
- New initiators of biologic therapies[1] with initiation captured during follow-up in Corrona registry from 1 January 2006 through 10 May 2016 with no prior history of tofacitinib use including tofacitinib trial participation will be used for malignancy analyses; initiations from 1 February 2009 through 10 May 2016 will be used for CV analyses to match tofacitinib trial timelines for CV adjudication;
- Meeting all inclusion criteria (Section 8.2.4).

Secondary cohorts include, but are not limited to, direct propensity score matched population, and RA initiators restricted to 'tofacitinib trial eligible' biologic initiators.

8.2.3.2. Index Date

For each patient, the index date is defined as the initiation date of the therapy of interest (i.e., tofacitinib or biologic therapy). For each specific event patients will be followed from the index date until occurrence of the event or the patient ends follow-up in the trial or LTE for tofacitinib patients or the patient discontinues biologics, initiates tofacitinib, exits from the registry or the end of study period (May 2016) for unexposed Corrona comparator patients, whichever comes first. Duration consistency will be examined (similar to censoring patterns). If the observation periods are not consistent in duration between the two cohorts (exposed and unexposed), data will be stratified by follow-up. If necessary, the follow-up time for unexposed comparator patients will be truncated so that all unexposed patients do not extend beyond the maximum trial follow-up for tofacitinib exposed patients.

8.2.4. Inclusion criteria

To maximize comparability of the tofacitinib and Corrona patients, Corrona patients must meet the following criteria of tofacitinib studies at the index date:

- Aged 18 years or older at index date;
- Diagnosis of RA (per American College of Rheumatology [ACR] criteria);
- ACR functional class of I, II or III;
- No Serious infections, defined as any infection (viral, bacterial, or fungal) requiring parenteral antimicrobial therapy or hospitalization for treatment, or meeting other criteria that require the infection to be classified as a serious adverse event, in the past year.

[1] Biologic therapies under evaluation include both TNF and non-TNF biologic DMARDs. For the Corrona population, an initiation is the first ever use of a therapy (i.e. first exposure) since a full history of therapies for RA is captured at enrollment in Corrona and updated at each visit.

- No current or past malignancies with the exception of non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ;

- No current uncontrolled clinically significant hepatic events or liver disorder, gastrointestinal (GI/bowel perforation), pulmonary, cardiac, or neurological disease (demyelinating disorder/other neurologic).

- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Additionally, to ensure completeness of Corrona patient data, Corrona patients must also meet the following criteria:

- Initiation and follow-up captured in the Corrona registry during anytime January 1, 2006 – May 10, 2016 for malignancy; and during February 1, 2009 – May 10, 2016 for CV analyses

- At least 1 follow-up visit after biologic initiation during follow-up in the registry.

- Evidence of a personally signed and dated informed consent document indicating that the

Note: for secondary cohorts the condition is at least one follow-up visit after the index date defined for each secondary cohort.

8.2.5. Exclusion criteria

Any Corrona patient that does not meet one or more of the inclusion criteria will be excluded.

8.3. Variables

8.3.1. Covariates

Covariates collected in common between the tofacitinib RA clinical trials and Corrona data will be considered. All covariates listed may be used in the propensity score estimation and for adjustment in the multivariable models. A combination of a priori chosen covariates and covariates selected based on standardized differences between the tofacitinib and comparator population will be used in the propensity score estimation and models.

Demographic characteristics

- Age at index date (and time from study start to compute age)
- Gender
- Race

Disease characteristics at index date

- Duration of RA
- Rheumatoid factor positive[2]
- Tender and Swollen joint counts (28 count)
- C-Reactive Protein (CRP)
- Patient and Physician Global Assessment
- Patient pain assessment
- Clinical Disease Activity Index (CDAI, Joint counts + Patient and Physician Global)
- Disease Activity Score (DAS28, CRP)
- Modified Health Assessment Questionnaire (mHAQ) (based on components of the HAQ)

CV risk factors at index date

- Age
- Gender
- RA disease duration
- RA disease activity
- CRP
- Personal history of CV disease
- Smoking history
- Body Mass Index (BMI)
- Statin Use (time varying if available)
- History of hypertension
- History of diabetes

Malignancy risk factors at index date

- Age
- Gender
- RA disease duration
- RA disease activity
- Smoking history
- History of NMSC or cervical carcinoma

RA treatment (background medications) at index date

- Methotrexate (MTX)
- Non-biologic DMARDs

[2] CORRONA does not mandate any laboratory measures, but only collects the values when the treating physician orders them for clinical care. For this reason, RF+ status is only available for approximately 57% of patients.

  - MTX and/or leflunomide
  - Any non-biologic DMARD excluding MTX and leflunomide
- History of bDMARD use

Concomitant medications

Other treatments associated with the endpoints of interest

- Prednisone (time varying if available)
- Lipid lowering medications (time varying if available)

8.3.2. Endpoints and Exposure variables

Exposure:

Exposure of interest is exposure to tofacitinib.

Unexposed are eligible Corrona patients with no exposure to tofacitinib.

Endpoints:

1. All malignancies (excluding NMSC);
2. Major adverse cardiovascular events (MACE) (a composite measure comprised of cardiovascular death, death due to acute myocardial infarction (MI), sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, death due to other cardiovascular causes (i.e., peripheral artery disease), non-fatal myocardial infarction (MI), and non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage);;
3. Non-fatal MI; and
4. Non-fatal stroke.

Specifications are operationalized within the SAP.

8.4. Data sources

8.4.1. Tofacitinib

The tofacitinib clinical dataset of the RA BID program used for this analysis will be based on data cutoff as of May 10, 2016. The analysis population will be all patients who received at

least 1 dose of tofacitinib in completed Phase 1, Phase 2, Phase 3 and the LTE RA studies (P123LTE), comprised of 6,300 patients exposed to tofacitinib, with a total of approximately 21,886 patient years of drug exposure. The CV analysis will exclude studies A3921019, A3921025, A3921035, and A3921039 (1,188 patients). Cumulative patient exposure was counted from the first dose of tofacitinib in the Phase 1, Phase 2 and Phase 3 studies to the last dose of tofacitinib plus 28 days, regardless of whether this occurred in the Phases 1-3 or in the LTE studies. Exposure time was summed across the Phases 1-3 and LTE studies. LTE exposures are limited to dosing within the LTE studies. The protocols included for the analysis include: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2 year data), A3921073, A3921109, A3921129, A3921130, A3921152 and A3921237.

8.4.2. Corrona

Patients are enrolled in the Corrona Data Collection Program during regularly-scheduled office visits. Upon enrollment, physicians complete a set of Enrollment Questionnaires, including a 28 joint count on RA patients. Patients also complete a Corrona Data Collection Program Enrollment Questionnaire along with Health Assessment and the European Quality of Life-5 Dimensions (EQ-5D) Questionnaires. Both patient and physician reported disease activity measures obtained at each visit are captured in Corrona; this includes tender and swollen joint counts (28 joint counts), patient and physician global disease assessment, patient pain assessment and health assessment questionnaire (HAQ) scores.

Physicians and patients complete Corrona Data Collection Program Questionnaires approximately every six months. During the course of a regularly-scheduled office visit, the physician performs assessments as mandated on the Corrona Data Collection Program Physician Questionnaires with recording of pertinent data. Results from certain laboratory tests are included, but not mandated. Patients are asked to complete Data Collection Program Questionnaires designed to capture information ranging from their general demographics and experience with prescription drug use to an overall global assessment of their disease. During their regularly-scheduled physician office visits, it is anticipated that patients will spend approximately five to ten minutes completing the questionnaires. Neither the questionnaires completed by physicians nor the questionnaires completed by patients contain personal identification information (i.e., names, addresses, telephone numbers, email addresses, or social security numbers). Follow-up questionnaires are also completed at the time of a new therapy start or therapy switch. The next regularly scheduled visit is calculated from the previous visit. Data are collected on patients for as long as they consent to remain in the study.

Corrona also has an established system (Solomon, 2010; Fisher, 2012; Curtis, 2009) to identify and capture endpoint data. The system uses TAE forms that correspond to the outcomes identified in Table 1. For events that are confirmed by the rheumatologist, source documentation appropriate to the type of event (e.g. pathology reports when the TAE is a cancer) is requested by Corrona. Confirmed events that have been completely reported to

include anonymized source documents (i.e., medical records) are adjudicated by specialists blinded to therapy (e.g. cardiologists adjudicate cardiovascular (CV) events) to confirm site-reported details, including: that the event occurred, the date of the event, and the specific type of event (See Figure 3). For purposes of this study, all MACE and Malignancy events that are complete with supporting documentation are required to undergo double-blind review with adjudication.

Table 1. Outcomes within the Corrona Registry Identified ("Flagged") on Physician Follow-Up Forms for Targeted Adverse Event Form Completion

Flagged Event	Targeted Adverse Event Report Type
Hypertension requiring hospitalization Cardiac revascularization procedure (CABG, stent, angioplasty) Ventricular arrhythmia Cardiac arrest Myocardial Infarction Acute Coronary Syndrome Unstable angina CHF requiring hospitalization Stroke Transient ischemic attack Other cardiovascular event ***(specify)*** Deep vein thrombosis Peripheral arterial thromboembolic event Urgent peripheral arterial revascularization Peripheral ischemia or gangrene (necrosis) Pulmonary embolism	Cardiovascular
Hemorrhage requiring hospitalization	Spontaneous Serious Bleeding
Lymphoma Lung cancer Breast cancer Skin cancer (melanoma) Skin cancer (basal/squamous cell) Other cancer ***(specify)***	Cancer, Malignancy
Infection requiring hospitalization or IV antibiotic	Serious Infection
GI perforation	GI Perforation
Hepatic event requiring biopsy or hospitalization	Hepatic
PML Other neurological requiring hospitalization/ other demyelinating disease	Neurologic
Biologic Infusion/Injection reaction (severe reaction/anaphylaxis)	Anaphylaxis or Severe Reaction
Other serious medical diagnosis or event ***(specify)***	Generic Serious Event*
* Events not meeting case definition for a more specific TAE type, resulting in any of the following: hospitalization, prolonged hospitalization, death, significant disability or incapacity, congenital anomaly/birth defect, are immediately life threatening, or otherwise medically important in the opinion of the investigator.) CABG=Coronary artery bypass grafting, CHF=congestive heart failure, GI=gastrointestinal, IV=intravenous, PML= Progressive multifocal leukoencephalopathy, TAE=targeted adverse event	

8.5. Study size

Power was estimated for the malignancy and CV outcomes under two estimated population follow-up counts as detailed within the associated statistical analysis plan.

The 'case' population was the tofacitinib population assumed to be 6,300 patients with approximately 21,886 patient years of follow-up.

Power was examined for comparison with four potential Corrona populations:

- Largest patient year estimate: Patient initiating a biologic in Corrona and (considering follow-up while still on that biologic) is approximately 21,000 patient years (we assumed 21,000 patients years in both groups);
- Smallest patient year estimate: We assumed restriction to a maximum of 5 years follow up and a matched population – assuming a 70% match – so 12,600 patient years assumed for both populations (70% of the 18,000 patient years with 5 year restriction);
- If we assume a 5-year follow up limit, the Corrona patient year estimate is approximately 18,000 patient years;
- If we assume a 70% match using all follow-up patient years (70% of 21,000 years, the estimate is 14,700.

These scenarios will give a range of estimated power under varying conditions.

Adverse event rates were estimated from the Corrona population provided in prior reports:

Malignancies (excluding non-melanoma skin cancer (NMSC)): 1.0/100 pt years (yrs) (0.01)

Major adverse cardiovascular events (MACE): 0.6/100 pt yrs (0.006)
MI: 0.24/100 pt yrs (0.0024)

The graphs summarize estimated power and illustrate power versus hazard rate ratio (HR). Power estimates derived using PASS 14 (Hintze, J. (2015). PASS 14. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

In the highest number of patient years scenario described above there is sufficient power (>80%) for an HR just over 1.3 for malignancy comparisons; in the lowest number of patient years scenario from above there is sufficient power for HR > 1.4. For MACE the range is 1.4-1.5 and for MI the range is 1.7-2.0 across the patient year scenarios described previously.

Figure 1. Power versus hazard rate ratio estimates assuming 21,000 patient years within the biologic initiator cohort

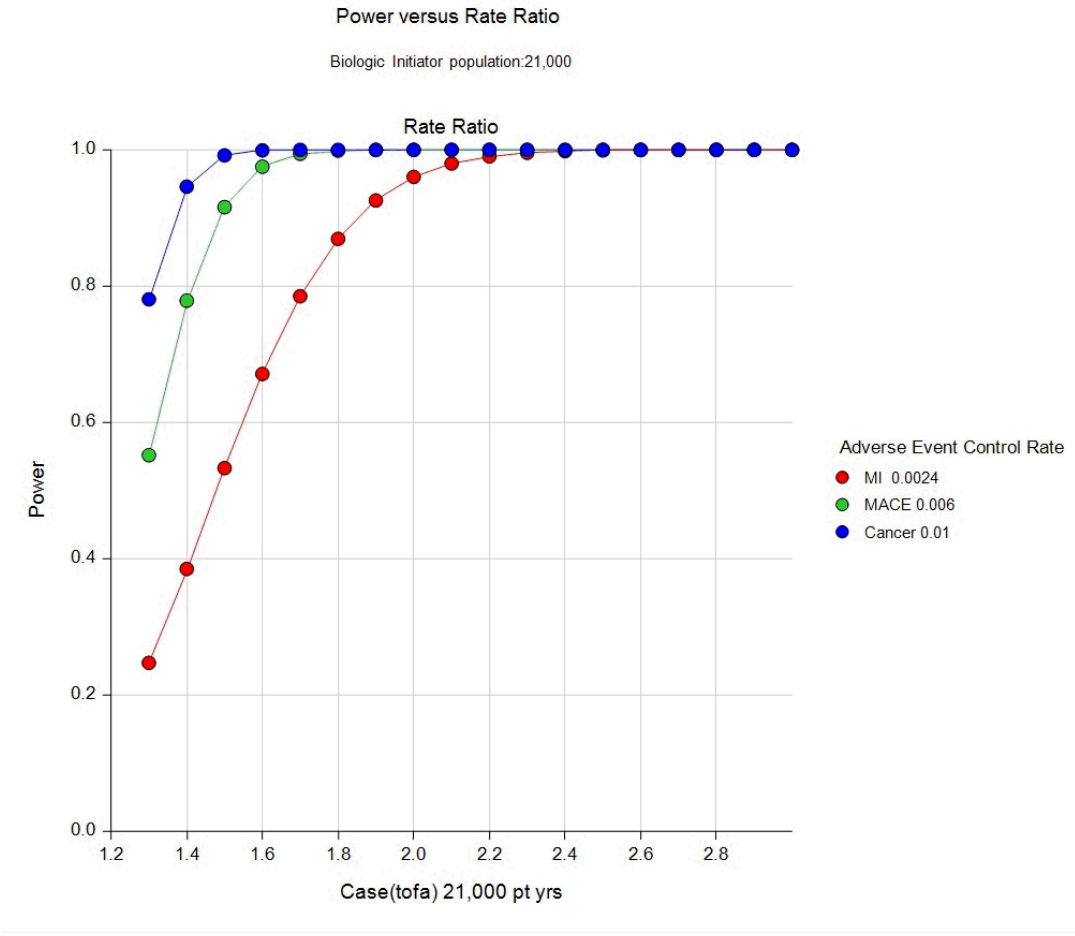
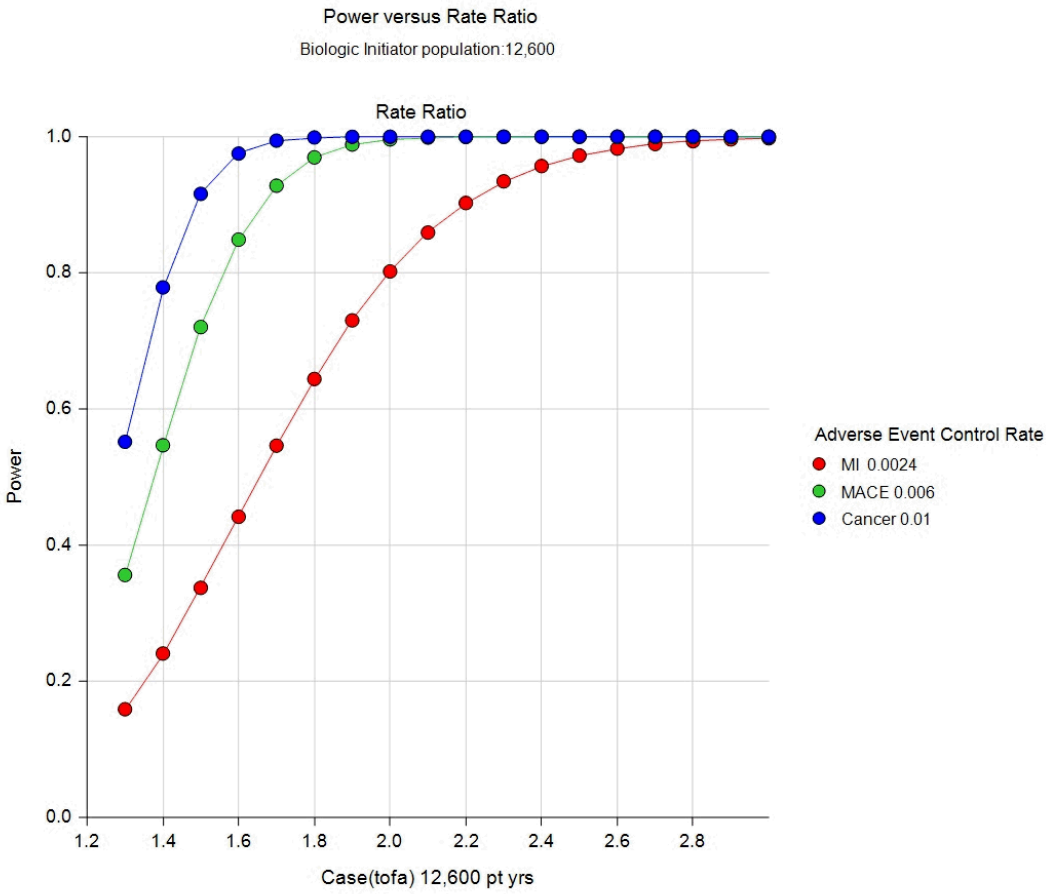


Figure 2. Power versus hazard rate ratio estimates assuming 12,600 patient years within the biologic initiator cohort



8.6. Data management

All statistical analyses will be performed using STATA 15 (StataCorp, LP, College Station, TX). All analyses will be carried out under the direction of Dr. George Reed, Statistician Emeritus for Corrona, and Professor of Medicine at University of Massachusetts Medical School. Detailed methodology for summary and statistical analyses of data collected in this study are documented in an SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.6.1. Methods to correct inconsistencies or errors

The Corrona registry has standard operating procedures (SOPs) in place to monitor, perform edit and logic checks, and make corrections to the data, as necessary. Quality control checks are built into the electronic data capture (EDC) system and provide immediate feedback

regarding inadvertent omissions and out of range or noncompliant values. Changes made at any time are recorded in an audit trail that includes the date, time, and electronic ID of the person making the change. Corrona will address and reconcile missing or discrepant data by requesting data clarifications from participating providers at regular intervals or as needed upon detection. Each provider is expected to designate a point of contact to address these requests. The site should respond to any queries within 30 days of the request date.

8.6.2. Methods to address missing data

Patients missing key characteristics such as age or gender will be excluded from analyses. Imputation will be used for data points where feasible. For example, CDAI with 3 of the 4 measures can be imputed by estimating the 4th measure based on the other 3 (regression estimates). Missing data for time varying covariates used in the model (i.e., medication use over time), will be imputed using last observation carried forward (LOCF) for all populations. Details regarding imputation are located within the protocol SAP.

8.7. Data analysis

The proposed study will evaluate incidence rates and corresponding hazard rate ratios of the following outcomes among persons exposed to tofacitinib and comparator. All outcomes described in this section are primary.

1. All malignancies (excluding NMSC);

2. Major adverse cardiovascular events (MACE) (a composite measure comprised of cardiovascular death, death due to acute myocardial infarction (MI), sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, death due to other cardiovascular causes (i.e., peripheral artery disease), non-fatal myocardial infarction (MI), and non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage);;

3. Non-fatal MI; and

4. Non-fatal stroke.

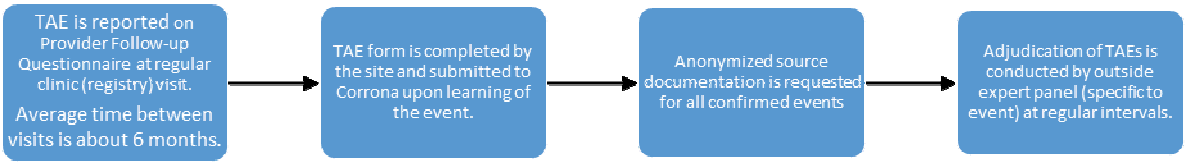
Figure 3 below illustrates the collection of targeted adverse events (TAEs) in the Corrona registry. All outcomes of interest are TAEs within Corrona. TAEs are provider reported information.

- Primary analysis of events will be operationalized in the following manner:
    - Use all events reported on MD forms except for events that are ‘not confirmed’ by the TAE form or reported as ‘not confirmed’ by the adjudication process.
    - Include events reported by the rheumatologist as confirmed on a TAE form (not reported on an MD form); excluding those ‘not confirmed’ by adjudication.

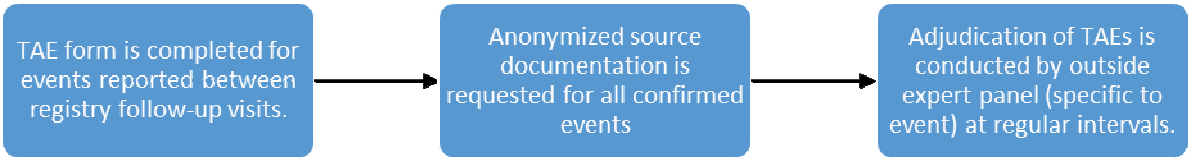
- Adjudicated events will be used to report the positive predictive value of confirmed TAE's.

Figure 3. Corrona Safety Endpoint Reporting Procedure Targeted Adverse Events (TAEs)

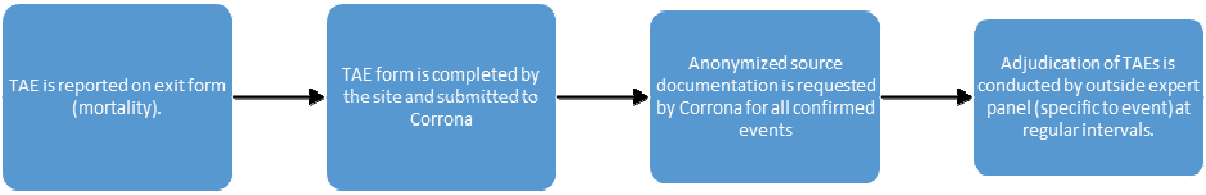
TAEs may be reported during a registry follow-up visit.



TAEs may be reported between registry follow-up visits, when the site learns of an event.



Less commonly, a TAE may be reported on an exit form when the reason for exit is death.



Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.7.1. Full analysis set

Tofacitinib

The tofacitinib-exposed population for this analysis includes the totality of exposure data (i.e., all doses combined) from the P123LTE dataset. This dataset includes all patients from the time of the first dose of tofacitinib to the final dose (plus 28 days) in the May 2016 data-cut. This represents the largest treatment experience in the tofacitinib RA program. This dataset will be used for all malignancy-related analyses. However, given that the CV adjudication procedures for the tofacitinib clinical trial program were implemented in February 2009, analyses concerning CV outcomes will restrict to tofacitinib initiators from February 2009 onward[3]. Doing so will permit better alignment, methodologically, with the Corrona database.

Corrona

The Corrona RA population enters the registry with recruitment and consent. Duration of RA, current and prior DMARD use, and disease activity will vary at enrollment. Corrona captures biologic and non-biologic DMARD initiations during enrollment and follow-up. Disease activity, comorbidity history and biologic and non-biologic DMARD history are known at the time of initiation. This provides the ability to examine multiple cohorts for comparison of malignancy and CV rates with the tofacitinib population rates. Varied cohorts will be analyzed but the choice of the primary comparative cohort is a trade-off between precision (power) and bias. With specific matching on all characteristics, eligibility criteria, past and background treatments, and similar exposure time there is reduction in bias but with more stringent matching there is reduction in precision (power) as the sample becomes smaller. This balance permits some (possible) small bias in exchange for enhanced precision. Secondary analyses may reduce the size of the comparative population, but will provide more precise matching, which will be used to verify the robustness of the results. The cohorts are defined as follows:

8.7.2. Safety analysis set

Primary cohort- Biologic initiator propensity trimmed population: the primary analysis cohort will be a cohort of patients initiating a biologic within Corrona with no prior tofacitinib exposure that overlaps with the tofacitinib population characteristics based on prior DMARD and TNF use, and patient characteristics. Overlap will be defined as the "common support" for the propensity score distribution, i.e. the range of propensity score values that both populations have in common. A propensity score for use of tofacitinib will be derived and only patients with common support (i.e., overlapping propensity distributions between tofacitinib population and Corrona populations; distributions will be trimmed where there is no overlap) will be used in a multivariable analysis (SAP, Section 9). The cohort from which this population will be derived will be active RA patients initiating a bDMARD with at least one follow-up and no prior tofacitinib exposure. As of May 2016 there was a total of approximately 21,000 person years of follow up after initiations. The propensity model will include DMARD history, eligibility criteria and other relevant factors as determined by a descriptive comparison of the Corrona and tofacitinib populations (SAP, Section 9.1).

[3] Patients from the following studies will be excluded from the CV analyses: A3921019, A3921025, A3921035, and A3921039.

Secondary cohorts- A series of secondary cohorts for sensitivity analyses will be defined as follows:

Propensity Score Matched

Initiators will be matched to tofacitinib patients using the propensity score with a "greedy matching procedure" (Austin, 2011).

Matching will be carried out between Corrona initiator groups and tofacitinib patients. Demographic and clinical characteristics at the time of initiation (index date) will be used to develop the propensity score (for initiation of tofacitinib vs Corrona initiations).

Characteristics with a standardized difference >0.1 will be considered, and a stepwise model will be used to develop the propensity score model. Matching will use the logit score and a caliper of 0.2 standard deviations (SD) of the logit score will be considered first (as suggested by Austin 2011). Varying the caliper will determine the tradeoff in matched samples and balance in characteristics.

Trial Eligible Initiators

Initiators in Corrona will be included based on eligibility criteria of tofacitinib trials, including disease activity criteria.

The multivariable analysis in a propensity trimmed population and the propensity score matching analysis carried out in the primary population will be replicated in the trial eligible population.

Tofacitinib trial patients restricted to US sites

US tofacitinib trial patients will be compared with the primary Corrona population.

The multivariable analysis in a propensity trimmed population and the propensity score matching analysis carried out in the primary population will be replicated using the US site tofacitinib trial patients.

8.7.3. Other analysis set

For the purpose of contextualization of rates, unadjusted event rates and 95% confidence intervals will be estimated for study safety endpoints in the full Corrona population. All RA patients in Corrona with at least one follow-up will be used in estimating time to first event for all malignancies excluding NMSC, MACE, non-fatal MI and non-fatal stroke.

8.8. Quality control

Corrona has examined the level of validity of three major areas of safety events in the registry, including malignancies and CV events. For this purpose, Corrona has requested and successfully obtained hospital and outpatient medical records on the majority of patients.

Medical records served as the gold standard for validation, with at least two physician adjudicators for each safety event (Solomon, 2010; Fisher, 2012).

8.9. Limitations of the research methods

This project seeks to compare the tofacitinib clinical trial population with patients enrolled in the Corrona registry. Given the differences in the source populations, matching will be employed for comparative purposes. However, patient matching in the cohorts is possible only using covariates measurable in both databases. Unmeasured factors in one or both of the cohorts may not be balanced, resulting in residual confounding.

Further, given the structure of the two databases, event reporting methods differ. While monitoring and validation efforts are used in both the clinical trial and observational settings, the direct comparability of case ascertainment cannot be quantified. However, malignancy and cardiovascular events explored in this study are well defined and adjudicated by relevant specialists.

The time frame covered by the two databases does not overlap completely. For matching purposes, data from the full Corrona population is required. The first patient was enrolled within the Corrona registry in October 2001; the first patient was enrolled in the tofacitinib clinical trial program in January 2005. Due to changes in treatment modalities over time and their influence on disease characteristics, sensitivity analyses will be completed focusing on patient disease characteristics and past therapies to explore their effects on the event measures.

8.10. 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.

Patient consent not applicable; analyses planned utilize data from secondary data sources that do not include patient identifiers.

9.2. Patient withdrawal

Not applicable; analyses planned utilize data from secondary data sources that do not include patient identifiers.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

This database does not contain any patient identification information (e.g., name), except for a unique number assigned for the purpose of linking files. All protocols are approved by the New England IRB (protocol number 02-021 with most recent approval on July 27, 2017). At Academic sites with Academic IRBs, the approval of the Academic IRBs is also obtained.

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 the FDA Guidance for Industry, Good Pharmacovigilance and Pharmacoepidemiologic Assessment. Per Pfizer's subscription to the Corrona database, analyses will be conducted by authorized third parties and in accordance with Corrona scientific review policies. The database does not contain any patient identification information (e.g., name), except for a unique number assigned for the purpose of linking files Per Pfizer's subscription to the Corrona database, analyses will be conducted by authorized third parties and in accordance with Corrona scientific review policies. The database does not contain any patient identification information (e.g., name), except for a unique number assigned for the purpose of linking files.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., 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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study results will be disseminated to the Xeljanz clinical program teams via the Pfizer Risk Management Committee and to the US Food and Drug Administration. Data may be used in regulatory communications external to the US for contextualization purposes. Manuscripts based on specific endpoints of interest may be developed for external publication purposes.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., 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 NI study protocol that the investigator becomes aware of.

12. REFERENCES

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Date	Title
1	9 Nov 2017	Malignancy and Cardiovascular Risk Assessment Using the Consortium of Rheumatology Researchers of North America Registry (Corrona) as an External Comparator for Tofacitinib-Exposed Patients within the Rheumatoid Arthritis BID Clinical Trial Program: A Comparative Safety Study Statistical Analysis Plan

Document Approval Record

Document Name:	A3921204_PROTOCOL_Final_9Nov2017
Document Title:	A3921204 Matched Analysis

Signed By:	Date(GMT)	Signing Capacity
Reynolds, Robert F	14-Nov-2017 00:58:32	Final Approval