Study information

Title	A Prospective Observational Study within the Corrona International Registry to Evaluate Safety and Effectiveness of Tofacitinib and Biologic Disease Modifying Antirheumatic Drugs in Japan among Patients Treated for Moderately to Severely Active Rheumatoid Arthritis
Protocol number	A3921256
Protocol version identifier	1.0
Date of last version of protocol	N/A
EU Post Authorisation Study (PAS) register number	Study not registered
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	The primary objectives of this study are to characterize patients prescribed tofacitinib, bDMARDs, or csDMARDs and to evaluate safety endpoints associated with these therapies within the Japanese clinical practice setting via: 1. The evaluation of baseline characteristics among tofacitinib exposed patients and comparator populations; 2. The evaluation and comparison of incidence rates of selected adverse events of interest (Appendix 1) among tofacitinib users versus comparator populations receiving bDMARDs (alone or in combination with non-biologic DMARD therapies) or conventional synthetic

	DMARDs (csDMARDs), with no prior exposure to tofacitinib. Secondary objectives of the study include evaluation of real-world clinical outcomes associated with tofacitinib and DMARD use, including, but not limited to: 1. Evaluation of rates of low disease activity state (LDAS) and remission among patients via pre-determined measures (Section 8.4.2.2) 2. Evaluation of patient-reported outcomes including Pain VAS, functional status (Health Assessment Questionnaire-DI), work productivity (WPAI), Healthcare Resource Utilization (HCRU) and EQ-5D
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American Colleague of Rheumatology
AE	Adverse Event
CABG	Coronary Artery Bypass Graft
CDAI	Clinical Disease Activity Index
CHF	Congestive Heart Failure
Corrona	Consortium of Rheumatology Researchers of North America
CNS	Central Nervous System
CRP	C-Reactive Protein
CV	Cardiovascular
DAS-28	Disease Activity Score-28
DMARD bDMARD csDMARD nbDMARD	Disease Modifying Anti-Rheumatic Drugs Biologic Disease Modifying Anti-Rheumatic Drugs Conventional Synthetic Disease Modifying Anti- Rheumatic Drugs Non-Biologic Disease Modifying Anti-Rheumatic Drugs
DMOC	Data Monitoring and Oversight Committee
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
EQ5D	EuroQol 5D
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
GI	Gastrointestinal

HAQ-DI	Health Assessment Questionnaire- Disability Index
ICF	Informed Consent Forms
IEC	International Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
JAK	Janus Kinase
LDAS	Low Disease Activity State
MACE	Major Adverse Cardiovascular Event
MD	Medical Doctor
MI	Myocardial Infarction
MTX	Methotrexate
NC	North Carolina
PASS	Post-Authorization Safety Study
PML	Progressive Multifocal Leukoencephalopathy
PPV	Positive Predictive Value
PSUR	Periodic Safety Update Report
RA	Rheumatoid Arthritis
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIAC	Site Investigator Advisory Committee
SOP	Standardized Operating Procedure
TAE	Targeted Adverse Event
TNFi	Tumor Necrosis Factor Inhibitor

US	United States
VAS	Visual Analogue Scale
WPAI	Work Productivity and Activity Impairment

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases. Corrona currently maintains a proprietary database of information concerning rheumatoid diseases from clinics in the United States (all elements of the database and its contents are referred to herein, individually and collectively, as the "Corrona US RA Registry"). Corrona populates the Corrona US RA Registry with information about patients diagnosed with rheumatoid arthritis and related conditions, who participate in the data collection program initiated by Corrona. The Corrona US RA Registry is used by Pfizer for research concerning the nature, treatment and prevention of rheumatic diseases.

Corrona plans to develop a similar registry and database in Japan ("Corrona Japan Database") that will permit the study of a range of safety outcomes, including infections, malignancies and cardiovascular events, other safety outcomes, and physician- and patient-reported effectiveness outcomes in comparison with comparator populations in Japanese populations where clinical practice and patient characteristics differ from North America.

The Corrona Japan RA Registry has a target enrollment of approximately 2,000 subjects who are being prescribed for the first-time ever a medication for RA from one of four drug classes: Methotrexate (any dose), anti-TNF inhibitors (adalimumab, etanercept, infliximab, infliximab biosimilar, golimumab, certolizumab pegol, and novel biosimilar introduced during the study period), non-TNF biologic DMARDs (abatacept, tocilizumab), and JAK inhibitors (tofacitinib).

If during follow-up a subject stops treatment with the eligible medication prescribed at enrollment, that subject should still be followed long-term in the registry.

This study will recruit patients from approximately 40 clinical sites from a broad geographic distribution in Japan. Enrollment will consist of four (4) cohorts of 500 patients each segmented by drug class. There are no enrollment restrictions other than initiation of an eligible medication at the time of enrollment. Each cohort will be open to recruiting at registry initiation and will close when the patient cap of 500 patients is reached. Investigators may recruit patients into any drug cohort in any order until the study cap is reached. The study design is open so that additional cohorts may be added as new drugs are approved and additional patients may be added to existing cohorts to maintain comparison cohorts.

Corrona will report to Pfizer agreed upon information from the Corrona Japan Database that characterize Japanese patients prescribed tofacitinib or biologic disease modifying anti-rheumatic drugs (bDMARDs), and to evaluate safety endpoints associated with these therapies within the Japanese clinical practice setting in line with the following objectives:

1. The evaluation and comparison of baseline characteristics among tofacitinib exposed patients and comparator populations;

2. The evaluation and comparison of incidence rates of selected adverse events of interest captured on the questionnaires among tofacitinib users versus comparator populations receiving bDMARDs (alone or in combination with csDMARD therapies) with no prior exposure to tofacitinib. The safety reporting is summarized in Appendix 1- Table 2

Corrona will also report to Pfizer on a quarterly basis (Appendix 1- Table 1) agreed upon information from the Corrona Japan Database to evaluate real-world clinical outcomes associated with tofacitinib and DMARD use, including, but not limited to:

1. The evaluation of rates and duration of low disease activity state (LDAS) and remission among incident users (new drug starts) via DAS28 and CDAI;

2. The evaluation of patient-reported outcomes including Pain VAS, Global VAS, functional status (Health Assessment Questionnaire-DI), work productivity (WPAI) and health care resource utilization.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestones	Planned date
Protocol Finalization	February 1, 2016
First Patient in	February 2016
Q1 2016 Interim Safety Report*	June 21, 2016
Q1 2016 Interim Registry Report*	July 15, 2016
End of Data Collection	March 21 2020
Final Study Registry Report	June 15, 2020
* Registry and Safety reports will be issued quarterly (on March 15, June 15, Sept 15 and Dec 15) after the initial report cycles.	

6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease characterized by erosive destruction of the joints. While there is considerable variation in the estimates of those affected by RA, the majority of studies from Northern European areas and North America estimate a prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05%.[1] Presentation of RA typically occurs between the ages of 20 to 40 years with a female predominance on the order of 3:1.[2,3]

A recent analysis from a Japanese health insurance dataset reported that the estimated prevalence of RA ranged from 706,000 to 1.2 million individuals, representing 0.6% to 1.0 % of the Japanese population.[4] Of note, methotrexate (MTX) was prescribed for approximately one-quarter (27%) of RA patients in this Japanese cohort, in marked contrast with both European and US cohorts with >50% of RA patients treated with MTX.[6,7] These data suggest that treatment patterns are markedly different in Japan versus those in North America and Europe highlighting the need for real-world disease-based registers to capture treatment patterns and corresponding effectiveness and safety data. [4,8] The Japanese College of Rheumatology (JCR) puts forth guidelines for the treatment of RA in Japanese patients, including specific recommendations for TNF biologics and tofacitinib which may differ or provide greater guidance, than the product label.[5] Real-world observational data can provide further evidence regarding comparative effectiveness and safety contextualized to a given

country, where background RA treatments (e.g. methotrexate) may vary, as well as patient comorbidities.

This protocol outlines the operational and clinical aspects of a disease-based registry in Japan to evaluate the effectiveness and safety of tofacitinib within the Japanese clinical practice setting through a subscription to the Corrona Japan registry data reports. The subscription will permit evaluation of comparative effectiveness and safety endpoints. The Corrona Japan registry queries will identify patients treated with tofacitinib or bDMARDs for comparative effectiveness and safety outcomes, as well as allow pooling of results from patients treated with tofacitinib and bDMARDs in the Corrona United States (US) registry with a parallel data structure and study design. This protocol outlines the analysis to be conducted upon 2000 patients in 4 drug treatment arms (methotrexate, TNF, Non-TNF biologics and JAK inhibitors).

This non-interventional study is considered a voluntary Post-Authorisation Safety Study (PASS).

7. RESEARCH QUESTION AND OBJECTIVES

The primary objectives of this study are to characterize patients prescribed tofacitinib, TNF bDMARDs, non-TNF bDMARDS or methotrexate (MTX) and to evaluate safety endpoints associated with these therapies within the Japanese clinical practice setting via:

1. The evaluation of baseline characteristics among tofacitinib exposed patients and comparator populations;

2. The evaluation and comparison of incidence rates of selected adverse events of interest (Appendix 1) among tofacitinib users versus comparator populations receiving bDMARDs (alone or in combination with non-biologic DMARD therapies) or MTX, with no prior exposure to tofacitinib.

Secondary objectives of the study include evaluation of real-world clinical effectiveness associated with tofacitinib and DMARD use, including, but not limited to:

1. The evaluation of rates of low disease activity state (LDAS) and remission among patients via DAS28 and CDAI (Section 8.4.2.2).

2. The evaluation of patient-reported outcomes including Pain visual analogue scale (VAS), functional status (Health Assessment Questionnaire-DI [HAQ-DI]) and work productivity (WPAI), Eurol-Quol-5D (EQ5D) and a Healthcare Resource Utilization (HCRU) Questionnaire.

8. RESEARCH METHODS

8.1. Study design

This is an observational study in a cohort of RA patients treated with biologic and nonbiologic DMARDs, including tofacitinib, collected as part of the Corrona Japan registry

in a prospective manner. Corrona captures patient enrollment and follow-up data as a part of routine medical practice; therapeutic strategies are not determined by this protocol. Enrollment is voluntary and eligibility is based on RA drug use at the time of enrollment, but duration of therapy and subsequent therapies, if any, are not mandated by Corrona guidelines or by this protocol.

8.2. Setting

The Corrona RA Registry was founded in 2000 as an independent registry run by a group of experienced academic and clinical rheumatologists throughout the United States (US). Data on patients with RA reported by their rheumatologists and the patients themselves are collected at the clinical point of care.

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases. Corrona currently maintains a proprietary database of information concerning rheumatoid diseases from clinics in the United States (all elements of the database and its contents are referred to herein, individually and collectively, as the "Corrona US RA Registry"). Corrona populates the Corrona US RA Registry with information about patients diagnosed with rheumatoid arthritis and related conditions, who participate in the data collection program initiated by Corrona. The Corrona US RA Registry is used by Pfizer for research concerning the nature, treatment and prevention of rheumatic diseases.

Corrona plans to develop a similar registry and database in Japan ("Corrona Japan Database") that will permit the study of a range of safety outcomes, including infections, malignancies and cardiovascular events, other safety outcomes, and physician- and patient-reported effectiveness outcomes in comparison with comparator populations in Japanese populations where clinical practice and patient characteristics differ from North America

The Corrona Japan RA Registry has a target enrollment of approximately 2,000 subjects who are being prescribed for the first-time ever a medication for RA from one of the four drug classes listed in Table 1. *To be eligible for the registry a patient must be initiating one of the following Eligible Medications at the Enrollment Visit:*

8.3. *Table 1. Eligible Medications Grouped by Drug Class*

Drug Class	***Eligible Medications***
Conventional synthetic DMARDs	methotrexate (any dose)
JAK inhibitors	tofacitinib
Anti-TNF biologic DMARDs	adalimumab certolizumab pegol etanercept golimumab infliximab (originator or biosimilar) any other anti-TNF biosimilar approved during the study period
Non-TNF biologic DMARDs	abatacept tocilizumab

If during follow-up a subject stops treatment with the eligible medication prescribed at enrollment, that subject should still be followed long-term in the registry.

This study will recruit patients from approximately 40 clinical sites from a broad geographic distribution in Japan. Enrollment will consist of four (4) cohorts of 500 patients each segmented by drug class. There are no enrollment restrictions other than initiation of an eligible medication at the time of enrollment. Each cohort will be open to recruiting at registry initiation and will close when the patient cap of 500 patients is reached. Investigators may recruit patients into any drug cohort in any order until the study cap is reached. The study design is open so that additional cohorts may be added as new drugs are approved and additional patients may be added to existing cohorts to maintain comparison cohorts.

8.3.1. Inclusion criteria

To be eligible for enrollment into the Corrona Japan RA Registry, a subject must satisfy all of the following Inclusion Criteria:

1) The subject must be diagnosed with rheumatoid arthritis according to the 1987 ACR[i] or the ACR/EULAR 2010 Rheumatoid Arthritis Classification Criteria[ii]

2) The subject must be at least 18 years of age or older (age ≥ 18 years)

3) The subject must be able and willing to provide written consent

4) The subject must be prescribed or switching to an *eligible medication* (Table 1) for the first time ever at the Enrollment Visit. History of or concomitant treatment with other *eligible medications* does not exclude a subject from enrollment.

8.3.2. Exclusion criteria

There are no exclusion criteria for this study.

8.4. Variables

8.4.1. Key Variables

Table 1. List of Variables and Definitions (non-exhaustive)

Variable	Role	Data source(s)	Operational definition
Xeljanz (tofacitinib)	Exposure	Physician Questionnaire	Current use at time of visit or newly prescribed
bDMARD	Exposure	Physician Questionnaire	Current use at time of visit or newly prescribed
nbDMARD	Exposure	Physician Questionnaire	Current use at time of visit or newly prescribed
Concomitant Therapies NSAID and steroids)	Exposure	Physician Questionnaire	Current use
Total serious infections[a]	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Pneumonia	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Septicemia	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Bone/Joint infection	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Cellulitis	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Diverticulitis	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Bronchitis	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Gastroenteritis	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Other serious infection	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Opportunistic infection	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Herpes Zoster infection (serious and non-serious)	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
TB	Outcome	Physician Questionnaire	Reported by Physician
Total Nonserious infection	Outcome	Physician Questionnaire	Reported by Physician
Total cardiac disorders	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
MACE[b]	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
CHF (Serious; new or worsening)	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Acute coronary syndrome[c]	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Other cardiac events[d]	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Serious Hypertension events	Outcome	Physician Questionnaire	Reported by Physician
CNS Disorders	Outcome	Physician Questionnaire	Reported by Physician
Demyelination	Outcome	Physician Questionnaire	Reported by Physician
TIA	Outcome	Physician Questionnaire and TAE Form	Reported by Physician

Variable	Role	Data source(s)	Operational definition
Stroke	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
PML	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Total hepatic events (serious)	Outcome	Physician Questionnaire	Reported by Physician
GI perforation	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Serious hemorrhage	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Total malignant events	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
All Malignancies excluding NMSC	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Lymphoma	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Lung cancer	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Breast cancer	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Skin cancers NMSC	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Skin cancers: Melanoma	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Other cancer	Outcome	Physician Questionnaire and TAE Form	Reported by Physician
Fracture	Outcome	Physician Questionnaire	Reported by Physician
Death	Outcome	Physician Questionnaire and TAE and Exit Forms	Reported by Physician
Pregnancy[e]	Outcome	Patient Questionnaire	Reported by Patient
Years since diagnosis	Baseline Characteristic	Physician Questionnaire	Reported by Physician
Age	Baseline Characteristic	Patient Questionnaire	Completed by Patient
Sex	Baseline Characteristic	Patient Questionnaire	Completed by Patient
Race	Baseline Characteristic	Patient Questionnaire	Completed by Patient
Ethnicity	Baseline Characteristic	Patient Questionnaire	Completed by Patient
HAQ-DI	Baseline Characteristic/Outcome	Patient Questionnaire	Completed by Patient
CDAI	Baseline Characteristic/Outcome	Physician and Patient Questionnaire	Calculated variable
DAS28-ESR	Baseline Characteristic/Outcome	Physician and Patient Questionnaire	Calculated variable
Tender Joint Count	Baseline Characteristic/Outcome	Physician Questionnaire	Reported by Physician
Swollen Joint Count	Baseline Characteristic/Outcome	Physician Questionnaire	Reported by Physician
ESR	Baseline Characteristic/Outcome	Lab Form	Lab data
CRP	Baseline Characteristic/Outcome	Lab Form	Lab data
MD Global	Baseline Characteristic/Outcome	Physician Questionnaire	Reported by Physician
WPAI	Outcome	Patient Questionnaire	Completed by Patient
Abbrev.: bDMARD, biologic disease modifying antirheumatic drug; CDAI, clinical disease activity index; CHF, congestive heart failure; CNS, central nervous system; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HAQ-			

Variable	Role	Data source(s)	Operational definition
DI, health assessment questionnaire disability index; MACE, major adverse cardiovascular event; MD, medical doctor; nbDMARD, non-biologic disease modifying antirheumatic drug; NMSC, non-melanoma skin cancer; NSAIDS, non-steroidal anti-inflammatory drugs; TB, tuberculosis; TIA, transient ischemic attack; PML, progressive multifocal leukoencephalopathy; WPAI, work productivity and activity impairment [a] Serious defined as infections requiring hospitalization or use of parenteral antibiotics. [b] Major Adverse Cardiovascular Event including: Nonfatal events from the physician follow-up form of myocardial infarction (MI), Stroke and Transient Ischemic Attack (TIA) in addition to Cardiovascular-related deaths from the Exit form of MI, Congestive Heart Failure, arrhythmia, sudden cardiac death, Pulmonary Embolism, stroke/cerebrovascular accident, and other CV-related deaths. [c] Acute Coronary Syndrome included MI and unstable angina. [d] Other cardiac events: CAD procedure, revascularization procedure, ventricular arrhythmia, cardiac arrest. [e] Corrona questionnaires currently do not record pregnancy outcome measures.			

8.4.2. Effectiveness and Safety Endpoint Reporting Measures and Procedures

8.4.2.1. Effectiveness Endpoint Measures

Corrona will capture all core elements of the ACR and EULAR response criteria as required fields involving physician or patient response. Composite indices of disease activity and response can be calculated from Corrona data. Directly calculated disease measures include the Clinical Disease Activity Index (CDAI), validated by Aletaha and Smolen, which includes joint counts, but does not require an acute phase reactant.[9] Collection of acute phase reactants are not required as a condition of Corrona registry participation, although there are data elements that capture the tests, if performed. Corrona captures standard of care, which may not involve a given lab test at any given visit. Over the past 5 years, Corrona has published using DAS28-ESR, with imputation of ESR if missing.[10] If C-reactive proteins (CRPs) are routinely captured, Corrona can also calculate DAS-28-CRP composite disease activity scores.

In addition to standard ACR and EULAR disease activity and response criteria that include the Health Assessment Questionnaire Disability Index (HAQ-DI), additional patient instruments have been proposed to capture additional domains of particular interest. These additional domains are: 1) work productivity using the Work Productivity and Activity Impairment (WPAI) Questionnaire; 2) EQ5D and 3) the Healthcare Resource Utilization questionnaire (HCRU)

WPAI: The WPAI Questionnaire has been utilized in other Corrona registries and is designed to collect data on health-related work productivity. The WPAI consists of six questions with a one-week recall period, and captures employment status, hours of work missed due to the health problem and hours missed due to other reasons, hours worked, and the effect of the health problem on productivity for work and for non-work activities. The four main outcomes generated are absenteeism, presenteeism, work productivity loss, and activity impairment. The WPAI has been validated in RA by Pfizer researchers.[11] The WPAI has been previously validated in Japan and translated into Japanese.

EQ5D: The EQ-5D-5L is a validated health outcomes instrument that generates a simple descriptive profile on 5 domains of health. The domains are rated on 5 levels, and the

instrument is composed of both a short, cognitively simple questionnaire and a VAS scale. It has been translated and validated in Japanese.

HCRU: This is a 6 item survey asking patients to recall their health care utilization over the last 6 months. This consists of a range of questions on the number of times the patient had to visit physician specialists, go to the emergency room, hospitalizations, or procedures related to the arthritis disease. It has been translated in Japanese and used in previous tofacitinib Phase 3 trials.

8.4.2.2. Effectiveness Endpoint Procedure

Corrona will capture all core elements of the ACR and EULAR response criteria as required elements in the registry visit protocol, with the exception of acute phase reactants, at the discretion of the treating rheumatologist. In addition, patient-reported outcomes (PROs) will be collected using patient questionnaires as described within this analytic protocol as well as health economic information in the forms of the WPAI and HCRU questionnaires. Using the elements of the ACR and EULAR response criteria that are collected at each registry visit, achievement of disease activity states (e.g. low disease or remission using disease activity scores such as the DAS28-ESR and CDAI) will be determined. Similarly, impact of treatment on PROs and health economics will be determined based on responses on patient questionnaire. Corrona has published on comparative effectiveness of biologic drugs using these endpoints. [12,13]

8.4.2.3. Safety Endpoint Measures

A detailed list of the adverse events of interest available from the Corrona Japan RA registry is summarized in Appendix 1, Table 2. These adverse events have been reported as part of the US RA registry. Additionally, herpes zoster and other opportunistic infections, even limited data that will be available for outpatient opportunistic infections, will be collected by investigators and reported. For all confirmed reports of Targeted Adverse Events (TAEs) that lead to hospitalization (e.g. serious infections that are hospitalized or requiring IV antibiotics), the study will require a separate TAE Questionnaire to be completed with additional information, and sites are required to make efforts to obtain supporting source documentation for case validation and/or adjudication.

8.4.2.4. Safety Endpoint Procedures

Corrona has established an endpoint reporting system used in other post-approval studies.[14,15,16] that identifies and captures endpoint data in an efficient and reliable manner. The system requires rheumatologists to complete TAE forms for events identified in Table 3. For events confirmed by the rheumatologist, source documentation appropriate to the type of event (e.g. pathology reports when the TAE is a cancer) are collected by the site. Events confirmed against source documents (i.e., medical records) are validated via clinical review and/or adjudicated by specialists blinded to therapy (e.g. cardiologists adjudicate cardiovascular events) to confirm the event occurred, the date of the event, and the specific type of event (See Figure 1). Event reports from Japan will be translated, validated via

clinical review and adjudicated by the global Corrona adjudication process, as applicable (based on type of event and other factors).

Corrona will incorporate and adapt the criteria used by Pfizer adjudication committees for malignancy, opportunistic infections and CV events. Final criteria for Corrona adjudication will be shared with Pfizer to ensure harmonization with previous studies.

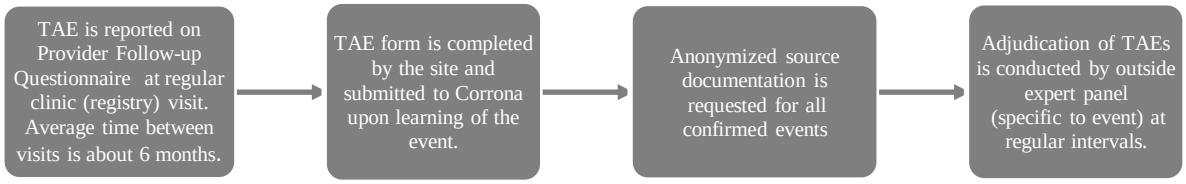
Table 3. Safety Outcomes within the Corrona Registry Identified ("Flagged") on Physician Follow-Up Forms for Targeted Adverse Event Form Completion

Flagged Event	Targeted Adverse Event Report Type
Serious Hypertension event Cardiac revascularization procedure (CABG, stent, angioplasty) Ventricular arrhythmia Cardiac arrest Myocardial Infarction Acute Coronary Syndrome Unstable angina Congestive Heart Failure (serious) 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
Serious Hemorrhage	Serious Bleeding events
Lymphoma Lung cancer Breast cancer Skin cancer (melanoma) Skin cancer (basal/squamous cell) Other cancer ***(specify)*** Solid tumor ***(specify type of tumor)***	Cancer, Malignancy
Serious infection (serious and/or requiring outpatient treatment with IV antibiotics)	Infection
Herpes Zoster (serious or non-serious)	Herpes Zoster
GI perforation	GI Perforation
Hepatic event (serious)	Hepatic
PML Other neurological disorder (serious) Demyelinating disease	Neurologic
Drug-induced hypersensitivity reaction (anaphylaxis or severe hypersensitivity)	Anaphylaxis or Severe Reaction
Other serious medical diagnosis or event ***(specify)***	General Serious Event*

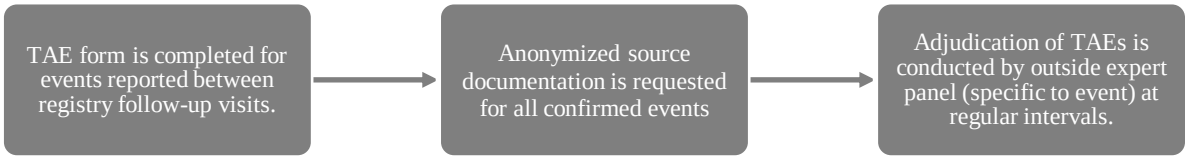
Abbrev.: CABG, coronary artery bypass graft; CHF, congestive heart failure; GI, gastrointestinal; IV, intravenous; PML, progressive multifocal leukoencephalopathy
* Events not meeting case definition for a more specific TAE type, resulting in any of the following: hospitalization, prolonged hospitalization, death, significant disability or incapacity, congenital anomaly/birth defect or otherwise medically important in the opinion of the investigator.)

Figure 1. Corrona Safety Endpoint Reporting Procedure

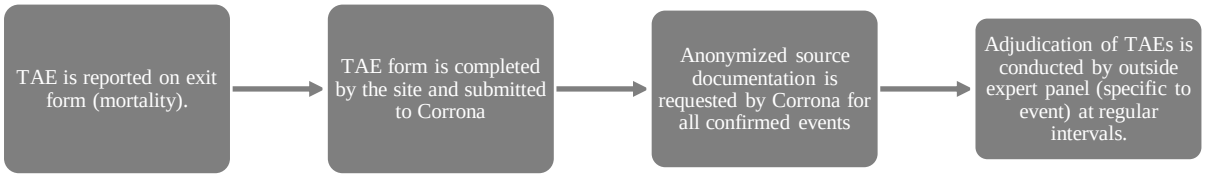
Targeted Adverse Events (TAEs) are most commonly reporting during a registry visit.



TAEs may also be reported in between registry visits.



A TAE may be reported on an exit form when the reason for exit is death.



Quarterly reporting will be performed for baseline characteristics of enrolled patients, as well as requested effectiveness, safety and effectiveness measures. Pre-specified safety endpoints will be reported as follows:

- For the quarterly reports, the following events will be included:
  - MD reported events confirmed by TAE forms
  - MD reported events for which TAE forms have not yet been completed

TAE events reported on the TAE form independent of any report on the MD questionnaire or those reported in connection with a Subject Exit (due to death) Safety endpoints will be reported for analysis (see Appendix 1)

- Primary analysis
  - MD reported events confirmed by TAE forms, TAE events reported on the TAE form independent of any report on the MD questionnaire, and TAEs reported in association with Subject Exit from the registry due to death.
- Secondary analyses including
  - All study endpoints noted by physician report only;
  - Fully adjudicated endpoints using available source documentation.

8.4.3. Endpoint validation

In the US registry, Corrona has examined the level of validity of malignancies, cardiovascular events and hospitalized infections within the registry by using two physician adjudication of medical records as the gold standard

- Malignancies

  Fisher and colleagues examined the accuracy of physician reported malignancies as compared with medical record review within the US Corrona registry.[17] For all incident malignancies reported from October 2001 to December 2007, the authors requested the completion of a TAE form to gather additional information as well as primary source documents for adjudication. (Note: Corrona established a prospective request for source documentation for malignancies in 2008.) Each malignancy was classified as definite, probable, possible, or not a malignancy.

  A total of 461 incident malignancies from 20,837 patients with RA were reported on physician questionnaires. After adjudication, 234 were defined as definite, 69 probable, 101 possible, and 57 as not an incident malignancy. The positive predictive value (PPV) of physician report versus "definite or probable" malignancy was 0.66 (95% CI: 0.61-0.70). The PPV was 0.68 (95% CI: 0.63-0.72) when the TAE form confirmed the presence of malignancy. When "possible" malignancies were included, the PPV increased to 0.86 (95% CI: 0.83-0.89) and 0.89 (95% CI: 0.85-0.91) with the inclusion of the TAE form.

- Cardiovascular Events

  The validity of rheumatologist-confirmed cardiovascular (CV) events within the Corrona registry (including MI, stroke or TIA) was assessed by Solomon and colleagues (Solomon, 2010). An adjudication committee reviewed cases reported by participating rheumatologists for which hospitalization records were available (56%, n=42). Events were classified into categories of definite, probable, possible and unlikely CV events. The PPV for confirmed cases (e.g. definite or probable) where hospitalization records were available was 96%.

- Hospitalized Infections

  Curtis and colleagues evaluated rheumatologist reports of hospitalized infections within the Corrona registry to establish their validity.[18] Using registry data collected between March 2002 and December 2007, the authors extracted 562 physician-reported events; 9% were classified as unlikely, leaving 509 hospitalized infectious episodes for evaluation.

  Of the 509 infectious episodes assessed, 53% of the episodes were classified as confirmed, 15% empirically treated (e.g. there was evidence that the physician was treating an infection but definitive data including positive cultures were not identified) and 32% possible. A total of 606 unique infections were identified during

the 509 hospitalized episodes; approximately 71% of the unique infections were classified as confirmed or empirically treated.

These validation studies will be replicated in the Japan registry, using a parallel process. The procedure for confirming Targeted Adverse Events in the Japanese cohort will be the same as for the US cohort. Provisions will be made for translation of source documents to English when necessary.

8.5. Risk Windows for Endpoints of Interest

Incidence rates will be based on two different definitions of the risk window, depending on the outcome of interest:

(1) For all targeted adverse events except malignancy and death, the risk window will begin with the start of the index therapy and continue until the visit closest to 90 days after the end of therapy or end of data collection, whichever comes first. TAEs which occur beyond this risk window will not be counted for purposes of incidence rate estimation. However, in instances when a patient starts a second agent (i.e., bDMARD) within the visit closest to 90 days after discontinuing a first one, the risk windows will overlap and the TAE will be attributed to both agents.

(2) For analyses of risk for malignancies and death, the risk window for any therapy will include all person-time in the designated time period (since starting therapy) and extend until the end of data collection, even in the case of subsequent switching to another agent. When a malignancy is diagnosed after a second agent has been begun, the event will be attributed to both agents in the incidence rate estimations. Cause of death will be reported where possible.

Note: At the conclusion of the study period, incidence rates will be recalculated with complete data, and will reflect appropriate risk windows for the TAEs of interest. Cancer incidence rates will also be calculated to reflect the experience of patients who have and have not switched therapies.

8.6. Data Sources

8.6.1. Corrona Data Collection Program Questionnaires

The Corrona Japan subscription includes data captured using Corrona data collection program questionnaires. Physicians and subjects 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 Provider Questionnaires with recording of pertinent data. Results from certain laboratory tests are included (where collected as part of standard of care), but laboratory testing is not mandated, as part of the registry protocol. Subjects 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 subjects will spend approximately five to ten minutes completing the questionnaires. Neither the questionnaires completed by physicians nor the questionnaires completed by subjects contain subject's names, addresses, telephone numbers or email addresses. To prevent duplicate counting of safety events reported in both the Japanese Post Marketing Surveillance (PMS) study and this protocol, patients recruited into this study will be requested to provide their PMS study number

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 subjects. Subjects also complete a Corrona Data Collection Program Enrollment Questionnaire along with\the HAQ-DI, and other Patient-Reported Outcome instruments that are part of the final set of questionnaires.

After the enrollment visit, patients with RA then complete Corrona Data Collection Program Follow-up Questionnaires during regularly scheduled clinical encounters approximately every six months. Follow-up questionnaires are also completed at the time of a new therapy start or therapy switch.

Data are collected on subjects for as long as they consent to remain in the study.

8.6.2. Subject Study Exit

In the event of a subject death, withdrawal from the study, loss to follow-up (defined as no study visits have occurred in the previous 15 months), or any other reason for non-participation (e.g., site withdrawal from participation), the Subject Exit Questionnaire is to be completed and submitted according to the submission procedures provided to the site by the Corrona Organization. In cases of death, corresponding TAE questionnaires are also to be submitted along with Subject Exit Questionnaires.

8.6.3. Targeted Adverse Event (TAE) Questionnaires

Adverse events of special interest which occur during participation in the Data Collection program are reported on the Targeted Adverse Event (TAE) Questionnaires. TAE Questionnaires are completed and submitted when a flagged event on a Corrona Data Collection Program Provider Follow-up Questionnaire has been selected. Sites are required to make efforts to obtain de-identified source documents (i.e. hospital records, laboratory results, etc.) in support of the reported TAE for purposes of event validation. The TAE should be reported to Corrona via TAE Questionnaire as soon as possible following site notification that a reportable event has occurred, and should be recorded on the Provider Follow-up Questionnaire at the time of the next scheduled registry Follow-up visit.

8.7. Study size

The study will include 4 arms of 500 patients grouped by drug class at time of enrollment, for a total of 2000 patients, with additional blocks of 500 patients to potentially be added, subject to mutual agreement by Pfizer and Corrona.

8.8. Data management

Statistical analyses conducted by Corona and provided to Pfizer will be performed using STATA 12.1 (StataCorp, LP, College Station, TX). All analyses will be carried out under the direction of Dr. George Reed, PhD, who is Chief Statistical Officer for Corrona, and Professor of Medicine at University of Massachusetts Medical School.

8.9. Data analysis

The primary summary of event rates will be time to first event based on an index date defined for each population. Time to first event or survival analysis allows an analytic framework for estimation, adjustment for possible confounders and comparison between treatment groups. This approach also allows for variable amount of follow-up and does not assume a constant risk over time. Within this framework, the total number of years of patient follow-up will be computed by total time up to an event or up to last follow-up as well as the total number of events (or in survival terminology, failures). The number of events (failures) divided by total person-years of follow-up will result in the event rate. Rates will be expressed as events/100 person-years of follow-up. Raw event numbers will also be reported to Pfizer.

Quarterly reports will be produced beginning in Quarter 2 (Q2) of 2016. Initially, reports will provide rates of the endpoints (section 8.4.2) by selected drug groups covering time from first reported tofacitinib use to the present time. Each report will provide cumulative rates from to the data cut used for each report. Reports will be for internal use. For details on safety reporting see section 10.

As additional patient follow-up time accumulates so that sufficient person-time is available, additional subgroups may be defined and included in the report including:

- Age and gender standardized rates
- Subgroups based on disease severity, concomitant medications, and prior comorbidity status
- Should significant differences in baseline characteristics be observed, additional statistical methodologies to account for these differences may be applied and will be detailed in a formal statistical analysis plan (SAP) for corresponding Ad Hoc analyses. These methodologies may range from various uses of propensity scores (matching or weighting) to multivariable analysis to test the robustness of the results.

A designated Data Monitoring and Oversight Committee (DMOC) will be created to determine the need for a full analytic comparison of rates using multivariable adjustment and/or propensity matching of patients. The DMOC will be comprised of 3 members: 1) a Rheumatologist familiar with the Corrona registry; 2) a Biostatistician familiar with the Corrona registry; and 3) an Epidemiologist familiar with the Corrona registry. An additional Japanese member familiar with Japanese standard of care and epidemiologic considerations may be added at Corrona's discretion and Pfizer's agreement. No member of the DMOC will

be an employee of either Pfizer or Corrona. The DMOC will receive the periodic report for review of rates of events. The primary comparator group for tofacitinib initiators is patients initiating biologic DMARDs.

Detailed analytic plans will depend, in part, on the sample size at the time of the requested comparison as well as patient characteristics in the populations and the specific events to be compared. When the determination of an analytic comparison of rates is made the specific details of the analytic plan can be documented.

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

8.10. Quality control

The data collected by the Corrona Japan registry are generated in accordance with standard operating procedures to monitor, perform edit and logic checks, and make corrections to the data, as necessary. Specifically, data for each site are reviewed according to a registry Data Review Plan for completeness and internal consistency at regular intervals by Corrona data quality monitors and contracted clinical research associates (CRAs). The CRAs generate monthly query listings for each site that are sent to the sites for response and resolution by the appropriate investigator or designee within 30 calendar days of receipt. The contracted CRAs enter corrected data into the electronic data capture (EDC) system. An audit trail of each correction to the data, the person making the change, and the date of change are logged in the EDC and stored with the data in the Corrona database.

8.11. Corrona Governance and Oversight

Corrona, LLC. is a Delaware State Limited Liability Corporation. Corrona is in compliance with State of Delaware regulations and maintains a formal Board of Directors and Executive Committee that oversee the operations of the company.

Formal Executive Roles include Chief Executive Officer, Chief Operating Officer, Chief Scientific Officer, Chief Medical Officer, Chief Statistical Officer, Chief Information Officer, Senior Vice President and General Counsel. The Board of Directors and Executive Committee must report any financial conflicts to the Corrona Ethics Subcommittee of the Board. Science and publication matters are reviewed by the Scientific Advisory Committee (SAC) and site issues are addressed by the Site Investigator Advisory Committee (SIAC).

Executive Leadership is as follows:

Joel Kremer, MD	Founder and Chief Medical Officer
Jeff Greenberg, MD, MPH	VP, Chief Scientific Officer
Raymond Hill	Executive Chairman of the Board

Corporate Counsel:

Jay Barker, JD	Drinker, Biddle and Reath, LLP
Robyn Shapiro, JD	Drinker, Biddle and Reath, LLP (Bioethics)
Jessica Eisenhaure, JD	Corrona LLC

8.12. Limitations of the research methods

This study is designed to assess the effectiveness and safety of tofacitinib within the clinical practice setting utilizing the Corrona registry, a Japan-based rheumatology registry. Despite the strengths of the registry, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channeling biases, endpoint misclassification, and generalizability are of concern when evaluating event rates.

As a new therapy in the RA treatment armamentarium, it is possible that patients treated with tofacitinib will represent those with the most severe cases of disease, longer disease duration, history of multiple failed RA therapies and physical comorbidities that place patients at risk for adverse events. Imbalances in MTX use between tofacitinib and bDMARD users due to following the JCR guidelines can be accounted for as described in Section 6. Biases resulting from channeling may present as increased rates of adverse events in the early phases of the study. Comparison to internal comparators may illuminate such channeling. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualization. Trend analyses may be conducted to evaluate rates over time.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While Corrona has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, a hybrid reporting system has been adopted to utilize the fullest extent of data available. As highlighted previously, primary analyses will include all confirmed endpoints via a combination of physician report and follow-up TAE forms. Secondary analyses will include reports by physician report only as well as fully adjudicated endpoints using available source documentation. Doing so will provide a range by which to estimate event rates in the study population.

8.13. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

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

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally authorized representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally authorized representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved targeted adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Independent Ethics Committee (IEC)

All investigational sites and the registry protocol are reviewed and approved by the respective governing IEC per standard Japanese procedures for observational, non-interventional research studies.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual.

While preparing the quarterly reports to permit Pfizer's execution of this protocol, Corrona may learn of and is obligated to report to Pfizer adverse events (AE) with explicit attribution to any Pfizer drug that appear in the defined dataset (defined per the patient population and study period specified in the protocol).

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes,

neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the adverse event page of the case report form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For purposes of safety reporting by Corrona 'within 24 hours of awareness' will imply within 24 hours of identification and validation of a reportable safety event from data extracted for inclusion in a scheduled quarterly report. Data collection of some of these scenarios are limited within the context of the observational registry and approved questionnaires but will be reported if Corrona should learn of such events (e.g. occupational exposures, medication errors/misuse/overdose, etc.)

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All Corrona research staff members involved in the review of data for a scheduled quarterly report will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Progress reports will be submitted to the Pfizer on a quarterly, semi-annual and / or annual basis, according to Pfizer preference, and as collaboratively defined in the Report Plan. More comprehensive, pre-specified reports may be requested on a yearly/Ad Hoc basis, as

required. A final study report will be submitted to Pfizer communicating the full study experience.

12. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if Corrona becomes aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, Corrona will inform Pfizer immediately of any urgent safety measures reported to have been taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that Corrona becomes aware of.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Appendix 1. Draft Table Shells

Table 1. Example of RA Clinical Outcomes Currently Captured at Baseline and Follow-up Visits in the Corrona RA International Registry

		Tofacitinib patients			Comparator Population		
		N	Mean	SD	N	Mean	SD
Years since diagnosis	Male						
	Female						
	Total						
HAQ-DI	Male						
	Female						
	Total						
DAS28	Male						
	Female						
	Total						
Tender Joint Count	Male						
	Female						
	Total						
Swollen Joint Count	Male						
	Female						
	Total						
ESR (where available)	Male						
	Female						
	Total						
CRP(where available)	Male						
	Female						
	Total						
MD Global	Male						
	Female						
	Total						

Abbrev: CRP= C-Reactive Protein, DAS= Disease Activity Score, ESR= Erythrocyte sedimentation rate, HAQ=Health Assessment Questionnaire, MD=Medical Doctor, mHAQ=Modified Health Assessment Questionnaire.

Table 2. Example of Adverse Event Reporting Table among Patients Exposed to Therapy of Interest, Overall and Stratified by Sex (Incidence Rates per 100 Person-Years)

	Male				Female				Total			
Events	**N**	**Rate**	**95% CI**		**N**	**Rate**	**95% CI**		**N**	**Rate**	**95% CI**	
Total serious infections[a]												
Pneumonia												
Septicemia												
Bone/Joint infection												
Cellulitis												
Diverticulitis												
Bronchitis												
Gastroenteritis												
Other serious infection												

Opportunistic infection												
Herpes Zoster infection												
TB												
Total nonserious infection												
Total cardiac disorders												
MACE[b]												
CHF (serious)												
Acute coronary syndrome[c]												
TIA												
Stroke												
Other cardiac events[d]												
Serious Hypertension event												
CNS Disorders												
Demyelination												
Progressive multifocal leukoencephalopathy (PML)												
Total hepatic events (serious)												
GI perforation												
Serious hemorrhage												
Total malignant events												
Malignancies excluding NMSC												
Lymphoma												
Lung cancer												
Breast cancer												
Skin cancers: NMSC												
Skin cancers: Melanoma												
other cancer												
Fracture												
Death												
Pregnancy[e]												

[a] Serious defined as infections requiring hospitalization or use of parenteral antibiotics.
[b] Major Adverse Cardiovascular Event including: Nonfatal events from the physician follow-up form of myocardial infarction (MI), Stroke and Transient Ischemic Attack (TIA) in addition to Cardiovascular-related deaths from the Exit form of MI, Congestive Heart Failure, arrhythmia, sudden cardiac death, Pulmonary Embolism, stroke/cerebrovascular accident, and other CV-related deaths.
[c] Acute Coronary Syndrome included MI and unstable angina.
[d] Other cardiac events: CAD procedure, revascularization procedure, ventricular arrhythmia, cardiac arrest.
[e] Neither the US nor the international Corrona questionnaires currently record pregnancy outcome measures.
Abbrev: CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; NMSC, non-melanoma skin cancer; PML, progressive multifocal leukoencephalopathy; TIA, transient ischemic attack.
All TAE events will be adjudicated, and the sample groupings in this report can be reported in various groupings (e.g. separating PML from other demyelinating events).

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