NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study 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
Version identifier of the final study report	1.0
Date	09 March 2021
EU Post Authorization Study (PAS) register number	EUPAS23344
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
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.
Author	Oladayo Jagun MD, MPH Pfizer, Inc. 235 East 42nd Street, 219/02/43 New York, New York 10017 USA

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Annex 1. List of Stand-Alone Documents

Appendix 1. SIGNATURE

Not applicable

Appendix 2. PROTOCOL

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Appendix 3.1. List of Investigators by Country

Not applicable

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Not applicable

Appendix 4. STATISTICAL ANALYSIS PLAN

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT))

Not applicable

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable

Appendix 8. ADDITIONAL DOCUMENTS

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, Final Appendices

Annex 2. Additional information

Sensitivity Analyses Tables

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
bDMARDs	biologic disease modifying antirheumatic drugs
BMI	body mass index
BID	bis in die (twice a day)
CABG	coronary artery bypass grafting
CDAI	clinical disease activity index
CI	confidence interval
CHF	congestive heart failure
Corrona	Consortium of Rheumatology Researchers of North America
CRP	c-reactive protein
csDMARDs	conventional synthetic disease modifying antirheumatic drugs
CV	cardiovascular
CVD	cardiovascular disease
DAS-28	disease activity score 28
DMARDs	disease modifying antirheumatic drugs
e-HRD	electronic health record data
ESI	emerging safety issue
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
GI	gastrointestinal
HR	hazards ratio
IL	interleukin
IEC	Institutional Ethics Committee
IPCW	inverse probability of censoring weights
IQR	Interquartile range
IRB	Institutional Review Board
IV	intravenous
JAK	janus kinase
LOCF	last observation carried forward
LTE	long term extension
MACE	major adverse cardiovascular events
mg	milligram
mHAQ/HAQ	Modified Health Assessment Questionnaire
MI	myocardial infarction
MTX	methotrexate
N	number
N/A	Not applicable

Abbreviation	Definition
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal antiinflammatory drugs
P2	phase 2
P3	phase 3
P2P3LTE	phase 2, phase 3, long term extension population
PASS	post-approval safety study
PML	progressive multifocal leukoencephalopathy
PY	person years
RA	rheumatoid arthritis
RF+	risk factor positive
RWD	real world data
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TAE	targeted adverse event
TIA	transient ischemic attack
TG	triglycerides
TNF	tumor necrosis factor
TyK2	tyrosine kinase 2
US	United States
y	year
yrs	years

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Oladayo Jagun MD, MPH	NI Study Lead Senior Director, Epidemiology Strategist, Inflammation and Immunology	Pfizer, Inc.
George W. Reed, PhD	Statistician Emeritus	Corrona, LLC
Amy Schrader, MS	Senior Biostatistician	Corrona, LLC
Kim Dandreo Gegear, MSc, PMP	Clinical Research Manager	Corrona, LLC
Ann Madsen, PhD	Senior Director, Epidemiology Strategist, Methodology and Vaccines	Pfizer, Inc.

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	15 February 2019	20 Nov 2019	Additional time needed to determine the contents and procedures for transferring the data files from Pfizer to Corrona
End of data collection	15 March 2019	16 May 2020	Additional time needed to determine the contents and procedures for transferring the data files from Pfizer to Corrona
Registration in the EU PAS register	29 March 2018	29 March 2018	
Final report of study results	31 July 2020	09 March 2021	Time of completion of the final study report reflects additional times for start and end of data collection.

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).[1] 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).[8,4,5] Tofacitinib reduces the production of proinflammatory mediators (Meyer et al, 2010)[6] 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 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 (ie, 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.

This study sought 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 was designated as a Post-Authorization Safety Study (PASS) and was a commitment to the US FDA.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study was 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 study evaluated incidence rates and corresponding hazard rate ratios of the following outcomes among persons exposed to tofacitinib versus comparator medications. All outcomes described in this section were 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 peripheral artery disease, non-fatal myocardial infarction (MI), 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. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment Number	Date	Substantial or administrative amendment	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	09 Nov 2017	Substantial	Setting and Analyses	Study population expansion	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.
1	09 Nov 2017	Substantial	Setting and Analyses	Data-cut update from tofacitinib RA BID P123LTE clinical 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.
1	09 Nov 2017	Substantial	Setting and Analyses	Update to secondary analyses	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.
1	09 Nov 2017	Substantial	Endpoints	Endpoint updates	The endpoints of interest have been refined to focus on 4 key endpoints: all malignancies (excluding NMSC), major adverse cardiovascular events, non-fatal myocardial infarction and non-fatal stroke.
1	09 Nov 2017	Substantial	Analyses	Update to exposure time definitions	Exposure time definitions in the Corrona cohort have been updated to include censoring at the time of any serious adverse event that is not the event of interest (in order to parallel a resulting exit in the tofacitinib trial).
1	09 Nov 2017	Substantial	Analyses	Specification of comparator population	A comparative analysis to the full Corrona population was not done. Rates of events using all follow-up time in Corrona were estimated for contextualization.
1	09 Nov 2017	Substantial	Analyses	Update to CV analytic plan	Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward. This adjustment will

					improve the comparability between the tofacitinib and Corrona databases, methodologically.
2	24 Nov 2019	Administrative	Analyses	Addition of sensitivity analyses	Preliminary analyses of the merged data from Corrona (persons initiating biologic DMARDS, bDMARDs) and Pfizer (tofacitinib initiations from the clinical trial program) showed differences in follow-up time between the two study cohorts in the trimmed populations (see Protocol Section 8.7.2, safety analysis set, primary cohort). Median follow-up for Corrona bDMARD initiators was 1.6 years vs 3.5 years for tofacitinib initiators. Due to this unexpected finding, the study team will conduct sensitivity analyses to evaluate the potential effects of the differences in follow-up between the study cohorts.
3	18 May 2020	Administrative	Analyses		Preliminary results suggest no association of treatment with cardiovascular events with estimates from different models (including sensitivity analyses). The data with respect to malignancy evaluations was less clear across the various models. The tofacitinib initiations from the clinical trials include both the currently approved dose of 5 mg BID and a higher dose of 10 mg BID. In order to examine the impact of dose on risk, additional analyses were completed to examine this association. Analyses restricted to the tofacitinib "trial eligible initiators", were not completed.

9. RESEARCH METHODS

9.1. Study Design

To meet the study objective, an external comparison retrospective cohort study was conducted. Exposed (patients exposed to tofacitinib as part of the RA BID clinical trial program) and unexposed (patients from Corrona Registry, described in Section 9.2.1, prescribed biologic therapies other than tofacitinib and never exposed to tofacitinib) were 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 (ie, those that may confound the malignancy effect but not CV effect and vice versa) were controlled as appropriate in the analysis (See SAP,

Appendix 4). Operational definitions of criteria for development of the propensity score are described in the statistical analysis plan (Appendix 4).

9.2. Setting

The tofacitinib clinical dataset of the RA BID program (conducted across multiple countries including the US) used for this analysis was based on a data cutoff of May 10, 2016. The analysis population was 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 excluded studies A3921019, A3921025, A3921035, and A3921039 (1,188 patients) given that these studies predated the adjudication of CV events. 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 or in the LTE studies. LTE exposures were limited to dosing within the LTE studies. The protocols included for the analysis were: 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.

9.2.1. 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 more than 686 participating academic and community rheumatologists at 174 sites in more than 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 disease modifying antirheumatic drugs (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 provider-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 are obtained at each visit and are captured in Corrona; this includes tender and swollen joint counts (28 joint counts), patient and physician global disease assessment, patient pain assessment and Modified Health Assessment Questionnaire (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 3.5 years.

9.3. Subjects

9.3.1. Subject Selection

The study population consisted 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 were 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 at time of initiation including tofacitinib trial participation were used for malignancy analyses; initiations from 1 February 2009 through 10 May 2016 were used for CV analyses to match tofacitinib trial timelines for CV adjudication;
  - Meeting all inclusion criteria (Section 9.3.2).

Secondary cohorts included a direct propensity score matched population, tofacitinib exposed population among only US sites, and tofacitinib exposed population divided out by dose (5 mg and 10 mg sub-cohorts).

9.3.1. Index Date

For each patient, the index date was defined as the initiation date of the therapy of interest (ie, tofacitinib or biologic therapy). For each specific event, patients were followed from the

[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 (ie, first exposure) since a full history of therapies for RA is captured at enrollment in Corrona and updated at each visit.

index date until occurrence of the event, the patient end of follow-up in the trial or LTE for tofacitinib patients, or if the patient discontinued the biologic, started tofacitinib, exited from the registry or the end of study period (May 2016) for unexposed Corrona comparator patients, whichever came first. Duration consistency was examined (similar to censoring patterns). When the observation periods were not consistent in duration between the two cohorts (exposed and unexposed), data were stratified by follow-up. If necessary, the follow-up time for unexposed comparator patients were truncated so that it did not extend beyond the maximum trial follow-up for tofacitinib exposed patients.

9.3.2. Inclusion Criteria

To maximize comparability of the tofacitinib and Corrona patients, Corrona patients had to 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;
- 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); and
- 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 between January 1, 2006 – May 10, 2016 for malignancy, and during February 1, 2009 – May 10, 2016 for CV analyses; and
- At least 1 follow-up visit after biologic initiation during follow-up in the registry.

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

9.3.3. Exclusion Criteria

Any Corrona patient that did not meet one or more of the inclusion criteria was excluded.

9.4. Variables

9.4.1. Covariates

Covariates collected in common between the tofacitinib RA clinical trials and Corrona data were considered. All covariates listed were considered as potential covariates 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 were 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).

[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.

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 history at index date

- History of bDMARD use.

Concomitant medications

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

- Conventional synthetic DMARDs (csDMARDs):
  - MTX and/or leflunomide;
  - Any non-biologic DMARD excluding MTX and leflunomide.

9.4.2. Endpoints and Exposure Variables

Exposure:

1. Exposure of interest is exposure to tofacitinib.
2. Unexposed are eligible Corrona patients with no exposure to tofacitinib.

Endpoints:

3. All malignancies (excluding NMSC).
4. 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 [ie, 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).
5. Non-fatal MI; and
6. Non-fatal stroke.

Specifications are operationalized within the statistical analysis plan (Appendix 4).

9.5. Data Sources and Measurement

9.5.1. Tofacitinib

The tofacitinib clinical dataset of the RA BID program used for this analysis was based on a May 2016 data cutoff. The analysis population was all patients who received at least 1 dose of tofacitinib in completed Phase 1, Phase 2, Phase 3 studies and the LTE RA studies (one of which was ongoing as of the May 2016 data cutoff)(P123LTE), comprised of 6300 patients exposed to tofacitinib, with a total of approximately 21,886 patient years of drug exposure. The CV analysis excluded 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 included: 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.

9.5.2. 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 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 (ie, names, addresses, telephone numbers, email addresses, or social security numbers). Each enrolled patient has a patient identification (ID) number that is used by sites to report information on patient and physician forms to ensure linkage across visits. The ID numbers are held by an honest broker for other linkage and is not part of the analytic data set. 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)[7,3,2] to identify and capture endpoint data. The system uses TAE forms that correspond to the outcomes identified in Table 2. For events that are confirmed by the rheumatologist, source documentation appropriate to the type of event (eg, pathology reports when the TAE is a cancer) is requested by Corrona. Confirmed events that have been completely reported to include anonymized source documents (ie, medical records) are adjudicated by specialists blinded to therapy (eg, 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 Table 2). 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 2. 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.

9.6. Bias

Comparison of clinical trial data to observational data may be biased due to differences in patient eligibility, patient follow-up and differences in data collection. This study assessed each of the potential differences and made efforts to assess and address those differences.

For patient eligibility, key eligibility factors for the clinical trial, like history of cancer or recent infections, were applied to the observational population and the two populations were compared at time of drug initiation across clinical and disease measures available in both data sources. Differences were quantitated and two methods of adjusting for these differences were carried out:

- Multivariate adjustment for differences in a population with common support based on a propensity score (propensity for treatment with tofacitinib vs biologics) (see Appendix 8, Section C); and

- Matched populations based on the propensity score.

For differences in patient follow-up (patients in an observational 'real-world' setting are more likely to switch medications and retention may be lower compared with subjects in clinical trial programs) two sets of sensitivity analyses were carried out to adjust for potential outcome differences due to differences in follow-up time.

For potential differences in data collection, in particular ascertainment of outcome events, the potential impact was estimated in a tipping point analysis that estimated the extent of ascertainment differences (or informative censoring) required to change the clinical significance of the results.

9.7. Study Size

A summary of the counts of events and follow up time is outlined in Table 3 below.

Table 3. Counts of Events and Person-Time in Cohorts Considered for Analysis

	Malignancy Events	Person-Years	MACE Events	Person-Years
All Tofacitinib	168	22,352.55	66	17,322.62
All Corrona bDMARD	113	21,259.83	66	14,388.33
US Tofacitinib	60	4,535.11	20	3,611.18
Tofacitinib 5mg	64	7,614.81	15	3,494.86
Tofacitinib 10mg	104	14,737.74	51	13,827.76
US tofacitinib 5mg	16	1,150.88	4	442.61
US tofacitinib 10 mg	44	3,384.23	16	3,168.57

MACE=major adverse cardiovascular event; mg=milligram; US=United States.
Note: the small number of events and person time for US tofacitinib divided out by dose. These analyses were done for 'completeness' of the dose analyses but any interpretation should be with number of events in mind.

Power was estimated for the malignancy and CV outcomes under two estimated population follow -up counts as detailed within the associated statistical analysis plan (Appendix 4).

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 patient 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 gave a range of estimated power under varying conditions.

Adverse event rates were estimated from the Corrona population:

- 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, 2015).[9]

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

Figure 1. Power Versus Hazard Rate Ratio Estimates Assuming 21,000 Patients Within the Biologic Initiator Cohort

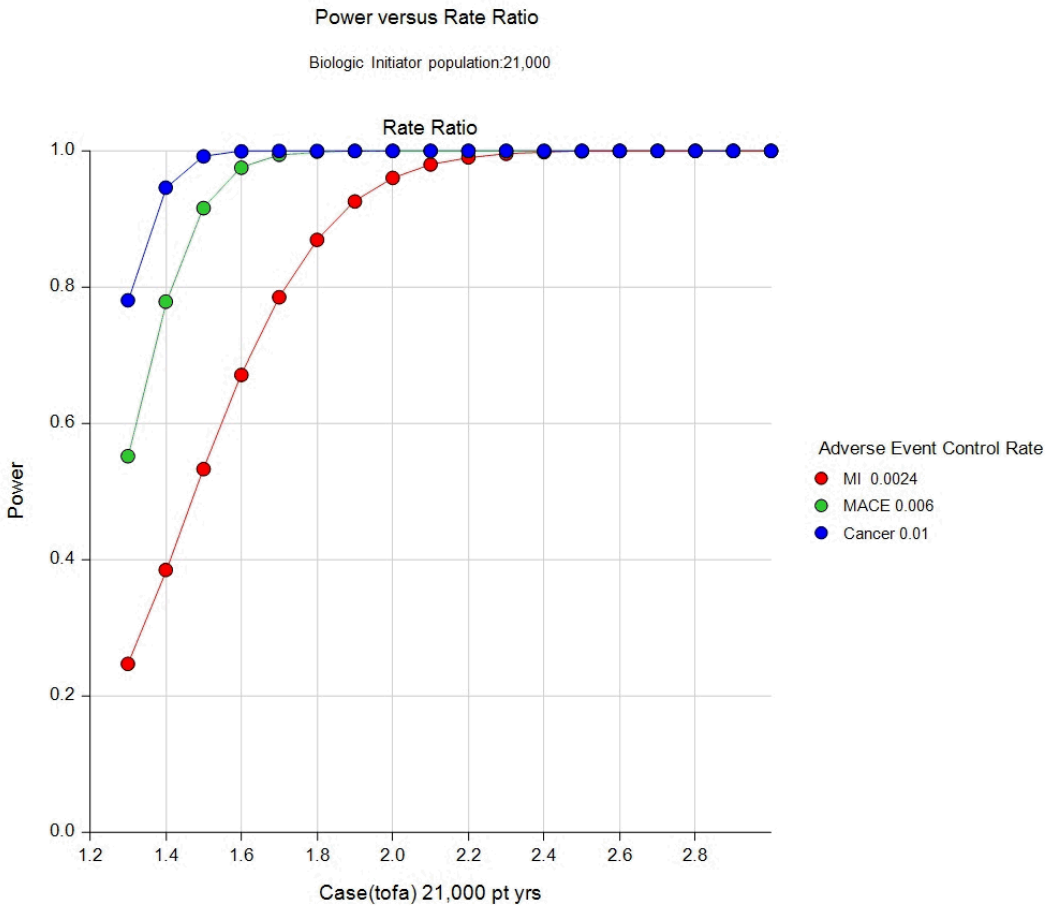
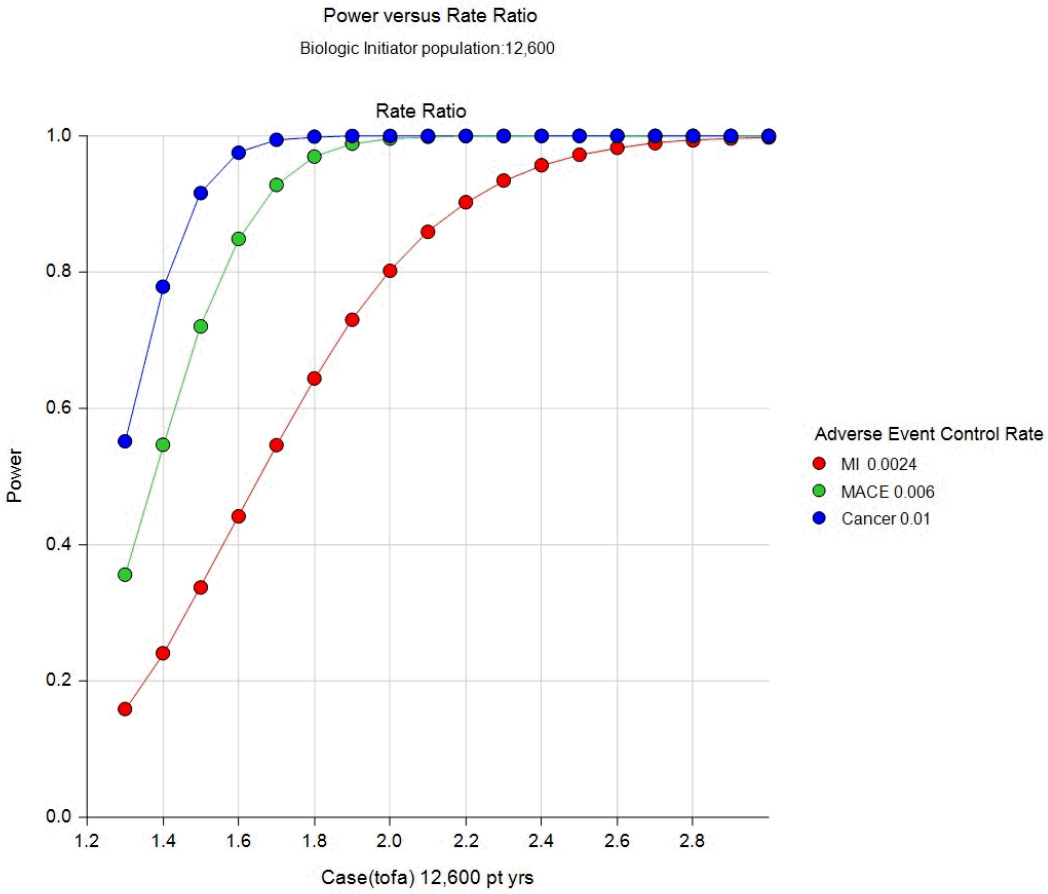


Figure 2. Power Versus Hazard Rate Ratio Estimates Assuming 12,600 Patients Within the Biologic Initiator Cohort



9.8. Data Transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the SAP (Appendix 4).

9.8.1. Data Management and Transformations

Standard Clinical indices and groupings were used (eg, CDAI or BMI categories of normal, overweight, obese) and were consistent for clinical and observational data.

Other calculations, groupings and choice of cut points for common support are detailed in the supporting document under Appendix 8:

Propensity Trimmed: All Tofacitinib & Corrona bDMARD Initiators.

Appendix C: Common support for primary cohort propensity models.

Appendix D: Functional form of continuous covariates.

Propensity Trimmed: US Tofacitinib & Corrona bDMARD Initiators.

Appendix W: Common support for secondary cohort propensity models.

Propensity Trimmed: All Tofacitinib 10mg BID & Corrona bDMARD Initiators.

Appendix C2: Common support for secondary cohort propensity models.

Propensity Trimmed: All Tofacitinib 5mg BID & Corrona bDMARD Initiators.

Appendix I2: Common support for secondary cohort propensity models.

Propensity Trimmed: US Tofacitinib 10mg BID & Corrona bDMARD Initiators.

Appendix O2: Common support for secondary cohort propensity models.

Propensity Trimmed: US Tofacitinib 5mg BID & Corrona bDMARD Initiators.

Appendix U2: Common support for secondary cohort propensity models.

9.9. Statistical Methods

9.9.1. Main Summary Measures

Characteristics at baseline: Baseline characteristics at the index date – the time of drug initiation - were summarized as means and standard deviation for continuous measures and proportions (count and percent) for categorical measures. Standardized differences were estimated for comparison of characteristics between initiator groups (see SAP, Appendix 4).

9.9.2. Main Statistical Methods

Incidence Rates: Unadjusted incidence rates and 95% confidence intervals were estimated for each cohort within each analysis. The rate of events was estimated from time to first event based on the index date. The total number of years of patient follow-up was computed by total time up to an event or up to last follow-up (includes discontinuation of biologic initiated, starts tofacitinib, exits from the registry or end of study period). The event rate was calculated as the number of events divided by the total person-years of follow-up. Rates are expressed as event/100 person-years of follow-up. Additional details are in the SAP (Appendix 4).

Before comparing incidence rates between treatments, tofacitinib incidence rates were verified with previous Pfizer calculations and the number of events among bDMARD initiators were compared with previous Corrona PASS reports covering the same time frame.

Prior to modeling of results, the distributions of follow-up time were examined between the Corrona registry biologic starts and the Pfizer clinical trial tofacitinib starts. A notable difference in the distribution of follow-up time was determined. Histograms showing the distribution of follow-up time within each analysis are detailed in the SAP (Appendix 4). So that there was complete overlap of follow-up time, observations were censored at 9 years for the malignancy analysis and at 6 years for the cardiovascular analysis. Due to the imbalance in follow-up time distributions sensitivity analyses were proposed to determine robustness of results (described below within statistical methods and in the SAP, Appendix 4).

Primary Cohort Analysis Methods: Using a logistic regression model with an outcome of bDMARD initiation (yes/no), a propensity score was estimated using the following covariates:

Covariates used in Malignancy propensity model		Covariates used in Cardiovascular propensity model	
• **Age.** • **Gender.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any Bdmard.**	• Smoking History. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • BMI. • History of Hypertension. • Current use of statins.	• **Age.** • **Gender.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any bDMARD.** • **BMI.** • **Current use of statins.**	• Smoking History. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • **History of Hypertension.** • **History of Diabetes.** • **History of CVD.**

Covariates listed above in bold were covariates that study investigators (Pfizer and Corrona) determined to include a priori (ie, forced into the model regardless of balance). All of the bolded covariates listed had a |standardized difference| >0.1 except for gender, history of CVD and history of Diabetes. Non-bolded covariates were included due to imbalance (|standardized difference|>0.1. Baseline characteristics tables with standardized differences can be found in Appendix 8, Section B for the primary cohort. Race was not included due to comparing an international group of patients to US only patients in the Corrona registry.

CRP and DAS28-CRP were not included since Corrona protocol does not require labs beyond normal clinical visit requests. Due to overlap/correlation among other similar covariates (prior use of any csDMARD and prior use of any bDMARD), current use of any csDMARD excluding MTX/or Leflunomide, prior use of MTX, TNF inhibitors and non-TNF inhibitors were excluded from the models.

The distribution of log odds was examined in both populations (tofacitinib and Corrona) and each population was trimmed for non-overlapping values (using patients on common support). Patients in one group with log odds higher or lower than scores in the other group were "trimmed" (ie, excluded from the analyses). Only patients with scores overlapping both distributions were included. Further trimming was recommended by collaborating investigators (Pfizer and Corrona) due to gaps among the tails and extreme points. Histograms showing the distribution of each study cohort and the common support cutoff can be found in Appendix 8. Cutoffs were agreed upon by study investigators prior to any additional analyses.

Using this trimmed population, multivariable Cox regression models were used to estimate risk of malignancy and CV events in exposed vs unexposed (estimated Hazard Ratios – HRs and 95% confidence intervals). Development of each model included the following:

- Testing and graphically examining the proportional hazard (PH) assumption for tofacitinib versus Corrona bDMARD in an unadjusted model.

- Unadjusted HRs (tofacitinib versus Corrona bDMARD population) were calculated primarily for comparison with adjusted HRs to understand the role of confounding and examine outliers that may cause large shifts in the estimated HRs.

- Adjusted models include the same factors used in the propensity model score estimation. Adjusted models for malignancy included categorical variables for age and CDAI. Due to the smaller number of cardiovascular events, adjusted models for cardiovascular endpoints included continuous variables for age and CDAI after investigating the linearity of both age and CDAI. Where applicable, categories were created for continuous covariates. The functional form of the association of outcomes with these continuous covariates can be found in Appendix 8.

The proportional hazard assumption for tofacitinib versus Corrona was examined for each outcome measure. Supporting figures and tests for each study cohort and outcome can be found in Appendix 8.

Secondary Cohort Analysis Methods: Using the propensity score developed for the primary analysis (SAP, Appendix 4), biologic DMARD initiators were matched to tofacitinib initiators using 1:1 matching based on the propensity score (log odds) with a caliper of 0.1.

Within the propensity trimmed malignancy study cohort, 2,618 tofacitinib were matched with 2,618 bDMARD initiators (total 5,236 patients). Within the propensity trimmed cardiovascular study cohort, 2,068 tofacitinib were matched with 2,068 bDMARD initiators (total 4,136 patients).

Using this matched population, Cox regression models were used to estimate risk of malignancy and CV events in exposed vs unexposed (estimated Hazard Ratios – HRs and 95% confidence intervals). Development of each model included the following:

- Testing and graphically examining the proportional hazard (PH) assumption for tofacitinib versus Corrona bDMARD in an unadjusted model.

- Covariance adjusted models adjust for matching using robust variance estimation for clusters (in this case matched pairs).

The proportional hazard assumption for tofacitinib versus Corrona bDMARD was examined for each outcome measure. Supporting figures and tests for each study cohort and outcome can be found in the Appendix 8, Section N.

9.9.3. Missing Values

In the Corrona and tofacitinib populations, missing data for drug treatment covariates (ie, time varying covariates for RA treatment and concomitant) were imputed using last observation carried forward (LOCF) for all populations. The selected Corrona population had complete baseline data. The sample excluded was compared with the analytic population on available parameters to examine differences between the populations.

9.9.4. Sensitivity Analyses

Preliminary analyses of the merged data from the Corrona (bDMARD initiations) and Pfizer (tofacitinib initiations from the clinical trial program) showed differences in follow-up time between the two study cohorts in the trimmed populations. To adjust for the potential of informative censoring, three sensitivity analyses were proposed in addition to the primary and secondary analyses previously described (SAP, Appendix 4):

1. Imputation of incidence rates over censored time: Patient characteristics were used to model rates of events and multiple imputation used to estimate hazard ratios with imputed rates for censored time (out to 5 years);

2. Inverse probability of censoring weighting: Patient characteristics were used to model censoring (out to 5 years) and patients re-weighted using probability of censoring. Weighted models estimated hazard ratios; and

3. Tipping point calculation: Calculating how large of an effect informative censoring would need to be to impact results.

Sensitivity analyses for both methods 1 and 2 were carried out separately for the primary events of malignancy (excluding non-melanoma skin cancers), MACE, non-fatal MI and non-fatal stroke. In both methods 1 and 2, after imputation of censored time or using inverse probability of censoring weights, the multivariate models described in the primary analysis were carried out. In both cases, the estimated Hazard Ratios (HRs) and 95% confidence intervals were generated as in the primary analysis.

Details of the models for censoring, distribution of the stabilized censoring weights, and Cox models using the weights as well as models for incidence rates and models using imputed data can be found in Appendix 8. Specifically, sensitivity model details for the propensity trimmed cohort can be found in Sections G, H, I, J and K, respectively. Sensitivity model details for the propensity matched cohort can be found in Sections P, Q, R, S and T, respectively.

Tipping point analysis methods: Follow-up time was considerably shorter and censored time was higher among bDMARD initiators than tofacitinib initiators. If some of the censoring was informative, then it may have had an impact on the estimated difference in rates of reported outcomes. This tipping point analysis presents varying proportions of informative censoring within the bDMARD initiators to determine how large or small an effect would be needed to change the clinical interpretation of the primary analysis results. Details of the assumptions and calculations for this tipping point analysis can be found in Appendix 8, Section L.

Time-varying covariates: Since covariates may change over time during follow-up, multivariate models described in the primary analysis were estimated to include two time-varying covariates suggested by Pfizer investigators: current prednisone use and current use of statins. Adjusted models included the same factors used in the primary analysis except that these two measures vary over time as patients start and stop use of these medications. Details of these models for the propensity trimmed cohort can be found in Appendix 8, Section M and for the propensity matched cohort in Appendix 8, Section U.

Tofacitinib trial patients restricted to US sites: Using a logistic regression model with an outcome of bDMARD initiation (yes/no), a propensity score was estimated using the following covariates:

Covariates used in Malignancy propensity model		Covariates used in Cardiovascular propensity model	
• **Age.** • **Gender.** • **Race.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any Bdmard.** • History of Diabetes.	• Smoking History. • Alcohol use. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • BMI. • History of Hypertension. • History of CVD.	• **Age.** • **Gender.** • **Race.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any bDMARD.** • **Current use of statins.**	• Smoking History. • Alcohol use. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • **History of Hypertension.** • **History of Diabetes.** • **History of CVD.** • **BMI.**

Covariates listed above in **bold** were covariates that study investigators (Pfizer and Corrona) determined to include a priori (ie, forced into the model regardless of balance). All of the covariates listed had a |standardized difference| >0.1 except for gender and current use of statins. Non-bolded covariates were included due to imbalance if |standardized difference| >0.1. Baseline characteristics tables with standardized differences can be found in Appendix 8, Section V. Race was included in this analysis comparing only US Tofacitinib trial patients to the Corrona registry consisting of only US patients. As in the primary analysis, a few covariates were not included since Corrona protocol does not require labs beyond normal clinical visit requests or were due to overlap/correlation among other similar covariates.

Using the methods as described in the primary cohort, propensity score trimming and propensity score matching were replicated in this US only cohort. Histograms showing the distribution of each study cohort and the common support cutoff can be found in the Appendix 8, Section W. Using the propensity score developed for the propensity trimmed cohort, biologic DMARD initiators were matched to US tofacitinib initiators using 1:1 matching based on the propensity score (log odds) with a caliper of 0.1.

Within the propensity trimmed malignancy study cohort, 1,010 US tofacitinib were matched with 1,010 bDMARD initiators (total 2,020 patients). Within the propensity trimmed cardiovascular study cohort, 846 US tofacitinib were matched with 846 bDMARD initiators (total 1,692 patients).

The proportional hazard assumption for US tofacitinib versus Corrona was examined for each outcome measure. Supporting figures and tests for both the propensity trimmed and matched cohorts can be found in the Appendix 8, Sections X and Z, respectively.

Tofacitinib Dose Analysis Methods: Tofacitinib clinical trial data had a dose indicator dividing the tofacitinib initiators into a high dose (10mg BID) and low dose (5mg BID) group. The dosing groups were divided based on average total daily dose with average daily dose <15mg in the low dose group and ≥15mg in the high dose group.

Using a logistic regression model with an outcome of bDMARD initiation (yes/no), a propensity score was estimated separately for each tofacitinib dosing group (5mg BID and 10mg BID) using the following covariates:

Covariates used in Malignancy propensity model		Covariates used in Cardiovascular propensity model	
• **Age.** • **Gender.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any bDMARD.** • Current use of statins.	• Smoking History. • Alcohol use*. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • BMI. • History of Hypertension.	• **Age.** • **Gender.** • **Duration of RA Disease.** • **Current use of Prednisone.** • **Prior use of any csDMARD.** • **Prior use of any bDMARD.** • **BMI.** • **History of CVD.**	• Smoking History. • Alcohol use*. • Patient reported Pain. • CDAI. • mHAQ. • Current use of MTX and/or Leflunomide. • **History of Hypertension.** • **History of Diabetes.** • **Current use of statins.**

*Included for only 5mg BID.

Covariates listed above in **bold** were covariates that study investigators determined to include a priori (ie, forced into the model regardless of balance). All of the bolded covariates listed had a |standardized difference| >0.1 except for gender, history of CVD and diabetes for both the 5mg BID and 10mg BID cohorts and history of hypertension in the 5mg BID cardiovascular cohort. Non-bolded covariates were included due to imbalance with |standardized difference| >0.1. Baseline characteristics tables with standardized differences can be found in Appendix 8, Sections B2 for 10mg BID and H2 for 5mg BID cohorts. As in the primary analysis, a few covariates were not included since Corrona protocol does not require labs beyond normal clinical visit requests or were due to overlap/correlation among other similar covariates.

Using the methods as described in the primary cohort, propensity score trimming and propensity score matching were replicated in these dosing cohorts. Histograms showing the distribution of each study cohort and the common support cutoff can be found in the Appendix 8, Sections C2 for 10mg BID and I2 for 5mg BID cohorts. Using the propensity score developed for the propensity trimmed cohort, biologic DMARD initiators were matched to 10mg BID and 5mg BID tofacitinib initiators separately using 1:1 matching based on the propensity score (log odds) with a caliper of 0.1.

Within the propensity trimmed malignancy study cohorts, 2,034 10mg BID tofacitinib were matched with 2,034 bDMARD initiators (total 4,068 patients) and 1,213 5mg BID tofacitinib were matched with 1,213 bDMARD initiators (total 2,426 patients). Within the propensity trimmed cardiovascular study cohorts, 1,745 10mg BID tofacitinib were matched with 1,745 bDMARD initiators (total 3,490 patients) and 750 5mg BID tofacitinib were matched with 750 bDMARD initiators (total 1,500 patients).

The proportional hazard assumption for both 10mg BID and 5mg BID tofacitinib versus Corrona were examined separately for each outcome measure. Supporting figures and tests for both the propensity trimmed and matched cohorts can be found in the Appendix 8, Sections D2 and F2 for 10mg BID and J2 and L2 for 5mg BID cohorts, respectively.

US Tofacitinib Dose Analysis Methods: For completeness the US tofacitinib cohort was divided by dose though sample size and number of events were much lower once divided out this way. Using a logistic regression model with an outcome of bDMARD initiation (yes/no), a propensity score was estimated separately for each US tofacitinib dosing group (US 5mg BID and US 10mg BID) using the following covariates:

Covariates used in Malignancy propensity model		Covariates used in Cardiovascular propensity model	
• **Age.**[2]	• Smoking History.	• **Age.**[2]	• Smoking History.
• **Gender.**[1,2]	• Alcohol use.	• **Gender.**[1,2]	• Alcohol use.
• **Race.**	• Patient reported Pain.	• **Race.**	• Patient reported Pain.
• **Duration of RA Disease.**[2]	• CDAI.	• **Duration of RA Disease.**[2]	• CDAI.
• **Current use of Prednisone.**	• mHAQ.	• **Current use of Prednisone.**	• mHAQ.
• **Prior use of any csDMARD.**	• Current use of MTX and/or Leflunomide.	• **Prior use of any csDMARD.**	• Current use of MTX and/or Leflunomide.
• **Prior use of any bDMARD.**	• History of Hypertension.	• **Prior use of any bDMARD.**	• **History of Hypertension.**
• BMI.	• History of CVD.	• **BMI**[2.]	• **History of Diabetes.**[1]
• History of Diabetes.		• **History of CVD.**	• **Current use of statins.**[1,2]

[1]Standardized difference <0.1 for US 10mg BID cohort; [2]Standardized difference <0.1 for US 5mg BID cohort.

Covariates listed above in **bold** were covariates that study investigators determined to include a priori (ie, forced into the model regardless of balance). All of the bold covariates listed had a |standardized difference| >0.1 except for those indicated in the table above (see footnote). Non-bolded covariates were included due to imbalance with |standardized difference| >0.1. Baseline characteristics tables with standardized differences can be found in Appendix 8, Sections N2 for US 10mg BID and T2 for US 5mg BID cohorts. As in the primary analysis, a few covariates were not included since Corrona protocol does not require labs beyond normal clinical visit requests or were due to overlap/correlation among other similar covariates.

Using the methods as described in the primary cohort, propensity score trimming and propensity score matching were replicated in these dosing cohorts. Histograms showing the distribution of each study cohort and the common support cutoff can be found in the Appendix 8, Sections O2 for US 10mg BID and U2 for US 5mg BID cohorts. Using the propensity score developed for the propensity trimmed cohort, biologic DMARD initiators were matched to US 10mg BID and US 5mg BID tofacitinib initiators separately using 1:1 matching based on the propensity score (log odds) with a caliper of no larger than 0.1.

Within the propensity trimmed malignancy study cohorts, 737 US 10mg BID tofacitinib were matched with 737 bDMARD initiators (total 1,474 patients) and 329 US 5mg BID tofacitinib were matched with 329 bDMARD initiators (total 658 patients). Within the propensity trimmed cardiovascular study cohorts, 697 US 10mg BID tofacitinib were matched with 697 bDMARD initiators (total 1,394 patients) and 177 US 5mg BID tofacitinib were matched with 177 bDMARD initiators (total 354 patients).

The proportional hazard assumption for both US 10mg BID and US 5mg BID tofacitinib versus Corrona were examined separately for each outcome measure. Supporting figures and tests for both the propensity trimmed and matched cohorts can be found in the Appendix 8, Sections P2 and R2 for US 10mg BID and V2 and X2 for US 5mg BID cohorts, respectively.

9.9.5. Amendments to the Statistical Analysis Plan

None.

9.10. 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).[7,3]

9.11. Protection of Human Subjects

Subject information and consent

Not applicable.

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

IEC/IRB review is not required for this secondary data study.

Ethical conduct of the study

The study was 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 were conducted by authorized third parties and in accordance with Corrona

scientific review policies. The database did not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

10. RESULTS

10.1. Participants

For the malignancy analysis, the primary comparator cohort consists of 6,300 tofacitinib exposed patients and 13,091 tofacitinib unexposed (Corrona bDMARD) patients. The number of patients for the CV analysis are lower due to exclusion of a select number of studies as previously stated in the report (Table 4).

A secondary cohort consisted of 1,508 tofacitinib US exposed patients, which was comprised of 443 tofacitinib 5 mg exposed patients and 1,065 tofacitinib 10 mg exposed patients. Another secondary cohort consisted of the 6,300 tofacitinib exposed patients sub-grouped by dose and was comprised of 2,306 tofacitinib 5 mg exposed patients and 3,994 tofacitinib 10 mg exposed patients. Event rates were estimated in all 38,439 patients in the Corrona RA registry for context. Patients included in the "All Corrona" cohort were age 18 or older at time of registry enrollment and had at least one follow-up visit after enrollment. Baseline characteristics for these patients were at time of enrollment.

Table 4. Number of Patients Within Each Study Cohort by Analysis (malignancy or cardiovascular)

Study Cohort	Malignancy	Cardiovascular
All Tofacitinib	6,300	5,112
Tofacitinib 5mg	2,306	1,394
Tofacitinib 10mg	3,994	3,718
Tofacitinib US Sites	1,508	1,259
US tofacitinib 5mg	443	266
US tofacitinib 10mg	1,065	993
Corrona: All bDMARD Initiators	13,091	10,156
All Corrona	38,439	38,439

Abbreviation: mg=milligram.

Primary cohort: The primary cohort consisted of the tofacitinib exposed patients and the Corrona bDMARD initiators. The cohort was limited to initiations on common support defined as a propensity trimmed cohort (SAP (Appendix 4) or Appendix 8, Section C4).

Secondary cohorts: All secondary cohorts used the same timeframes as the primary cohort for malignancy and CV analyses. The series of secondary cohorts were defined as follows:

- Propensity Score Matched: Biologic DMARD initiators were matched to tofacitinib patients using the propensity score with a "greedy matching procedure."

- Tofacitinib trial patients restricted to US sites: US tofacitinib trial patients were compared with the primary Corrona bDMARD initiators using both the propensity trimmed and propensity matched patients.

- Tofacitinib Dose: Tofacitinib trial patients on 5mg BID and on 10 mg BID were compared with the primary Corrona bDMARD initiators separately using both the propensity trimmed and propensity matched patients. Analyses were replicated in each dosing group (5mg and 10mg) among US tofacitinib sites. Note: Dose analysis was proposed and SAP and protocol amended after examining the primary cohort analyses.

10.2. Descriptive Data

Table 5 shows the baseline characteristics among the primary and secondary study cohorts for the malignancy study timeframe. Overall, patients initiating tofacitinib were younger, had shorter disease duration, and fewer previous RA therapies than the bDMARD initiators. Tofacitinib initiators had higher disease activity with higher mean tender and swollen joints, CDAI, DAS28, CRP and mHAQ as well as higher mean scores for physician global assessment, patient reported pain and patient global assessment. Concomitant Prednisone use is higher among the tofacitinib initiators, but concomitant lipid lowering medications and csDMARD use are lower than the Corrona bDMARD patients. Prior exposure to any csDMARD including MTX is lower among the tofacitinib exposed patients. Table 6 shows the baseline characteristics among the same study cohorts, but for the cardiovascular study timeframe. Similar differences between exposure groups were observed.

Table 5. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Overall Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry Study Populations for the Malignancy Study Timeframe

	All Tofacitinib N= 6,300	Tofacitinib US Sites N= 1,508	Corrona: All bDMARD Initiators N=13,091	All Corrona N=38,439
Age[a] in years, N	6,300	1,508	13,029	38,154
Mean (SD)	52.3 (11.9)	54.4 (11.2)	56.7 (12.8)	58.2 (13.5)
Median (IQR)	53.0 (45.0, 61.0)	55.0 (47.5, 62.0)	57.0 (49.0, 66.0)	59.0 (50.0, 68.0)
Age <65, n(%)	5374 (85.3)	1250 (82.9)	9369 (71.9)	25339 (66.4)
Age ≥65, n(%)	926 (14.7)	258 (17.1)	3660 (28.1)	12815 (33.6)
Gender	6,300	1,508	13,047	38,220
Female, n(%)	5199 (82.5)	1172 (77.7)	10416 (79.8)	29215 (76.4)
Race	6,300	1,508	13,091	38,439
White, n(%)	3993 (63.4)	1247 (82.7)	11555 (88.3)	33778 (87.9)
Duration of RA, N	6,300	1,508	12,954	37,990
Mean (SD)	8.0 (8.1)	9.5 (9.2)	10.6 (9.6)	8.9 (9.7)
Median (IQR)	5.3 (1.9, 11.7)	6.7 (2.3, 14.0)	8.0 (3.0, 15.0)	5.0 (1.0, 13.0)
Rheumatoid Factor Positive1, N	6,026	1,349	7,717	20,549
Yes, n(%)	4402 (73.1)	922 (68.3)	5425 (70.3)	13995 (68.1)
Tender Joint Count, N	6,007	1,325	11,145	38,082
Mean (SD)	13.5 (7.4)	14.6 (7.6)	7.0 (7.1)	4.4 (6.1)

Table 5. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Overall Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry Study Populations for the Malignancy Study Timeframe

	All Tofacitinib N= 6,300	Tofacitinib US Sites N= 1,508	Corrona: All bDMARD Initiators N=13,091	All Corrona N=38,439
Median (IQR)	13.0 (8.0, 19.0)	14.0 (9.0, 21.0)	5.0 (1.0, 10.0)	2.0 (0.0, 6.0)
Swollen Joint Count, N	6,007	1,325	11,145	38,099
Mean (SD)	10.2 (5.8)	11.2 (6.1)	5.7 (5.7)	4.1 (5.4)
Median (IQR)	9.0 (6.0, 14.0)	10.0 (7.0, 15.0)	4.0 (1.0, 8.0)	2.0 (0.0, 6.0)
Tender and Swollen Joint Count, N	6,007	1,325	11,145	38,060
Mean (SD)	23.6 (12.1)	25.8 (12.3)	12.7 (11.1)	8.5 (10.1)
Median (IQR)	22.0 (15.0, 32.0)	25.0 (17.0, 35.0)	10.0 (4.0, 19.0)	5.0 (1.0, 12.0)
C-Reactive Protein (CRP), N	6,046	1,333	4,514	14,549
Mean (SD)	18.8 (24.2)	17.3 (22.3)	14.1 (31.6)	11.7 (27.8)
Median (IQR)	9.4 (4.0, 23.9)	9.1 (4.1, 21.4)	5.0 (2.0, 14.0)	5.0 (2.0, 11.0)
Patient Global Assessment (0-100), N	5,991	1,320	11,013	37,035
Mean (SD)	57.1 (24.5)	56.2 (24.9)	45.4 (26.6)	32.3 (26.9)
Median (IQR)	58.0 (41.0, 76.0)	58.0 (39.0, 75.0)	50.0 (24.0, 68.0)	25.0 (8.0, 50.0)
Physician Global Assessment (0-100), N	5,984	1,320	11,150	38,106
Mean (SD)	56.8 (20.9)	58.0 (21.8)	34.5 (22.3)	25.0 (21.9)
Median (IQR)	59.0 (44.0, 72.0)	61.0 (44.0, 74.0)	30.0 (16.0, 50.0)	20.0 (7.0, 39.0)
Patient Pain (0-100), N	5,995	1,320	11,018	37,107
Mean (SD)	56.6 (24.8)	56.1 (24.8)	48.1 (27.8)	34.9 (28.0)
Median (IQR)	59.0 (40.0, 75.0)	59.0 (37.0, 75.0)	50.0 (25.0, 70.0)	30.0 (10.0, 56.0)
CDAI, N	5,891	1,310	10,979	36,649
Mean (SD)	34.7 (14.3)	37.1 (14.8)	20.7 (13.7)	14.3 (13.1)
Median (IQR)	33.9 (25.1, 44.2)	36.6 (26.9, 47.6)	18.7 (10.2, 28.6)	10.5 (4.0, 20.8)
DAS28-CRP, N	6,093	1,382	4,476	14,307
Mean (SD)	5.2 (1.1)	5.3 (1.1)	4.0 (1.4)	3.3 (1.4)
Median (IQR)	5.2 (4.5, 6.0)	5.4 (4.7, 6.1)	4.0 (3.0, 4.9)	3.1 (2.1, 4.3)
mHAQ, N	6,101	1,427	10,925	37,387
Mean (SD)	0.9 (0.6)	0.8 (0.5)	0.5 (0.5)	0.4 (0.5)
Median (IQR)	0.9 (0.4, 1.3)	0.9 (0.4, 1.1)	0.5 (0.1, 0.9)	0.3 (0.0, 0.6)
Smoking Status, N	6,086	1,456	12,995	38,040
Never, n(%)	3,899 (64.1)	661 (45.4)	6,590 (50.7)	22,099 (58.1)
Former, n(%)	1,092 (17.9)	463 (31.8)	3,946 (30.4)	10,209 (26.8)
Current, n(%)	1,095 (18.0)	332 (22.8)	2,459 (18.9)	5,732 (15.1)
Alcohol Use, N	6,089	1,456	12,732	32,544
Yes, n(%)	1267 (20.8)	482 (33.1)	2918 (22.9)	7234 (22.2)
Body Mass Index (BMI)a, N	6,298	1,506	13,076	37,850
Mean (SD)	27.0 (6.4)	31.2 (7.4)	30.1 (7.4)	29.4 (7.1)
Median (IQR)	25.9 (22.5, 30.4)	30.2 (25.9, 34.9)	28.8 (24.8, 34.1)	28.1 (24.4, 33.0)
History of Comorbidities, N	6,300	1,508	13,091	38,439
Cardiovascular Disease, n(%)	2253 (35.8)	676 (44.8)	4451 (34.0)	14293 (37.2)
Hypertension, n(%)	2203 (35.0)	665 (44.1)	3846 (29.4)	12154 (31.6)
Diabetes, n(%)	489 (7.8)	182 (12.1)	1109 (8.5)	3263 (8.5)
Current Treatment, N	6,300	1,508	13,091	38,439
Prednisone, n(%)	3575 (56.7)	694 (46.0)	4192 (32.0)	11382 (29.6)
Lipid Lowering Medications, n(%)	667 (10.6)	324 (21.5)	2826 (21.6)	7550 (19.6)
MTX and/or Leflunomide, n(%)	3628 (57.6)	907 (60.1)	8686 (66.4)	26797 (69.7)

Table 5. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Overall Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry Study Populations for the Malignancy Study Timeframe

	All Tofacitinib N= 6,300	Tofacitinib US Sites N= 1,508	Corrona: All bDMARD Initiators N=13,091	All Corrona N=38,439
Any csDMARD excluding MTX and Leflunomide, n(%)	346 (5.5)	63 (4.2)	1094 (8.4)	4579 (11.9)
History of prior csDMARD use, N	6,300	1,508	13,091	38,439
Any csDMARD including MTX, n(%)	5692 (90.3)	1331 (88.3)	12713 (97.1)	33800 (87.9)
Methotrexate, n(%)	5136 (81.5)	1252 (83.0)	11845 (90.5)	29247 (76.1)
History of bDMARD use, N	6,300	1,508	13,091	38,439
TNF inhibitors, n(%)	1270 (20.2)	612 (40.6)	9079 (69.4)	17064 (44.4)
Non-TNF inhibitors, n(%)	324 (5.1)	179 (11.9)	3000 (22.9)	3422 (8.9)
Biologic Naïve, n(%)	4892 (77.7)	841 (55.8)	3693 (28.2)	20513 (53.4)

[a]At time of study entry.

[1]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+ is only available for approximately 52% of visits.
Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation.

Table 6. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Overall Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry Study Populations for the Cardiovascular Study Timeframe

	All Tofacitinib N= 5,112	Tofacitinib US Sites N= 1,259	Corrona: All bDMARD Initiators N=10,156	All Corrona N=38,439
Age[a] in years, N	5,112	1,259	10,111	38,154
Mean (SD)	52.3 (11.8)	54.5 (11.2)	56.8 (12.8)	58.2 (13.5)
Median (IQR)	53.0 (45.0, 61.0)	55.0 (47.0, 62.0)	57.0 (49.0, 66.0)	59.0 (50.0, 68.0)
Age <65, n(%)	4375 (85.6)	1042 (82.8)	7230 (71.5)	25339 (66.4)
Age ≥65, n(%)	737 (14.4)	217 (17.2)	2881 (28.5)	12815 (33.6)
Gender	5,112	1,259	10,120	38,220
Female, n(%)	4207 (82.3)	973 (77.3)	8088 (79.9)	29215 (76.4)
Race	5,112	1,259	10,156	38,439
White, n(%)	3156 (61.7)	1048 (83.2)	8970 (88.3)	33778 (87.9)
Duration of RA, N	5,112	1,259	10,049	37,990
Mean (SD)	7.7 (8.0)	9.3 (9.2)	10.4 (9.6)	8.9 (9.7)
Median (IQR)	5.0 (1.7, 11.2)	6.6 (2.1, 14.0)	8.0 (3.0, 15.0)	5.0 (1.0, 13.0)
Rheumatoid Factor Positive,[1] N	4,935	1,117	5,867	20,549
Yes, n(%)	3571 (72.4)	762 (68.2)	4028 (68.7)	13995 (68.1)
Tender Joint Count, N	4,820	1,077	8,587	38,082
Mean (SD)	13.4 (7.5)	14.4 (7.7)	7.1 (7.1)	4.4 (6.1)
Median (IQR)	12.0 (8.0, 19.0)	14.0 (8.0, 21.0)	5.0 (1.0, 10.0)	2.0 (0.0, 6.0)
Swollen Joint Count, N	4,820	1,077	8,587	38,099
Mean (SD)	10.0 (5.8)	10.9 (6.1)	5.5 (5.5)	4.1 (5.4)
Median (IQR)	9.0 (6.0, 13.0)	10.0 (6.0, 15.0)	4.0 (1.0, 8.0)	2.0 (0.0, 6.0)
Tender and Swollen Joint Count, N	4,820	1,077	8,587	38,060
Mean (SD)	23.3 (12.1)	25.4 (12.4)	12.6 (10.9)	8.5 (10.1)
Median (IQR)	22.0 (15.0, 31.0)	24.0 (16.0, 34.0)	10.0 (4.0, 18.0)	5.0 (1.0, 12.0)
C-Reactive Protein (CRP), N	4,891	1,084	3,784	14,549
Mean (SD)	18.5 (23.9)	16.8 (21.4)	13.5 (29.3)	11.7 (27.8)
Median (IQR)	9.2 (3.9, 23.8)	8.7 (4.0, 21.1)	5.0 (2.0, 13.3)	5.0 (2.0, 11.0)
Patient Global Assessment (0-100), N	4,814	1,073	8,543	37,035
Mean (SD)	56.7 (24.5)	55.3 (24.6)	46.1 (26.8)	32.3 (26.9)
Median (IQR)	58.0 (41.0, 75.0)	57.0 (39.0, 74.0)	50.0 (25.0, 70.0)	25.0 (8.0, 50.0)
Physician Global Assessment (0-100), N	4,803	1,074	8,585	38,106
Mean (SD)	56.2 (21.0)	57.3 (21.9)	35.4 (22.6)	25.0 (21.9)
Median (IQR)	59.0 (43.0, 71.0)	60.0 (43.0, 74.0)	32.0 (17.0, 50.0)	20.0 (7.0, 39.0)
Patient Pain (0-100), N	4,816	1,074	8,542	37,107
Mean (SD)	56.4 (24.7)	55.4 (24.6)	49.0 (28.0)	34.9 (28.0)
Median (IQR)	58.0 (40.0, 75.0)	59.0 (36.0, 74.0)	50.0 (25.0, 75.0)	30.0 (10.0, 56.0)
CDAI, N	4,907	1,112	8,519	36,649
Mean (SD)	34.7 (14.4)	36.8 (14.7)	20.7 (13.7)	14.3 (13.1)
Median (IQR)	33.8 (25.1, 44.1)	36.0 (26.7, 47.2)	19.0 (10.5, 29.0)	10.5 (4.0, 20.8)
DAS28-CRP, N	4,944	1,134	3,763	14,307
Mean (SD)	5.2 (1.1)	5.3 (1.0)	4.0 (1.4)	3.3 (1.4)
Median (IQR)	5.2 (4.5, 5.9)	5.3 (4.6, 6.0)	4.0 (3.0, 4.9)	3.1 (2.1, 4.3)
mHAQ, N	4,919	1,181	8,438	37,387
Mean (SD)	0.9 (0.6)	0.8 (0.5)	0.5 (0.5)	0.4 (0.5)
Median (IQR)	0.9 (0.4, 1.3)	0.9 (0.4, 1.1)	0.5 (0.1, 0.9)	0.3 (0.0, 0.6)
Smoking Status, N	5,109	1,259	10,062	38,040

Table 6. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Overall Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry Study Populations for the Cardiovascular Study Timeframe

	All Tofacitinib N= 5,112	Tofacitinib US Sites N= 1,259	Corrona: All bDMARD Initiators N=10,156	All Corrona N=38,439
Never, n(%)	3,300 (64.6)	570 (45.3)	5,131 (51.0)	22,099 (58.1)
Former, n(%)	908 (17.8)	401 (31.9)	3,058 (30.4)	10,209 (26.8)
Current, n(%)	901 (17.6)	288 (22.9)	1,873 (18.6)	5,732 (15.1)
Alcohol Use, N	5,112	1,259	9,907	32,544
Yes, n(%)	1066 (20.9)	409 (32.5)	2372 (23.9)	7234 (22.2)
Body Mass Index (BMI)a, N	5,111	1,258	10,141	37,850
Mean (SD)	27.0 (6.5)	31.2 (7.6)	30.2 (7.4)	29.4 (7.1)
Median (IQR)	25.9 (22.5, 30.4)	30.0 (25.9, 34.8)	29.0 (24.9, 34.4)	28.1 (24.4, 33.0)
History of Comorbidities, N	5,112	1,259	10,156	38,439
Cardiovascular Disease, n(%)	1836 (35.9)	570 (45.3)	3542 (34.9)	14293 (37.2)
Hypertension, n(%)	1787 (35.0)	559 (44.4)	3031 (29.8)	12154 (31.6)
Diabetes, n(%)	407 (8.0)	152 (12.1)	885 (8.7)	3263 (8.5)
Current Treatment, N	5,112	1,259	10,156	38,439
Prednisone, n(%)	2859 (55.9)	574 (45.6)	3158 (31.1)	11382 (29.6)
Lipid Lowering Medications, n(%)	579 (11.3)	284 (22.6)	2286 (22.5)	7550 (19.6)
MTX and/or Leflunomide, n(%)	2984 (58.4)	778 (61.8)	6538 (64.4)	26797 (69.7)
Any csDMARD excluding MTX and Leflunomide, n(%)	296 (5.8)	55 (4.4)	880 (8.7)	4579 (11.9)
History of prior csDMARD use, N	5,112	1,259	10,156	38,439
Any csDMARD including MTX, n(%)	4529 (88.6)	1089 (86.5)	9854 (97.0)	33800 (87.9)
Methotrexate, n(%)	4017 (78.6)	1015 (80.6)	9146 (90.1)	29247 (76.1)
History of bDMARD use, N	5,112	1,259	10,156	38,439
TNF inhibitors, n(%)	1108 (21.7)	540 (42.9)	7292 (71.8)	17064 (44.4)
Non-TNF inhibitors, n(%)	311 (6.1)	171 (13.6)	2623 (25.8)	3422 (8.9)
Biologic Naïve, n(%)	3871 (75.7)	667 (53.0)	2586 (25.5)	20513 (53.4)

aAt time of study entry.

[1]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+ is only available for approximately 52% of visits.

Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation.

Table 7 and Table 8 show the baseline characteristics among the trimmed tofacitinib and Corrona bDMARD initiators for the malignancy and cardiovascular study timeframes, respectively. Demographic characteristics among this trimmed cohort are similar to the characteristics described in the overall study population.

Table 7. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Trimmed Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Malignancy Study Timeframe

	All Tofacitinib N= 5,551	Corrona: All bDMARD Initiators N=10,463	Standardized Differences
Age[a] in years, N	5,551	10,463	
Mean (SD)	52.4 (11.8)	56.6 (12.8)	
Median (IQR)	53.0 (45.0, 61.0)	57.0 (49.0, 65.0)	0.35
Age <65, n(%)	4737 (85.3)	7599 (72.6)	
Age ≥65, n(%)	814 (14.7)	2864 (27.4)	
Gender	5,551	10,463	
Female, n(%)	4594 (82.8)	8340 (79.7)	0.08
Race	5,551	10,463	
White, n(%)	3417 (61.6)	9336 (89.2)	0.68
Duration of RA, N	5,551	10,463	
Mean (SD)	7.9 (8.0)	10.3 (9.6)	
Median (IQR)	5.1 (1.8, 11.3)	7.0 (3.0, 15.0)	0.27
Rheumatoid Factor Positive,[1] N	5,344	6,312	
Yes, n(%)	3928 (73.5)	4450 (70.5)	0.07
Tender Joint Count, N	5,551	10,463	
Mean (SD)	13.1 (7.3)	7.1 (7.1)	
Median (IQR)	12.0 (7.0, 18.0)	5.0 (1.0, 10.0)	0.83
Swollen Joint Count, N	5,551	10,463	
Mean (SD)	9.9 (5.6)	5.8 (5.7)	
Median (IQR)	9.0 (6.0, 13.0)	4.0 (1.0, 9.0)	0.71
Tender and Swollen Joint Count, N	5,551	10,463	
Mean (SD)	22.9 (11.7)	12.9 (11.1)	
Median (IQR)	22.0 (14.0, 31.0)	10.0 (4.0, 19.0)	0.88
C-Reactive Protein (CRP), N	5,537	4,257	
Mean (SD)	18.3 (23.5)	13.9 (31.2)	
Median (IQR)	9.3 (4.0, 23.6)	5.0 (2.0, 14.0)	0.16
Patient Global Assessment (0-100), N	5,551	10,463	
Mean (SD)	56.5 (24.5)	45.6 (26.5)	
Median (IQR)	57.0 (40.0, 75.0)	50.0 (25.0, 68.0)	0.43
Physician Global Assessment (0-100), N	5,551	10,463	
Mean (SD)	56.1 (20.9)	34.9 (22.2)	
Median (IQR)	59.0 (44.0, 71.0)	30.0 (17.0, 50.0)	0.98
Patient Pain (0-100), N	5,551	10,463	
Mean (SD)	56.1 (24.7)	48.1 (27.7)	
Median (IQR)	58.0 (39.0, 75.0)	50.0 (25.0, 70.0)	0.30
CDAI, N	5,551	10,463	
Mean (SD)	34.2 (14.0)	21.0 (13.7)	
Median (IQR)	33.5 (24.9, 43.5)	19.0 (10.5, 29.0)	0.95
DAS28-CRP, N	5,544	4,260	
Mean (SD)	5.1 (1.1)	4.0 (1.4)	
Median (IQR)	5.2 (4.5, 5.9)	4.1 (3.0, 5.0)	0.90
mHAQ, N	5,551	10,463	
Mean (SD)	0.9 (0.6)	0.6 (0.5)	
Median (IQR)	0.9 (0.4, 1.3)	0.5 (0.1, 0.9)	0.56
Smoking Status, N	5,551	10,463	
Never, n(%)	3,574 (64.4)	5,287 (50.5)	0.28
Former, n(%)	976 (17.6)	3,181 (30.4)	0.30

Table 7. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Trimmed Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Malignancy Study Timeframe

	All Tofacitinib N= 5,551	Corrona: All bDMARD Initiators N=10,463	Standardized Differences
Current, n(%)	1,001 (18.0)	1,995 (19.1)	0.03
Alcohol Use, N	5,551	10,233	
Yes, n(%)	1143 (20.6)	2336 (22.8)	0.05
Body Mass Index (BMI)a, N	5,551	10,463	
Mean (SD)	26.9 (6.4)	30.0 (7.2)	
Median (IQR)	25.7 (22.4, 30.1)	28.7 (24.7, 33.9)	0.45
History of Comorbidities, N	5,551	10463	
Cardiovascular Disease, n(%)	1980 (35.7)	3602 (34.4)	0.03
Hypertension, n(%)	1934 (34.8)	3119 (29.8)	0.11
Diabetes, n(%)	424 (7.6)	885 (8.5)	0.03
Current Treatment, N	5,551	10463	
Prednisone, n(%)	3141 (56.6)	3353 (32.0)	0.51
Lipid Lowering Medications, n(%)	578 (10.4)	2236 (21.4)	0.30
MTX and/or Leflunomide, n(%)	3262 (58.8)	7060 (67.5)	0.18
Any csDMARD excluding MTX and Leflunomide, n(%)	314 (5.7)	843 (8.1)	0.10
History of prior csDMARD use, N	5,551	10463	
Any csDMARD including MTX, n(%)	5022 (90.5)	10195 (97.4)	0.30
Methotrexate, n(%)	4506 (81.2)	9528 (91.1)	0.29
History of bDMARD use, N	5,551	10463	
TNF inhibitors, n(%)	1093 (19.7)	7140 (68.2)	1.12
Non-TNF inhibitors, n(%)	247 (4.4)	2329 (22.3)	0.54
Biologic Naïve, n(%)	4352 (78.4)	3078 (29.4)	1.13

[a]At time of study entry

[1]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+ is only available for approximately 52% of visits.

Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation

Table 8. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Trimmed Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Cardiovascular Study Timeframe

	All Tofacitinib N= 4,417	Corrona: All bDMARD Initiators N= 7,989	Standardized Differences
Age[a] in years, N	4,417	7,989	
Mean (SD)	52.4 (11.7)	56.7 (12.8)	
Median (IQR)	53.0 (45.0, 61.0)	57.0 (49.0, 66.0)	0.35
Age <65, n(%)	3777 (85.5)	5762 (72.1)	
Age ≥65, n(%)	640 (14.5)	2227 (27.9)	
Gender	4,417	7,989	
Female, n(%)	3648 (82.6)	6380 (79.9)	0.07
Race	4,417	7,989	
White, n(%)	2657 (60.2)	7124 (89.2)	0.71
Duration of RA, N	4,417	7,989	
Mean (SD)	7.7 (8.0)	10.1 (9.6)	
Median (IQR)	5.0 (1.8, 11.2)	7.0 (3.0, 14.0)	0.27
Rheumatoid Factor Positive,[1] N	4,286	4,746	
Yes, n(%)	3125 (72.9)	3270 (68.9)	0.09
Tender Joint Count, N	4,417	7,989	
Mean (SD)	12.8 (7.2)	7.3 (7.2)	
Median (IQR)	12.0 (7.0, 18.0)	5.0 (2.0, 11.0)	0.77
Swollen Joint Count, N	4,417	7,989	
Mean (SD)	9.5 (5.5)	5.6 (5.5)	
Median (IQR)	9.0 (6.0, 13.0)	4.0 (1.0, 8.0)	0.72
Tender and Swollen Joint Count, N	4,417	7,989	
Mean (SD)	22.3 (11.5)	12.9 (10.9)	
Median (IQR)	21.0 (14.0, 30.0)	11.0 (4.0, 19.0)	0.84
C-Reactive Protein (CRP), N	4,404	3,515	
Mean (SD)	17.8 (22.9)	13.4 (28.7)	
Median (IQR)	8.9 (3.8, 23.1)	5.0 (2.0, 13.6)	0.17
Patient Global Assessment (0-100), N	4,417	7,989	
Mean (SD)	56.0 (24.5)	46.2 (26.7)	
Median (IQR)	57.0 (40.0, 75.0)	50.0 (25.0, 70.0)	0.38
Physician Global Assessment (0-100), N	4,417	7,989	
Mean (SD)	55.4 (21.1)	35.9 (22.5)	
Median (IQR)	58.0 (43.0, 70.7)	35.0 (20.0, 50.0)	0.90
Patient Pain (0-100), N	4,417	7,989	
Mean (SD)	55.8 (24.7)	49.0 (28.0)	
Median (IQR)	58.0 (39.0, 75.0)	50.0 (25.0, 75.0)	0.26
CDAI, N	4,417	7,989	
Mean (SD)	33.4 (13.7)	21.1 (13.7)	
Median (IQR)	32.9 (24.5, 42.3)	19.0 (10.6, 29.2)	0.90
DAS28-CRP, N	4,412	3,517	
Mean (SD)	5.1 (1.1)	4.0 (1.4)	
Median (IQR)	5.1 (4.4, 5.8)	4.1 (3.0, 5.0)	0.85
mHAQ, N	4,417	7,989	
Mean (SD)	0.8 (0.6)	0.5 (0.5)	
Median (IQR)	0.9 (0.4, 1.1)	0.5 (0.1, 0.9)	0.53
Smoking Status, N	4,417	7,989	
Never, n(%)	2,849 (64.5)	4,081 (51.1)	0.27
Former, n(%)	784 (17.7)	2,410 (30.2)	0.29
Current, n(%)	784 (17.7)	1,498 (18.8)	0.03

Table 8. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Trimmed Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Cardiovascular Study Timeframe

	All Tofacitinib N= 4,417	Corrona: All bDMARD Initiators N= 7,989	Standardized Differences
Alcohol Use, N	4,417	7,841	
Yes, n(%)	916 (20.7)	1878 (24.0)	0.08
Body Mass Index (BMI)a, N	4,417	7,989	
Mean (SD)	27.0 (6.5)	30.1 (7.3)	
Median (IQR)	25.8 (22.5, 30.2)	28.9 (24.8, 34.1)	0.45
History of Comorbidities, N	4,417	7,989	
Cardiovascular Disease, n(%)	1569 (35.5)	2787 (34.9)	0.01
Hypertension, n(%)	1526 (34.5)	2453 (30.7)	0.08
Diabetes, n(%)	345 (7.8)	694 (8.7)	0.03
Current Treatment, N	4,417	7,989	
Prednisone, n(%)	2438 (55.2)	2496 (31.2)	0.50
Lipid Lowering Medications, n(%)	494 (11.2)	1771 (22.2)	0.30
MTX and/or Leflunomide, n(%)	2598 (58.8)	5210 (65.2)	0.13
Any csDMARD excluding MTX and Leflunomide, n(%)	251 (5.7)	679 (8.5)	0.11
History of prior csDMARD use, N	4,417	7,989	
Any csDMARD including MTX, n(%)	3982 (90.2)	7770 (97.3)	0.30
Methotrexate, n(%)	3527 (79.9)	7219 (90.4)	0.30
History of bDMARD use, N	4,417	7,989	
TNF inhibitors, n(%)	982 (22.2)	5650 (70.7)	1.11
Non-TNF inhibitors, n(%)	237 (5.4)	2012 (25.2)	0.57
Biologic Naïve, n(%)	3334 (75.5)	2132 (26.7)	1.12

[a]At time of study entry.

[1]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+ is only available for approximately 52% of visits.

Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation.

Table 9 and Table 10 show the baseline characteristics among the propensity score matched tofacitinib and Corrona bDMARD initiators for the malignancy and cardiovascular study timeframes, respectively. Demographic characteristics among this matched cohort are well balanced between treatment and differ from their corresponding propensity trimmed cohort. Compared to patients initiating tofacitinib in the propensity trimmed cohort, patients initiating tofacitinib in the matched cohort were older, had longer disease duration, more previous RA therapies and lower disease activity with lower mean tender and swollen joints, CDAI, DAS28, CRP and mHAQ as well as lower mean scores for physician global assessment, patient reported pain and patient global assessment. Similarly, the inverse is true for Corrona bDMARD initiators within the matched cohort when compared to bDMARD initiators in the trimmed cohort. Specifically, bDMARD initiators in the matched cohort

were younger, had shorter disease duration, fewer previous RA therapies and higher disease activity. Table 10 shows the baseline characteristics among the matched patients for the cardiovascular study timeframe. Similar differences between the propensity trimmed and matched cohorts were observed.

Table 9. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Matched Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Malignancy Study Timeframe

	All Tofacitinib N= 2,618	Corrona: All bDMARD Initiators N= 2,618	Standardized Differences
Age[a] in years, N	2,618	2,618	
Mean (SD)	54.2 (11.3)	54.3 (13.4)	
Median (IQR)	55.0 (47.0, 62.0)	55.0 (46.0, 63.0)	0.01
Age <65, n(%)	2153 (82.2)	2058 (78.6)	
Age ≥65, n(%)	465 (17.8)	560 (21.4)	
Gender	2,618	2,618	
Female, n(%)	2080 (79.4)	2091 (79.9)	0.01
Race	2,618	2,618	
White, n(%)	1769 (67.6)	2304 (88.0)	0.51
Duration of RA, N	2,618	2,618	
Mean (SD)	8.8 (8.4)	8.5 (9.0)	
Median (IQR)	6.1 (2.3, 12.6)	5.0 (2.0, 12.0)	0.03
Rheumatoid Factor Positive,1 N	2,498	1,616	
Yes, n(%)	1761 (70.5)	1151 (71.2)	0.02
Tender Joint Count, N	2,618	2,618	
Mean (SD)	10.3 (6.9)	10.6 (8.4)	
Median (IQR)	9.0 (5.0, 14.0)	9.0 (4.0, 17.0)	0.04
Swollen Joint Count, N	2,618	2,618	
Mean (SD)	7.9 (5.1)	8.7 (6.8)	
Median (IQR)	7.0 (4.0, 11.0)	8.0 (4.0, 12.0)	0.14
Tender and Swollen Joint Count, N	2,618	2,618	
Mean (SD)	18.2 (10.8)	19.3 (13.2)	
Median (IQR)	17.0 (11.0, 25.0)	17.0 (9.0, 28.0)	0.09
C-Reactive Protein (CRP), N	2,610	1,019	
Mean (SD)	15.0 (19.6)	16.3 (31.8)	
Median (IQR)	7.9 (3.1, 18.3)	6.0 (2.0, 17.0)	0.05
Patient Global Assessment (0-100), N	2,618	2,618	
Mean (SD)	51.2 (25.1)	50.1 (26.7)	
Median (IQR)	52.0 (32.0, 70.0)	50.0 (30.0, 70.0)	0.04
Physician Global Assessment (0-100), N	2,618	2,618	
Mean (SD)	50.1 (22.6)	44.4 (23.4)	
Median (IQR)	52.0 (34.0, 68.0)	42.0 (25.0, 61.0)	0.25
Patient Pain (0-100), N	2,618	2,618	
Mean (SD)	51.6 (25.5)	50.8 (27.4)	
Median (IQR)	53.0 (32.0, 71.0)	50.0 (29.0, 75.0)	0.03
CDAI, N	2,618	2,618	
Mean (SD)	28.4 (13.5)	28.8 (15.7)	
Median (IQR)	27.7 (19.7, 37.3)	27.0 (16.8, 40.0)	0.03
DAS28-CRP, N	2,614	1,021	
Mean (SD)	4.7 (1.1)	4.6 (1.4)	
Median (IQR)	4.7 (4.0, 5.4)	4.7 (3.7, 5.7)	0.02

Table 9. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Matched Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Malignancy Study Timeframe

	All Tofacitinib N= 2,618	Corrona: All bDMARD Initiators N= 2,618	Standardized Differences
mHAQ, N	2,618	2,618	
Mean (SD)	0.7 (0.5)	0.7 (0.6)	
Median (IQR)	0.6 (0.3, 1.0)	0.6 (0.3, 1.0)	0.00
Smoking Status, N	2,618	2,618	
Never, n(%)	1,479 (56.5)	1,505 (57.5)	0.02
Former, n(%)	601 (23.0)	595 (22.7)	0.01
Current, n(%)	538 (20.6)	518 (19.8)	0.02
Alcohol Use, N	2,618	2,560	
Yes, n(%)	634 (24.2)	537 (21.0)	0.08
Body Mass Index (BMI)a, N	2,618	2,618	
Mean (SD)	28.2 (7.0)	28.2 (6.4)	
Median (IQR)	26.8 (23.3, 31.8)	27.3 (23.7, 31.8)	0.00
History of Comorbidities, N	2,618	2,618	
Cardiovascular Disease, n(%)	917 (35.0)	985 (37.6)	0.05
Hypertension, n(%)	889 (34.0)	901 (34.4)	0.01
Diabetes, n(%)	217 (8.3)	186 (7.1)	0.04
Current Treatment, N	2,618	2,618	
Prednisone, n(%)	1234 (47.1)	1242 (47.4)	0.01
Lipid Lowering Medications, n(%)	399 (15.2)	385 (14.7)	0.01
MTX and/or Leflunomide, n(%)	1780 (68.0)	1809 (69.1)	0.02
Any csDMARD excluding MTX and Leflunomide, n(%)	130 (5.0)	194 (7.4)	0.10
History of prior csDMARD use, N	2,618	2,618	
Any csDMARD including MTX, n(%)	2525 (96.4)	2513 (96.0)	0.02
Methotrexate, n(%)	2332 (89.1)	2350 (89.8)	0.02
History of bDMARD use, N	2,618	2,618	
TNF inhibitors, n(%)	987 (37.7)	1047 (40.0)	0.05
Non-TNF inhibitors, n(%)	212 (8.1)	398 (15.2)	0.22
Biologic Naïve, n(%)	1539 (58.8)	1544 (59.0)	0.00

[a]At time of study entry.

[1]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+ is only available for approximately 52% of visits.

Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation.

Table 10. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Matched Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Cardiovascular Study Timeframe

	All Tofacitinib N= 2,068	Corrona: All bDMARD Initiators N= 2,068	Standardized Differences
Age[a] in years, N	2,068	2,068	
Mean (SD)	54.3 (11.0)	54.1 (13.6)	
Median (IQR)	55.0 (47.0, 62.0)	55.0 (45.0, 63.0)	0.02
Age <65, n(%)	1708 (82.6)	1610 (77.9)	
Age ≥65, n(%)	360 (17.4)	458 (22.1)	
Gender	2,068	2,068	
Female, n(%)	1668 (80.7)	1671 (80.8)	0.00
Race	2,068	2,068	
White, n(%)	1383 (66.9)	1807 (87.4)	0.50
Duration of RA, N	2,068	2,068	
Mean (SD)	8.8 (8.5)	8.5 (9.4)	
Median (IQR)	6.0 (2.3, 13.0)	5.0 (2.0, 12.0)	0.03
Rheumatoid Factor Positive,1 N	1,985	1,269	
Yes, n(%)	1396 (70.3)	865 (68.2)	0.05
Tender Joint Count, N	2,068	2,068	
Mean (SD)	10.3 (6.9)	10.6 (8.2)	
Median (IQR)	9.0 (5.0, 14.0)	9.0 (4.0, 16.0)	0.04
Swollen Joint Count, N	2,068	2,068	
Mean (SD)	7.9 (5.1)	8.2 (6.5)	
Median (IQR)	7.0 (4.0, 11.0)	7.0 (3.0, 12.0)	0.05
Tender and Swollen Joint Count, N	2,068	2,068	
Mean (SD)	18.2 (10.7)	18.8 (12.8)	
Median (IQR)	17.0 (11.0, 25.0)	17.0 (9.0, 28.0)	0.05
C-Reactive Protein (CRP), N	2,062	883	
Mean (SD)	15.1 (20.2)	16.1 (33.7)	
Median (IQR)	7.7 (3.0, 18.2)	6.0 (2.0, 16.0)	0.03
Patient Global Assessment (0-100), N	2,068	2,068	
Mean (SD)	51.0 (25.3)	51.1 (26.9)	
Median (IQR)	52.0 (32.0, 71.0)	50.0 (30.0, 74.0)	0.00
Physician Global Assessment (0-100), N	2,068	2,068	
Mean (SD)	49.9 (23.0)	45.7 (23.5)	
Median (IQR)	52.0 (33.0, 68.0)	45.0 (29.0, 65.0)	0.18
Patient Pain (0-100), N	2,068	2,068	
Mean (SD)	51.7 (25.6)	51.8 (27.9)	
Median (IQR)	53.8 (32.0, 72.0)	50.0 (30.0, 75.0)	0.00
CDAI, N	2,068	2,068	
Mean (SD)	28.3 (13.4)	28.5 (15.4)	
Median (IQR)	27.9 (19.5, 37.3)	26.5 (16.9, 39.5)	0.01
DAS28-CRP, N	2,065	883	
Mean (SD)	4.7 (1.1)	4.6 (1.4)	
Median (IQR)	4.7 (4.0, 5.4)	4.6 (3.6, 5.7)	0.05
mHAQ, N	2,068	2,068	
Mean (SD)	0.7 (0.5)	0.7 (0.6)	
Median (IQR)	0.6 (0.3, 1.0)	0.6 (0.3, 1.0)	0.01
Smoking Status, N	2,068	2,068	
Never, n(%)	1,182 (57.2)	1,156 (55.9)	0.03
Former, n(%)	480 (23.2)	486 (23.5)	0.01
Current, n(%)	406 (19.6)	426 (20.6)	0.02

Table 10. Demographics, Disease Characteristics, Comorbidities and Treatment History within the "Matched Study Populations" for the Comparative Safety Study Consisting of Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE) or Corrona RA Registry bDMARD Initiator Population for the Cardiovascular Study Timeframe

	All Tofacitinib N= 2,068	Corrona: All bDMARD Initiators N= 2,068	Standardized Differences
Alcohol Use, N	2,068	2,031	
Yes, n(%)	514 (24.9)	429 (21.1)	0.09
Body Mass Index (BMI)a, N	2,068	2,068	
Mean (SD)	28.4 (7.1)	28.4 (6.4)	
Median (IQR)	26.8 (23.5, 32.0)	27.5 (23.8, 32.0)	0.01
History of Comorbidities, N	2,068	2,068	
Cardiovascular Disease, n(%)	765 (37.0)	753 (36.4)	0.01
Hypertension, n(%)	725 (35.1)	717 (34.7)	0.01
Diabetes, n(%)	163 (7.9)	177 (8.6)	0.02
Current Treatment, N	2,068	2,068	
Prednisone, n(%)	929 (44.9)	963 (46.6)	0.03
Lipid Lowering Medications, n(%)	326 (15.8)	320 (15.5)	0.01
MTX and/or Leflunomide, n(%)	1393 (67.4)	1406 (68.0)	0.01
Any csDMARD excluding MTX and Leflunomide, n(%)	109 (5.3)	155 (7.5)	0.09
History of prior csDMARD use, N	2,068	2,068	
Any csDMARD including MTX, n(%)	1999 (96.7)	1967 (95.1)	0.08
Methotrexate, n(%)	1832 (88.6)	1830 (88.5)	0.00
History of bDMARD use, N	2,068	2,068	
TNF inhibitors, n(%)	852 (41.2)	909 (44.0)	0.06
Non-TNF inhibitors, n(%)	197 (9.5)	385 (18.6)	0.26
Biologic Naïve, n(%)	1131 (54.7)	1125 (54.4)	0.01

[a]At time of study entry.

[1]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+ is only available for approximately 52% of visits.

Anti-TNF=Anti-Tumor necrosis factor; bDMARD=biologic disease modifying antirheumatic drug; BID=bis in die (twice daily); BMI=body mass index; CDAI=Clinical disease activity index; CRP=C-reactive protein; csDMARD=conventional synthetic disease modifying antirheumatic drug; DAS=Disease activity score; DMARD=disease modifying antirheumatic drug; IQR=interquartile range; mHAQ=Modified health assessment questionnaire; MTX=methotrexate; N=number; N/A=not-applicable; P123LTE=Phase 1, Phase 2, Phase 3 and Long-term extension; RA=rheumatoid arthritis; SD=standard deviation.

10.2.1. Descriptive Data Stratified by Dose and Geography

Descriptive data stratified by tofacitinib dose and restricted to US tofacitinib subjects can be found in Annex 2.

10.3. Outcome Data

A total of 6,300 and 5,112 patients in Tofacitinib clinical program (P123LTE) were included in the malignancy and cardiovascular analyses respectively. In addition, 13,091 and 10,156 patients were included for the malignancy and cardiovascular analysis respectively. Additional information about patient counts by dose and US clinical trial sites is available in Table 4 above.

10.4. Main Results

As shown in Table 11, the statistical methods for this study serve as the structure for the results which follow.

Table 11. Statistical Method Summary

Models	Outcomes			
	Malignancy	**MACE**	**Nonfatal MI**	**Nonfatal Stroke**
Overall	Unadjusted comparison of populations			
	Propensity score for biologic used to trim the population (common support)			
Trimmed	Multivariable Cox Regression adjusted model to estimate Hazard Ratios Unadjusted shown for comparison			
Unadjusted	Primary Analysis			
Adjusted				
Unadjusted (5y)	5 year follow-up for comparison with sensitivity analysis			
Adjusted (5y)				
Imputed rates unadjusted	Model rates based on patient characteristics and impute censored time Cox			
Imputed rates adjusted	Model fit- Multiple Imputation used (50-60 imputations)			
IPCW unadjusted	Model censoring and create inverse probability of censoring weights			
IPCW adjusted	Estimate Cox Model using weights			
Matched	Use propensity score for 1:1 matching			
Overall	Matched patients			
Overall (5y)	5 year follow-up for comparison with sensitivity analyses			
Imputed rates	Impute rates as described above			
IPCW	Estimate weights as above			

Abbreviations: MACE=major adverse cardiovascular events; MI=myocardial infarction; IPCW=inverse probability of censoring weights; y=years.

10.4.1. Overall Model: Incidence Rates

Unadjusted incidence rates and 95% confidence intervals among all tofacitinib initiators and Corrona bDMARD initiators as well as all Corrona RA registry patients are shown in Table 12 and Table 13. These rates include all patients within their respective cohorts which is prior to any propensity score trimming or matching. Consistent with the analysis populations, malignancy analyses were censored at 9 years and cardiovascular analyses were censored at 6 years.

Table 12. Unadjusted Incidence Rates (IR) and 95% Confidence Intervals (CI) within the Comparative Safety Study among all Eligible Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE), All Tofacitinib Initiators and US Tofacitinib Initiators Only[a]

	Tofacitinib Initiators				Tofacitinib US Sites			
	N	PY	IR	95% CI	N	PY	IR	95% CI
All malignancies excluding NMSC	168	22,352.55	0.75	(0.65, 0.87)	60	4,535.11	1.32	(1.03, 1.70)
MACE[b]	66	17,322.62	0.38	(0.30, 0.48)	20	3,611.18	0.55	(0.36, 0.86)
Non-fatal MI	25	17,375.71	0.14	(0.10, 0.21)	9	3,626.74	0.25	(0.13, 0.48)
Non-fatal stroke	29	17,357.50	0.17	(0.12, 0.24)	8	3,629.78	0.22	(0.11, 0.44)

[a]Malignancy and CV populations are defined in study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; IR=incidence rate; N=number; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PY=person-years; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

Table 13. Unadjusted Incidence Rates (IR) and 95% Confidence Intervals (CI) within the Comparative Safety Study among all Eligible Patients from the Tofacitinib RA BID Clinical Trial Program (P123LTE), all Corrona RA Registry bDMARD Initiators and all Corrona RA Registry Patients[a]

	Corrona bDMARD Initiators				All Corrona Patients			
	N	PY	IR	95% CI	N	PY	IR	95% CI
All malignancies excluding NMSC	113	21,259.83	0.53	(0.44, 0.64)	1,365	149,739.25	0.91	(0.86, 0.96)
MACE[b]	66	14,388.33	0.46	(0.36, 0.58)	623	130,404.50	0.48	(0.44, 0.52)
Non-fatal MI	36	14,410.17	0.25	(0.18, 0.35)	313	130,980.00	0.24	(0.21, 0.27)
Non-fatal stroke	26	14,422.92	0.18	(0.12, 0.26)	303	131,005.00	0.23	(0.21, 0.26)

[a]Malignancy and CV populations are defined in study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; IR=incidence rate; N=number; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PY=person-years; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

Table 14 shows the unadjusted incidence rates and 95% confidence intervals among the propensity trimmed tofacitinib initiators and Corrona bDMARD initiators.

Table 14. Unadjusted Incidence Rates (IR) and 95% Confidence Intervals (CI) within the Comparative Safety Study "Trimmed Population" among Tofacitinib RA BID Clinical Trial Program (P123LTE) Initiators and Corrona RA Registry bDMARD Initiators[a]

	Tofacitinib Initiators				Corrona bDMARD Initiators			
	N	PY	IR	95% CI	N	PY	IR	95% CI
All malignancies excluding NMSC	156	20,613.41	0.76	(0.65, 0.89)	96	17,027.50	0.56	(0.46, 0.69)
MACE[b]	59	15,454.32	0.38	(0.30, 0.49)	58	11,361.00	0.51	(0.39, 0.66)
Non-fatal MI	24	15,502.67	0.15	(0.10, 0.23)	31	11,381.08	0.27	(0.19, 0.39)
Non-fatal stroke	27	15,489.16	0.17	(0.12, 0.25)	23	11,391.08	0.20	(0.13, 0.30)

[a]Malignancy and CV populations are defined in study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke).

BID=bis in die (twice daily); CI=confidence interval; IR=incidence rate; N=number; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PY=person-years; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug.

10.4.2. Trimmed Models (Primary Cohort)

10.4.2.1. Hazard Ratios

Unadjusted and adjusted hazard ratios (HRs) as well as corresponding 95% confidence intervals are shown in Table 15 for all patients in the primary cohort and the propensity score trimmed cohort. The unadjusted estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.29 (95% CI: 0.99, 1.68) and adjusted HR is 1.71 (95% CI: 1.22, 2.40) among patients in the propensity trimmed cohort. The unadjusted HR for risk of MACE in tofacitinib vs bDMARDs in the propensity trimmed cohort is 0.78 (95% CI: 0.53, 1.14) and adjusted HR is 1.12 (95% CI: 0.67, 1.87).

Table 15. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study Comparing Initiators from the Tofacitinib RA BID Clinical Trial Program (P123LTE)[a] with Patient bDMARD Initiator Study Cohorts from the Corrona RA Registry

Hazard Ratios with 95% confidence intervals[b]	All Tofacitinib versus Corrona RA bDMARD Initiators		Tofacitinib versus Corrona RA bDMARD Initiators in **Trimmed Population**		Tofacitinib versus Corrona RA bDMARD Initiators in **Adjusted Trimmed Population**	
Events	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
All malignancies excluding NMSC	1.33	(1.04, 1.71)	1.29	(0.99, 1.68)	1.71	(1.22, 2.40)
MACE[c]	0.84	(0.58, 1.20)	0.78	(0.53, 1.14)	1.12	(0.67, 1.87)
Non-fatal MI	0.56	(0.33, 0.96)	0.58	(0.33, 1.02)	0.81	(0.39, 1.69)
Non-fatal stroke	1.00	(0.57, 1.73)	0.97	(0.54, 1.73)	1.64	(0.74, 3.61)

[a]Malignancy and CV populations are defined in study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.

[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

10.4.2.2. Censored at 5 years

For comparative purposes with the sensitivity analyses, unadjusted and adjusted HRs (95% CI) are shown in Table 16 using 5 years as a fixed cut point. The unadjusted estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.29 (95% CI: 0.98, 1.69) and adjusted HR is 1.61 (95% CI: 1.13, 2.28) among patients in the propensity trimmed cohort. The unadjusted HR for risk of MACE in tofacitinib vs bDMARDs in the propensity trimmed cohort is 0.76 (95% CI: 0.51, 1.11) and adjusted HR is 1.10 (95% CI: 0.65, 1.84).

Table 16. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study Comparing Initiators from the Tofacitinib RA BID Clinical Trial Program (P123LTE)[a] censored at 5 years with Patient bDMARD Initiator Study Cohorts from the Corrona RA Registry

Hazard Ratios with 95% confidence intervals[b]	All Tofacitinib versus Corrona RA bDMARD Initiators		Tofacitinib versus Corrona RA bDMARD Initiators in **Trimmed Population**		Tofacitinib versus Corrona RA bDMARD Initiators in **Adjusted Trimmed Population**	
Events	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
All malignancies excluding NMSC	1.34	(1.04, 1.73)	1.29	(0.98, 1.69)	1.61	(1.13, 2.28)
MACEc	0.81	(0.57, 1.17)	0.76	(0.51, 1.11)	1.10	(0.65, 1.84)
Non-fatal MI	0.53	(0.31, 0.92)	0.55	(0.31, 0.98)	0.81	(0.38, 1.71)
Non-fatal stroke	0.98	(0.56, 1.71)	0.95	(0.53, 1.71)	1.60	(0.72, 3.55)

[a]Malignancy and CV populations are defined in study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses weree restricted to patients enrolled from February 2009 and onward.

[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.

[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

10.4.2.3. Imputation of Censored Time

As shown in Table 17, the unadjusted estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.25 (95% CI: 1.00, 1.55) and adjusted HR is 1.37 (95% CI: 1.02, 1.83) among patients in the propensity trimmed cohort. The unadjusted HR for risk of MACE in tofacitinib vs bDMARDs in the propensity trimmed cohort is 0.76 (95% CI: 0.57, 1.01) and adjusted HR is 1.05 (95% CI: 0.71, 1.56).

10.4.2.4. Inverse Probability of Censored Time

As shown in Table 17, the unadjusted estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.42 (95% CI: 1.07, 1.87) and adjusted HR is 1.66 (95% CI: 1.15, 2.38) among patients in the propensity trimmed cohort. The unadjusted HR for risk of MACE in tofacitinib vs bDMARDs in the propensity trimmed cohort is 0.82 (95% CI: 0.55, 1.24) and adjusted HR is 1.06 (95% CI: 0.59, 1.90).

Table 17. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study "Trimmed Population" among Tofacitinib RA BID Clinical Trial Program (P123LTE) Initiators and Corrona RA Registry bDMARD Initiators[a]

Hazard Ratios with 95% confidence intervals[b]	Tofacitinib versus Corrona bDMARD Initiators using **IPCW (unadjusted)**		Tofacitinib versus Corrona bDMARD Initiators using **IPCW (adjusted)**		Tofacitinib versus Corrona bDMARD Initiators using **Imputation (unadjusted)**		Tofacitinib versus Corrona bDMARD Initiators using **Imputation (adjusted)**	
Events	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
All malignancies excluding NMSC	1.42	(1.07, 1.87)	1.66	(1.15, 2.38)	1.25	(1.00, 1.55)	1.37	(1.02, 1.83)
MACE[c]	0.82	(0.55, 1.24)	1.06	(0.59, 1.90)	0.76	(0.57, 1.01)	1.05	(0.71, 1.56)
Non-fatal MI	0.56	(0.31, 1.02)	0.82	(0.38, 1.78)	0.61	(0.39, 0.97)	0.90	(0.49, 1.65)
Non-fatal stroke	1.02	(0.55, 1.91)	1.43	(0.51, 4.03)	0.84	(0.54, 1.32)	1.24	(0.67, 2.31)

[a]Malignancy and CV populations are defined in the study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history of hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.

[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

IPCW (Inverse Probability of Censoring Weighting): Model of censoring based on patient characteristics used to create weights for patients representative of censored patients for Cox regression model of events.

Imputation: Regression model using patient characteristics to predict events in order to impute events during censored time periods. Multiple imputation used for Cox regression models of HRs.

10.4.2.5. Tipping Point Analysis

Table 18 below shows values for R, the unknown malignancy rate for bDMARD initiators in the unobserved time, and the proportion of informative censoring necessary to drive the IRR to values lower than the estimated 1.35. Rates are shown as number of events per 100 person years of follow-up.

Among the 5,551 tofacitinib patients, there are 141 malignancy events in 18,067.4 observed person years which accounts for 65% of the overall time such that the incidence rate of malignancies is 0.78 per 100 person-years. Among the 10,463 bDMARD patients, there are 92 malignancy events in 15,930.9 observed person years which accounts for 30% of the overall time such that the incidence rate of malignancies is 0.58 per 100 person-years. For the trimmed primary cohort (malignancy), the IRR comparing tofacitinib to bDMARD is 1.35 per 100 person-years.

Table 18. Estimated Malignancy Rates for Informative Censoring to Move IRR Towards 1

Proportion Informative Censoring	IRR			
	1.0	1.1	1.2	1.3
100%	0.87	0.77	0.68	0.61
75%	1.07	0.94	0.83	0.73
50%	1.49	1.28	1.11	0.97
25%	2.72	2.31	1.97	1.68

Abbreviations: IRR=incidence rate ratio.

10.5. Other Analyses

10.5.1. Propensity Score Matched Models (Primary Cohort)

10.5.1.1. Propensity Score Matched Models: Incidence Rates

Table 19 shows the unadjusted incidence rates and 95% confidence intervals among the propensity matched tofacitinib initiators and Corrona bDMARD initiators. Consistent with the primary analysis populations, malignancy analyses were censored at 9 years and cardiovascular analyses were censored at 6 years.

Table 19. Unadjusted Incidence Rates (IR) and 95% Confidence Intervals (CI) within the Comparative Safety Study "Propensity Score Matched Population" among Tofacitinib RA BID Clinical Trial Program (P123LTE) Initiators and Corrona RA Registry bDMARD Initiators[a]

	Tofacitinib Initiators				Corrona bDMARD Initiators			
	N	PY	IR	95% CI	N	PY	IR	95% CI
All malignancies excluding NMSC	88	9,597.36	0.92	(0.74, 1.13)	31	4,682.50	0.66	(0.47, 0.94)
MACE[b]	33	7,146.31	0.46	(0.33, 0.65)	21	3,103.33	0.68	(0.44, 1.04)
Non-fatal MI	15	7,174.80	0.21	(0.13, 0.35)	11	3,111.25	0.35	(0.20, 0.64)
Non-fatal stroke	14	7,175.26	0.20	(0.12, 0.33)	9	3,114.92	0.29	(0.15, 0.56)

[a]Malignancy and CV populations are defined in the study population section 5.1. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; IR=incidence rate; N=number; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; PY=person-years; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

10.5.1.2. Propensity Score Matched Models: Hazards Ratios

Hazard ratios (HRs) as well as the corresponding 95% confidence intervals are shown in Table 20 for patients in the matched cohort. The estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.32 (95% CI: 0.88, 1.99) among patients in the propensity matched cohort. The estimated HR for risk of MACE in tofacitinib vs bDMARDs in the propensity matched cohort is 0.72 (95% CI: 0.42, 1.24).

Table 20. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study Comparing Initiators from the Tofacitinib RA BID Clinical Trial Program (P123LTE)a with Patient bDMARD Initiator Study Cohorts from the Corrona RA Registry

Hazard Ratios with 95% confidence intervals[b] Events	Matched Tofacitinib versus Corrona bDMARD Initiators HR	95% CI
All malignancies excluding NMSC	1.32	(0.88, 1.99)
MACE[c]	0.72	(0.42, 1.24)
Non-fatal MI	0.61	(0.29, 1.30)
Non-fatal stroke	0.83	(0.35, 1.98)

[a]Malignancy and CV populations are defined in the study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.

[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

10.5.1.3. Propensity Score Matched Models: Censored at 5 years

For comparative purposes with the sensitivity analyses, unadjusted and adjusted HRs (95% CI) are shown in Table 21 using 5 years as a fixed cut point. The estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.24 (95% CI: 0.82, 1.88) among patients in the propensity matched cohort. The estimated HR for risk of MACE in tofacitinib vs bDMARDs in the propensity matched cohort is 0.69 (95% CI: 0.39, 1.20).

Table 21. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study Comparing Initiators from the Tofacitinib RA BID Clinical Trial Program (P123LTE)[a] censored at 5 years with Patient bDMARD Initiator Study Cohorts from the Corrona RA Registry

Hazard Ratios with 95% confidence intervals[b]	Matched Tofacitinib versus Corrona bDMARD Initiators	
Events	HR	95% CI
All malignancies excluding NMSC	1.24	(0.82, 1.88)
MACE[c]	0.69	(0.39, 1.20)
Non-fatal MI	0.59	(0.27, 1.27)
Non-fatal stroke	0.80	(0.33, 1.95)

[a]Malignancy and CV populations are defined in the study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.

[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.

[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug

10.5.1.4. Propensity Score Matched Models: Sensitivity Analyses

Hazard ratios (HRs) as well as corresponding 95% confidence intervals using imputation of censored time and inverse probability of censoring weights are shown in Table 22 for patients in the propensity score matched cohort.

Table 22. Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study "Propensity Score Matched Population" among Tofacitinib RA BID Clinical Trial Program (P123LTE) Initiators and Corrona RA Registry bDMARD Initiators[a]

Hazard Ratios with 95% confidence intervals[b]	Tofacitinib versus Corrona bDMARD Initiators using **IPCW (covariance adjusted)**		Tofacitinib versus Corrona bDMARD Initiators using **Imputation (covariance adjusted)**	
Events	**HR**	**95% CI**	**HR**	**95% CI**
All malignancies excluding NMSC	1.28	(0.84, 1.96)	1.28	(0.94, 1.74)
MACE[c]	0.69	(0.39, 1.23)	0.81	(0.52, 1.26)
Non-fatal MI	0.58	(0.26, 1.30)	0.79	(0.43, 1.45)
Non-fatal stroke	0.77	(0.31, 1.88)	0.73	(0.36, 1.47)

[a]Malignancy and CV populations are defined in the study population section. Due to the timing of the tofacitinib CV adjudication procedures, CV analyses were restricted to patients enrolled from February 2009 and onward.
[b]Covariates adjusted include: age, gender, smoking history, duration of RA disease, CDAI, mHAQ, patient reported pain, current Prednisone use, current MTX and/or Leflunomide use, prior biologic use and prior csDMARD use, BMI, current statin use and history of hypertension. Cardiovascular models include the following additional covariates: history of cardiovascular disease and diabetes.
[c]Major Adverse Cardiovascular Event (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 peripheral artery disease, non-fatal myocardial infarction (MI), non-fatal stroke)

BID=bis in die (twice daily); CI=confidence interval; HR=hazard ratio; MACE=major adverse cardiovascular event; MI=myocardial infarction; NMSC=non-melanoma skin cancer; P123LTE=Phase 1, Phase 2, Phase 3, Long-term extension; RA=rheumatoid arthritis; bDMARD=biologic disease modifying antirheumatic drug.

IPCW (Inverse Probability of Censoring Weighting): Model of censoring based on patient characteristics used to create weights for patients representative of censored patients for Cox regression model of events.

Imputation: Regression model using patient characteristics to predict events in order to impute events during censored time periods. Multiple imputation used for Cox regression models of HRs.

10.5.1.4.1. Matched Models: Imputation of Censored Time

The estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.28 (95% CI: 0.94, 1.74) among patients in the propensity matched cohort. The estimated HR for risk of MACE in tofacitinib vs bDMARDs in the propensity matched cohort is 0.81 (95% CI: 0.52, 1.26).

10.5.1.4.2. Matched Models: Inverse Probability of Censored Time

The estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.28 (95% CI: 0.84, 1.96) among patients in the propensity matched cohort. The estimated HR for risk of MACE in tofacitinib vs bDMARDs in the propensity matched cohort is 0.69 (95% CI: 0.39, 1.23).

10.5.1.4.3. Matched Models: Tipping Point Analysis

Among the 2,618 tofacitinib patients, there are 80 malignancy events in 8,453.1 observed person years which accounts for 65% of the overall time such that the incidence rate of malignancies is 0.95 per 100 person-years. Among the 2,618 bDMARD patients, there are 31 malignancy events in 4,331.6 observed person years which accounts for 33% of the overall time such that the incidence rate of malignancies is 0.72 per 100 person-years. For

the matched primary cohort (malignancy), the IRR comparing tofacitinib to bDMARD is 1.32 per 100 person-years.

Table 23 below shows values for R, the unknown malignancy rate for bDMARD initiators in the unobserved time, and the proportion of informative censoring necessary to drive the IRR to values lower than the estimated 1.32. Rates are shown as number of events per 100 person years of follow-up.

For the IRR to equal 1.0, the unknown malignancy rate for bDMARD initiators in unobserved time would need to be 1.06/100 person years assuming 100% informative censoring and 1.77/100 person years assuming 50% informative censoring.

Table 23. Estimated Malignancy Rates for Informative Censoring to Move IRR Towards 1 in Matched Cohorts

Proportion Informative Censoring	IRR			
	1.0	1.1	1.2	1.3
100%	1.06	0.93	0.82	0.73
75%	1.30	1.12	0.98	0.86
50%	1.77	1.57	1.30	1.11
25%	3.18	2.67	2.24	1.87

Abbreviations: IRR=incidence rate ratio.

10.5.2. Time Varying Covariates

Using the time-varying data, unadjusted and adjusted hazard ratios (HRs) as well as corresponding 95% confidence intervals are shown in Table 24 for the propensity score trimmed cohort and propensity score matched cohort. The adjusted estimated HR for risk of malignancy in tofacitinib vs bDMARDs is 1.70 (95% CI: 1.21, 2.39) among patients in the propensity trimmed cohort. The adjusted HR for risk of MACE in tofacitinib vs bDMARDs in the propensity trimmed cohort is 1.05 (95% CI: 0.63, 1.75).

Table 24. Using Time Varying Data, Hazard Ratios (HR) and 95% Confidence Intervals (CI) within the Comparative Safety Study "Trimmed" and "Matched Population" among Tofacitinib RA BID Clinical Trial Program (P123LTE) Initiators and Corrona RA Registry bDMARD Initiators[a]

	Outcomes			
Models	Malignancy[a]	MACE	Nonfatal MI	Nonfatal Stroke
Trimmed				
Unadjusted	1.29 (0.99, 1.68)	0.78 (0.53, 1.14)	0.58 (0.33, 1.02)	0.97 (0.54, 1.73)
Adjusted	1.70 (1.21, 2.39)	1.05 (0.63, 1.75)	0.79 (0.38, 1.63)	1.55 (0.70, 3.43)
Matched (CI adjusted for matching)				
Overall	1.32 (0.88, 1.99)	0.72 (0.42, 1.24)	0.61 (0.29, 1.30)	0.83 (0.35, 1.98)

a. Excluding non-melanoma skin cancer.
Abbreviations: CI=confidence interval; MACE=major adverse cardiovascular endpoint; MI=myocardial infarction.

10.5.3. Incidence Rates and Hazards Ratios, Additional Analyses

Annex 2, Section 2 shows the unadjusted incidence rates for the outcomes of interest by tofacitinib dose and restricted to US clinical trial participants. Hazards ratios comparing the different study cohorts are shown within Annex 2, Section 3. Estimated results in the sub-cohorts parallel the main results with estimated HR>1 for malignancy and close to 1 for CV events. HR was slightly higher in 5mg vs 10mg dose groups and HR was higher using the US cohort than the full cohort. But in both cases confidence intervals were much wider due to smaller sample sizes.

10.6. Adverse Events/Adverse Reactions

This study involved data that existed as structured data by the time of study start or a combination of existing structured data and unstructured data, which were 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 were not retrieved or validated, and it was 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. DISCUSSION

The utility of real-world data and evidence generation in the context of clinical research is an emerging area of study. Under the 21st Century Cures Act (enacted on 13Dec2016), the FDA was mandated to create a framework to evaluate the use of real-world evidence to support new therapy indications and post-approval study requirements. In the context of this framework, the FDA highlighted electronic health records, medical claims and billing data, data from product and disease registries and patient-generated data as RWD sources which could augment interventional clinical trial data collection and study designs (US FDA, 2018).[10] Under the auspices of this work, researchers have published efforts using RWD to replicate the results of RCTs (eg, Patorno et al., 2019)[11] and for therapy dosing considerations (eg, Kothare et al, 2017).[12] To the best of our knowledge, this is the first study to statistically compare subject safety data from a clinical trial to that from patients within an observational registry setting as a post-marketing commitment to FDA.

11.1. Key Results

Overall, as shown in Table 25, the results demonstrated that patients with RA who initiated tofacitinib within the clinical trial setting had a higher incidence of malignancies (excluding NMSC) when compared with bDMARD initiators within the Corrona RA Registry. Rates of CV events, including MACE, were similar between the patient populations. When stratified by dose, similar trends were noted (See Annex 2). Each analysis creates a potentially varied tradeoff of precision and bias. The multivariable analyses provide the greatest precision while matched analyses may provide less bias. In addition, fewer events for nonfatal MI and stroke provide less precision.

Table 25. Overall Summary Table for the Primary Cohort across all methods, Hazards Ratio (95% CI)

	Outcomes			
Models	Malignancy[a]	MACE	Nonfatal MI	Nonfatal Stroke
Overall	1.33 (1.04, 1.71)	0.84 (0.58, 1.20)	0.56 (0.33, 0.96)	1.00 (0.57, 1.73)
Trimmed				
Unadjusted	1.29 (0.99, 1.68)	0.78 (0.53, 1.14)	0.58 (0.33, 1.02)	0.97 (0.54, 1.73)
Adjusted	1.71 (1.22, 2.40)	1.12 (0.67, 1.87)	0.81 (0.39, 1.69)	1.64 (0.74, 3.61)
Unadjusted (5 years)	1.29 (0.98, 1.69)	0.76 (0.51, 1.11)	0.55 (0.31, 0.98)	0.95 (0.53, 1.71)
Adjusted (5 years)	1.61 (1.13, 2.28)	1.10 (0.65, 1.84)	0.81 (0.38, 1.71)	1.60 (0.72, 3.55)
Imputed rates unadjusted	1.25 (1.00, 1.55)	0.76 (0.57, 1.01)	0.61 (0.39, 0.97)	0.84 (0.54, 1.32)
Imputed rates adjusted	1.37 (1.02, 1.83)	1.05 (0.71, 1.56)	0.90 (0.49, 1.65)	1.24 (0.67, 2.31)
IPCW unadjusted	1.42 (1.07, 1.87)	0.82 (0.55, 1.24)	0.56 (0.31, 1.02)	1.02 (0.55, 1.91)
IPCW adjusted	1.66 (1.15, 2.38)	1.06 (0.59, 1.90)	0.82 (0.38, 1.78)	1.43 (0.51, 4.03)
Matched (CI adjusted for matching)				
Overall	1.32 (0.88, 1.99)	0.72 (0.42, 1.24)	0.61 (0.29, 1.30)	0.83 (0.35, 1.98)
Overall (5 years)	1.24 (0.82, 1.88)	0.69 (0.39, 1.20)	0.59 (0.27, 1.27)	0.80 (0.33, 1.95)
Imputed rates	1.28 (0.94, 1.74)	0.81 (0.52, 1.26)	0.79 (0.43, 1.45)	0.73 (0.36, 1.47)
IPCW	1.28 (0.84, 1.96)	0.69 (0.39, 1.23)	0.58 (0.26, 1.30)	0.77 (0.31, 1.88)

a. Excluding NMSC.
Abbreviations: CI=confidence interval; IPCW=inverse probability censoring weights, MACE=major adverse cardiovascular event, MI=myocardial infarction.

Data suggest that patients with RA have an increased risk of some malignancies (Simon, 2015).[13] Integrated data from the tofacitinib RA clinical program used in this study showed that 168 out of 6,300 subjects developed a malignancy excluding NMSC (IR 0.75 [0.65, 0.87]). This rate was numerically higher than those among bDMARD initiators within the Corrona Registry (0.53 [0.44, 0.64]) but similar to those within the US 5-year prospective PASS for tofacitinib embedded within the Corrona RA Registry (A3921205; 0.88 [0.58, 1.27]).

CV disease is the most common cause of death in RA patients (Young, 2007),[14] and it occurs more frequently in patients with RA versus the general population (Aviña-Zubieta, 2012).[15] In this analysis, data from the tofacitinib RA clinical program showed IRs for MACE of 0.38 (0.30, 0.48). Rates reported within the US PASS for tofacitinib (A3921205) among tofacitinib initiators (IR 0.64 [0.39, 1.00]), primarily prescribed 5 mg BID, were numerically higher than rates reported in the clinical program, which included patients prescribed 5 mg BID and other doses including a substantial proportion taking 10 mg BID. Tofacitinib and bDMARD initiators had a similar incidence of MACE in this study.

11.2. Limitations

This project sought to compare the tofacitinib clinical trial population with similar patients enrolled in the Corrona registry and initiating bDMARDs. Given the differences in the source populations, multivariable adjustment and matching were employed for comparative purposes. However, covariate adjustment and patient matching in the cohorts was possible only using covariates measurable in both databases. Unmeasured factors in one or both of

the cohorts may not have been balanced even after balancing measured factors, 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 were well defined and adjudicated by relevant specialists.

For some of the sub-cohort analyses (eg, by tofacitinib dose group or restricted to U.S. clinical trial sites), the sample sizes are more limited and power is much smaller than the primary cohort analyses

Strengths and Limitations of the Sensitivity Analyses

The first 2 sensitivity analyses utilized different methodologies to adjust for differences in follow-up time. Consistency in output would suggest evidence of robustness of the results. However, any differences noted would indicate that our assumptions must be examined in detail. This would make the third method (tipping point imputation analysis) of greater importance as it permits some understanding of the sensitivity due to differences in informative censoring or event reporting. The analysis provides the magnitude of the impact of these potential differences on the clinical differences estimated.

The first method provides imputation of censored time with rates of events associated with measured covariates. If rates of events are similar over time, and there are no unmeasured covariates associated with events, this will provide unbiased estimates.

The second method is a weighting methodology that weights patients with uncensored time who are “like’ the censored patients. If the measured covariates provide an appropriate score of similarity, then the weighting adjusts for differences due to informative censoring in a manner similar to using propensity scores. If there are unmeasured covariates that are important to the differences the third method provides a measure of how large or small of an effect is needed to impact the conclusions.

These adjusted models have similar strengths and weaknesses as an adjusted model – if the assumptions and models are correct, they provide best estimates of effects.

11.3. Interpretation

Overall, the results of this study are consistent with the known safety profile of tofacitinib. MACE and MI have been determined to be new important potential risks, and the core labelling document (core data sheet) is being updated accordingly, based on final data from a Phase 3b/4 study not included in the P123LTE data (March 2021 Follow up to ESI Notification for A3921133, Sections 2.1.10 and 2.10).[16] Malignancies (excluding NMSC), are an important potential risk in the core labelling document.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

In conclusion, these results provide evidence that the rates of MACE, nonfatal MI and nonfatal stroke are comparable in patients with RA who received tofacitinib in the multi-country clinical trial setting versus similar bDMARD initiators in a large U.S. patient population participating in a non-interventional study. While there was some variability in estimated HR across the models, patients receiving tofacitinib in the clinical trial setting had a higher rate of malignancies (excluding NMSC) than similar bDMARD initiators in a large US patient population participating in a non-interventional study.

14. REFERENCES

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005;4(3):130-6.

2. Curtis JR, Patkar NM, Jain A, et al. The validity of physician-reported hospitalized infections in an observational U.S. arthritis registry. Rheumatology (Oxford) 2009 October; 48(10):1269-72.

3. Fisher MC, Furer V, Hochberg MC, et al. Malignancy validation in a United States registry of rheumatoid arthritis patients. BMC Musculoskelet Disord 2012;13:85.

4. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007; 7(6):429-42.

5. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011; 365(23):2205-19.

6. Meyer DM, Jesson MI, Li XO, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm 2010; 7:41.

7. Solomon DH, Kremer J, Curtis JR, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010; 69(11): 1920-5.

8. Walker JG, and Smith MD. The Jak-STAT pathway in rheumatoid arthritis. J Rheumatol, 2005;32(9):1650-3.

9. Hintze, J. (2015). PASS 14. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

10. US Food and Drug Administration. Framework for FDA's Real-World Evidence Program, 2018. Available from https://www.fda.gov/media/120060/download. Accessed 20Nov2020.

11. Patorno E, Schneeweiss S, Gopalakrishnan C, et al. Using Real-World Data to Predict Findings of an Ongoing Phase IV Cardiovascular Outcome Trial: Cardiovascular Safety of Linagliptin Versus Glimepiride. Diabetes Care, 2019; 42(12): 2204-2210.

12. Kothare S, Kluger G, Sachdeo R, et al. Dosing considerations for rufinamide in patients with Lennox-Gastaut syndrome: Phase III trial results and real-world clinical data. Seizure, 2017: 35-33.

13. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther, 2015; 17(1): 212.

14. Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology, 2007; 46(2): 350-357.

15. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, et al., Risk of Cardiovascular Mortality in Patients with Rheumatoid Arthritis: A Meta-Analysis of Observational Studies. Arthritis & Rheumatism, 2008; 59 (12): 1690-1697.

16. Pfizer Inc. March 2021 Follow-up to ESI Notification for Tofacitinib RA Study A3921133. Available upon request.

15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable.

Document Approval Record

Document Name:	CT24-WI-GL15-RF02 2.0 NI Study Report 09 March 2021
Document Title:	A3921204

Signed By:	Date(GMT)	Signing Capacity
Campbell, Ulka	31-Mar-2021 02:20:57	Final Approval
De Bernardi, Barbara	08-Apr-2021 17:34:34	EUQPPV Approval