NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	A Descriptive Retrospective Database Study to Evaluate Serious Clinical Manifestations and Outcomes among SARS-CoV-2 Diagnosed Patients with RA, PsA or UC treated with systemic therapies: A Post-Approval Safety Study of Tofacitinib in the Context of the COVID-19 Pandemic
Protocol number	A3921380
Protocol version identifier	3.0
Date	29 August 2023
EU Post Authorization Study (PAS) register number	EUPAS35384
Active substance	L04AA29 Tofacitinib
Medicinal product	Xeljanz (tofacitinib)
Research question and objectives	The research questions addressed by this study are: What proportions of SARS-CoV-2 diagnosed patients have a diagnosis of RA, PsA, or UC (ie, indicated subcohorts) or not (ie, non-indicated subcohort) and what is risk of serious clinical manifestations and outcomes of interest in these subcohorts? Within the indicated subcohorts of SARS-CoV-2 diagnosed patients, what is the proportion treated at baseline with the following systemic therapies: tofacitinib, JAK inhibitors, bDMARD (TNFi and

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	non-TNFi), and csDMARD and what is risk of serious clinical manifestations and outcomes of interest within strata? Primary objectives: Within subcohorts of SARS-CoV-2 diagnosed patients, determine the proportions of patients with a diagnosis of RA, PsA, and UC (indicated subcohorts) and patients without any of these conditions (non-indicated subcohort). For each indicated subcohort and non-indicated subcohort, describe baseline demographic characteristics, treatment history and comorbidities. Within each indicated subcohort and non-indicated subcohort, estimate proportion experiencing serious clinical manifestations and outcomes of interest. Within each indicated subcohort of SARS-CoV-2 diagnosed patients, determine the proportions of patients treated with the following systemic therapies (class) at baseline: tofacitinib, JAK inhibitors, TNFi, non-TNFi and csDMARD (as monotherapy and combination therapy, as applicable). Describe patient characteristics, treatment history and comorbidities within baseline treatment strata. Estimate risk of serious clinical manifestations and outcomes of interest within baseline treatment strata. Determine the proportions of patients that continue baseline treatment after SARS-CoV-2 diagnosis within indicated subcohorts.

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting ernzyme
ACR	American College of Rheumatology
AE	adverse event
AIDS	acquire immunodeficiency syndrome
ARB	angiotensin receptor blockers
ARDS	acute respiratory distress syndrome
bDMARD	biologic disease modifying antirheumatic drug
CDC	Centers for Disease Control
CRF	case report form
CI	confidence interval
CKD	chronic kidney disease
COVID-19	Coronavirus Disease 2019
CPT	current procedural terminology
csDMARD	conventional synthetic disease modifying antirheumatic drugs
CQ	chloroquine
DMARD	disease modifying antirheumatic drugs
DVT	deep vein thrombosis
ECMO	extracorporeal membrane oxygenation
EHR	electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ER	emergency room
EU	European Union
GPP	Guidelines for Good Pharmacoepidemiology Practices
H	high
HCP	healthcare professional
HCPCS	Healthcare Common Procedure Coding System
HCQ	hydroxychloroquine
HIPAA	Health Insurance Portability and Accountability Act
HIV	uman immunodeficiency virus
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification

Abbreviation	Definition
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICU	intensive care unit
IEC	Independent Ethics Committee
IL-6	interleukin-6
ILD	interstitial lung disease
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
JAK	janus kinase
L	low
LEF	leflunomide
M	moderate
MTX	methotrexate
NC	North Carolina
NDC	National Data Center
NSAIDS	non-steroidal anti-inflammatory drugs
PASS	Post-Authorization Safety Study
PE	pulmonary embolism
PsA	psoriatic arthritis
RA	rheumatoid arthritis
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SLE	systemic lupus erythematosus
SSZ	sulfasalazine
tDMARD	traditional disease modifying anti-rheumatic drug
TNFi	tumor necrosis factor inhibitor
UC	ulcerative colitis
US/USA	United States/United States of America
VTE	venous thromboemolism
WHO	World Health Organization
XR	extended release

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

See ANNEX 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	20 July 2021	Title page	Added PASS number	Administrative
		Section 4 Abstract	Deleted as this is a stand alone document	Administrative
		Section 6 Milestones	Updated	Administrative
		Section 9.1 Study Design	Aligned with Milestones	Administrative
		ANNEX 1	Aligned with Abstract	Administrative
2	29 August 2023	Title Page	Updated Author	Administrative
		Section 3. Responsible Parties	Updated Responsible Parties	Administrative
		Section 6. Milestones	Aligned Dates with Study Report	Administrative

6. MILESTONES

Milestone	Planned Date
Registration in the EU PAS register	17 May 2020
Start of data collection	18 May 2020
End of data collection	11 October 2022
Final study report	11 September 2023

7. RATIONALE AND BACKGROUND

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) emerged from China. The World Health Organization (WHO) declared the SARS-CoV-2 outbreak and associated disease (Coronavirus disease 2019 (COVID-19)) a global pandemic in March 2020 (WHO, 2020).[5] Despite public health efforts, the incidence of COVID-19 continues to rise, largely affecting middle-aged persons with worsening clinical sequelae linked to increasing age and comorbid conditions (eg, diabetes and chronic lung disease) (CDC, 2020).[1]

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The clinical presentation of SARS-CoV-2 pneumonia follows a continuum, ranging from asymptomatic disease, to mild upper respiratory tract illness often characterized by fever and dry cough, to severe pneumonia resulting in respiratory failure. In the absence of specific anti-viral therapy, management of SARS-CoV-2 remains supportive. Although several compounds are under investigation, no clinically-rigorous data are available at this time to inform patient management.

The early stages of the outbreak were characterized by a rapidly changing landscape of viral exposure, testing methods, testing recommendations, and patient management, which has obscured insights into true risk of infection in the population as well as subpopulations who might be at higher risk of infection, serious or prolonged illness, hospitalization or death.

Patients with chronic rheumatic and gastrointestinal disease are considered a high-risk group for SARS-CoV-2 infection, given their susceptibility to infection, largely related to use of immunosuppressant therapies (eg, Murdaca, 2019).[3] On 14 April 2020, American College of Rheumatology issued draft guidelines, finalized 31 April 2020. for the management of rheumatology patients in light of the pandemic, recommending that in the context of documented or presumptive COVID-19 infection anti-malarial therapies (HCQ/CQ) may be continued, but SSZ, MTX, LEF, immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped or held due to fact that immunosuppressants disrupt signaling pathways essential to viral clearance, eg, interferon signaling disruption by janus kinase inhibitors. More detailed recommendations were made that distinguished between combination of pandemic setting, infections, exposures for patients newly diagnosed or with active disease(Appendix 1). Nonetheless, an early case series study of patients with SARS-CoV-2 infection prior to issuance of the guidelines concluded that the baseline use of biologics is not associated with worse COVID-19 outcomes (Haberman, 2020).[6] Emerging data are conflicting as to whether compounds used to treat autoimmune conditions modify the clinical course of serious effects of late stage infection via interruption of the proinflammatory cytokine storm (Sarzi-Puttini, 2020).[4] It remains unknown whether persons with RA, PsA or UC treated with Pfizer therapies, like Xeljanz, are more susceptible to, or protected from, COVID-19.

Tofacitinib is a potent selective inhibitor of the Janus kinase (JAK) family of kinases that preferentially inhibits signaling by heterodimeric receptors associated with JAK1 and/or JAK3, with functional selectivity over receptors that signal via pairs of JAK2. Tofacitinib received first marketing authorisation on 06 November 2012 for rheumatoid arthritis (RA) in the United States (US). The currently approved indications for tofacitinib in the US are:

- Rheumatoid Arthritis: treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

- Psoriatic Arthritis: treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).

- Ulcerative Colitis: treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.

The objective of this study is to assess whether tofacitinib modifies the risk of serious clinical manifestations and outcomes of SARS-CoV-2 diagnosis in order to inform patients and prescribers of the safety of tofacitinib use in patients with indications for approved use. This protocol has been developed in consideration of existing available information at the time it was written and may be amended as additional information become available. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) voluntarily conducted by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The research questions that could be addressed by this study are:

What proportions of SARS-CoV-2 diagnosed patients have a diagnosis of RA, PsA, or UC (ie, indicated subcohorts) or not (ie, non-indicated subcohort) and what is risk of serious clinical manifestations and outcomes of interest in these subcohorts?

Within the indicated subcohorts of SARS-CoV-2 diagnosed patients, what is the proportion treated at baseline with the following systemic therapies: tofacitinib, JAK inhibitors, TNFi, non-TNFi, and csDMARD and what is risk of serious clinical manifestations and outcomes of interest within strata?

Primary objectives:

- Within subcohorts of SARS-CoV-2 diagnosed patients, determine the proportions of patients with a diagnosis of RA, PsA, and UC (indicated subcohorts) and patients without any of these conditions (non-indicated subcohort).

- For each indicated subcohort and non-indicated subcohort, describe baseline demographic characteristics, treatment history and comorbidities.

- Within each indicated subcohort and non-indicated subcohort, estimate proportion experiencing serious clinical manifestations and outcomes of interest (Section 9.3).

- Within each indicated subcohort of SARS-CoV-2 diagnosed patients, determine the proportions of patients treated with the following systemic therapies (class) at baseline: tofacitinib, JAK inhibitors, TNFi, non-TNFi and csDMARD (as monotherapy and combination therapy, as applicable).

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- Describe patient characteristics, treatment history and comorbidities within baseline treatment strata.

- Estimate risk of serious clinical manifestations and outcomes of interest within baseline treatment strata (Section 9.3).

- Determine the proportions of patients that continue baseline treatment after SARS-CoV-2 diagnosis within indicated subcohorts.

9. RESEARCH METHODS

9.1. Study Design

This is a retrospective cohort study involving secondary analysis of Optum administrative databases in the US consisting of longitudinal health information about patients tested for or diagnosed with SARS-CoV-2. The data source will be periodically updated and evaluated throughout the course of the study period.

The dataset consists of longitudinal data for patients from a subset of healthcare systems that expedite reporting of SARS-CoV-2 diagnoses, tests and their results. This dataset has been selected in the study in order to identify early insights into the potential risks of SARS-CoV-2 for indicated patients overall and by therapy.

This study is an active surveillance study consisting of repeat analyses over multiple timepoints, beginning with an 30 April 2020 data cut and repeated (summarized per status update as well as cumulatively) in order to understand the SARS-CoV-2 infected patients over time and across geographies as the virus spreads.

Any addition of post-hoc formal comparisons between groups will be described in a SAP pending feasibility based on sample size and data quality considerations.

This study period begins on 1 February 2020 and continues through 30 June 2022.

The study seeks to understand the serious clinical manifestations and outcomes of SARS-CoV-2 diagnosis among patients with RA, PsA, and UC and whether manifestations differ by treatment or by indication.

9.2. Setting

9.2.1. OPTUM Electronic Health Record Data for COVID-19

Analyses will be conducted using data from Optum's "Electronic Health Record Data for COVID-19" database, which contains a subset of the Optum EHR data set. This subset includes longitudinal EHR information for patients within the Optum network who have been tested for or diagnosed with SARS-CoV-2. This dataset has been curated specifically to provide access to near real-time structured, longitudinal health data for patients diagnosed

with or tested for SARS-CoV-2. Due to concerns about patient privacy, the COVID-19 database uses a distinct set of patient and encounter IDs from the overall Optum dataset.

Optum's EHR repository is derived from dozens of healthcare provider organizations in the United States, that include more than 700 Hospitals and 7000 Clinics; treating more than 100 million patients receiving care in the United States. The data is certified as de-identified by an independent statistical expert following HIPAA statistical de-identification rules, and managed according to Optum customer data use agreements.[1],[2] Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory electronic health records (EHRs), practice management systems and numerous other internal systems; and is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum data elements include demographics; medications prescribed and administered; immunizations; allergies; lab results (including microbiology); vital signs and other observable measurements; clinical and inpatient stay administrative data and coded diagnoses and procedures.

Over the duration of the study, other structured data sources may be incorporated and will accordingly be described in an SAP or protocol amendment as appropriate.

9.2.2. SARS-COV-2 Pandemic

The first known case of SARS-CoV-2 infection in the US is thought to have occurred in the US in late January 2020. Testing to detect SARS-CoV-2 infection in the US began in late February 2020. Due to limited number of tests available, testing was extremely limited and selective throughout February until early March 2020. In March, CDC removed certain restrictions on who could perform and receive the tests. In April 2020 antibody testing became widely available but difficult to interpret. This study will include patients identified at the beginning of the emergence of the SARS-CoV-2 pandemic in the US, when diagnostic tests were limited and of varying reliability, access to care was potentially restricted, and availability and standards of treatment were evolving. The study will continue over two years during which testing availability, reliability and recommendations, case contact tracing, and treatment will evolve.

With respect to testing, as of 22 April 2020 the following CDC guidelines, initially proposed on 19 March 2020, were still in place (https://www.coronavirus.gov/):

"Clinicians should use their judgment to determine if a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested. Most patients with

[1] 45 CFR 164.514(b)(1).

[2] Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as September 4, 2012, as first released on November 26, 2012).

confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness (eg, cough, difficulty breathing)."

The CDC assigned priorities for who should be tested:

Priority 1:

- Hospitalized patients;
- Healthcare facility workers with symptoms.

Priority 2:

- Patients in long-term care facilities with symptoms;
- Patients 65 years of age and older with symptoms;
- Patients with underlying conditions with symptoms;
- First responders with symptoms.

Priority 3:

- Critical infrastructure workers with symptoms;
- Individuals who do not meet any of the above categories with symptoms;
- Healthcare facility workers and first responders;
- Individuals with mild symptoms in communities experiencing high numbers of COVID-19 hospitalizations.

Nonpriority:

- Individuals without symptoms.

CDC provided additional guidance that state and local guidelines should adapt these recommendations to reflect potentially rapidly changing local circumstances.

In the US approximately 10,000 SARS-CoV-2 infection tests had been conducted by March 12 with roughly 2,200 testing positive. By April 1, nearly 1.2 million tests had been performed with 215,329 positives. By 22 April 2020 over 4.4 million tests had been performed with 826,936 positive tests (Note: Two tests are recommended to be performed on the same individual so this is not an estimate of affected persons) (The COVID Tracking Project).[2] As of 22 April 2020 SARS-CoV-2 infection testing is largely limited to patients who are symptomatic.

As of April 22, there is a lack of universal SARS-CoV-2 infection or antibody screening therefore, no US data exist that would allow for the study of asymptomatic infected persons, the true rate of SARS-CoV-2 infection, or rates of COVID-19 illness among SARS-CoV-2-infected persons.

Patients with chronic conditions, such as those treated with tofacitinib, may have different rates of infection from the general population for a variety of reasons. For example, the condition or its treatment may be associated with higher risk of infections generally, thus, patients and their HCP may take extra precautions to avoid exposure to the virus. On the other hand, patients may be more likely to be referred for testing and therefore diagnosed if they are perceived to be at higher risk of infection or of more serious clinical course of infection. However, within an indicated population, patient characteristics or prescribed treatment regimens are not likely to determine probability of referral for testing, barring an association with symptomatic disease. Thus, understanding the course of disease in patients with confirmed SARS-CoV-2 infection will inform our understanding of how different conditions, patient characteristics, and treatments impact the course of SARS-CoV-2 in a population known to be infected.

9.2.3. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. SARS-CoV-2 diagnosis (as defined in SAP) (index date).
2. At least 6 months of continuous enrollment prior to index date.
3. Age 18 or older at index date.

For indicated subcohort:

1. Evidence of RA, PsA, or UC diagnosis (Section 9.3) within baseline period (to be defined in SAP) prior to index date.

For non-indicated subcohort:

1. No evidence of RA, PsA, or UC diagnosis (Section 9.3) within baseline period (to be defined in SAP) prior to index date

9.2.4. Exclusion Criteria

There are no exclusion criteria for this study.

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9.3. Variables

Variable	Role	Operational definition[a]
SARS-CoV-2 Diagnosis	Inclusion criteria	SARS-CoV-2 diagnosis.
Rheumatoid Arthritis	Subcohort identification	RA diagnosis in baseline period.
Psoriatic Arthritis	Subcohort identification	PsA diagnosis in baseline period.
Ulcerative Colitis	Subcohort identification	UC diagnosis in baseline period.
Non-indicated subcohort	Inclusion criteria/Subcohort identification	Absence of RA, PsA, and UC codes within baseline period.
SARS-CoV-2 Diagnosis Date	Exposure/Index date	Date associated with SARS-CoV-2 diagnosis.
Baseline systemic therapy	Baseline Characteristic/Exposure	Evidence of therapy prescribed 6 months prior to index date. Categorical: csDMARD, TNFi, non-TNFi, tofacitinib, JAK inhibitor (as monotherapy or combination therapy).
Baseline csDMARD	Baseline Characteristic/Exposure (Comedication)	Evidence of therapy prescribed within 6 months prior to index date.
Baseline TNFi	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months prior to index date.
Baseline Non-TNFi	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months prior to index date.
Baseline bDMARD	Baseline Characteristic/Exposure	TNFi or non-TNFi prescribed within 6 months prior to index date.
Baseline tofacitinib	Baseline characteristic/Exposure	Tofacitinib Evidence of therapy prescribed within 6 months prior to index date.
Baseline JAK inhibitor	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months prior to index date.
Baseline Monotherapy	Baseline characteristic/Exposure	No evidence of MTX or other csDMARD concomitant with baseline advanced systemic therapy (ie, TNFi, non-TNFi, tofacitinib, JAK inhibitor).
Baseline Combination therapy	Baseline characteristic/Exposure	Evidence of MTX or other csDMARD concomitant with baseline advanced systemic therapy (ie, tofacitinib, bDMARD, JAK inhibitor, csDMARD) and MTX or other csDMARD.

Variable	Role	Operational definition[a]
Post-SARS systemic therapy	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months after index date. Categorical: csDMARD, TNFi, non-TNFi, tofacitinib, JAK inhibitor (as monotherapy or combination therapy).
Post-SARS csDMARD	Baseline Characteristic/Exposure (Comedication)	Evidence of therapy prescribed within 6 months on or after index date.
Post-SARS TNFi	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months on or after index date.
Post-SARS Non-TNFi	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months on or after index date.
Post-SARS bDMARD	Baseline Characteristic/Exposure	Evidence of TNFi or non-TNFi on or after index date.
Post-SARS tofacitinib	Baseline characteristic/Exposure	Evidence of therapy prescribed within 6 months on or after index date.
Post-SARS JAK inhibitor	Baseline Characteristic/Exposure	Evidence of therapy prescribed within 6 months on or after index date.
Post-SARS Monotherapy	Baseline characteristic/Exposure	No evidence of MTX or other csDMARD concomitant with post-index advanced systemic therapy (ie, TNFi, non-TNFi, tofacitinib, JAK inhibitor).
Post-SARS Combination therapy	Baseline characteristic/Exposure	Evidence of MTX or other csDMARD concomitant with post-index advanced systemic therapy (ie, bDMARD, tDMARD) and MTX or other csDMARD.
Region	Baseline/potential confounder	Distribution of geographic region at index date.
Insurance	Baseline/potential confounder	Insurance type at index date.
Age	Baseline/potential confounder/risk factor	Continuous age at index date.
Gender	Baseline/potential confounder/risk factor	Woman; Male; Unknown.

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Variable	Role	Operational definition[a]
Race	Baseline/potential confounder/risk factor	Race recorded.
Hypertension	Baseline/potential confounder	Diagnosis of hypertension within 6 month baseline period.
Hyperlipidemia	Baseline/potential confounder	Diagnosis of hyperlipidemia within 6 month baseline period.
History of coronary artery disease	Baseline/potential confounder	Diagnosis of coronary heart disease within 6 month baseline period.
History of serious infections	Baseline/potential confounder	Hospitalized infections or use of parenteral antibiotics within 6 month baseline period.
History of hospitalization	Baseline/potential confounder	Days hospitalized within 6 month baseline period.
ILD	Comorbidity/Risk factor	Diagnosis of ILD within 6 month baseline period.
Asthma	Comorbidity/Risk factor	Diagnosis or asthma within 6 month baseline period.
VTE	Comorbidity/Risk factor	Diagnosis of PE or DVT within 6 month baseline period.
Cancer	Risk factor	Diagnosis of cancer within 6 month baseline period.
Other immune deficiencies	Risk factor	Diagnosis of immunodeficiency within 6 month baseline period.
HIV/AIDS	Risk factor	Diagnosis of HIV/AIDS within 6 month baseline period.
Diabetes	Risk factor	Diagnosis of diabetes within 6 month baseline period.
CKD/Dialysis	Risk factor	Diagnosis of CKD or dialysis procedure within 6 month baseline period.
Liver Disease	Risk factor	Diagnosis of liver disease within 6 month during baseline period.
Corticosteroid Use	Risk factor	Evidence of use within 6 month baseline period.
SARS diagnosis site	Endpoint	Facility location where SARS-CoV-2 was diagnosed (eg, ER, ICU, outpatient).
Hospitalization	Primary Endpoint	Yes/No: hospitalization within 30 days post-SARS-CoV-2 diagnosis.

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Variable	Role	Operational definition[a]
ICU admission	Primary Endpoint	Yes/No admission to ICU within 30 days post-SARS-CoV-2 diagnosis.
In hospital death	Endpoint	Discharge diagnosis = death post hospitalization associated with SARS-CoV-2 diagnosis.
All-cause mortality	Endpoint	Death within 90 days post-SARS-CoV-2 infection.
Length of hospital stay	Endpoint	Duration of inpatient stay for visit associated with SARS-CoV-2 diagnosis.
Length of ICU stay	Endpoint	Duration of ICU stay for visit associated with SARS-CoV-2 diagnosis.
Respiratory failure	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
Kidney failure	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
Thrombosis/coagulation events/stroke	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
ARDS	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
Heart failure	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
Sepsis/septic shock	Endpoint	Diagnosis in conjunction with SARS-CoV-2 diagnosis.
Invasive ventilation	Endpoint	Procedure performed during hospitalization associated with SARS-CoV-2 diagnosis.
Non-invasive ventilation	Endpoint	Procedure performed during hospitalization associated with SARS-CoV-2 diagnosis.
ECMO	Endpoint	Procedure performed during hospitalization associated with SARS-CoV-2.
Oxygen therapy	Endpoint	Procedure performed during hospitalization associated with SARS-CoV-2 diagnosis.
IV immunoglobulin	Endpoint	Procedure performed during hospitalization associated with SARS-CoV-2 diagnosis.

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Variable	Role	Operational definition[a]
Discharge Disposition	Endpoint	Disposition at discharge from hospital stay associated with SARS-CoV-2 diagnosis.

a. Where applicable codes and other definitions to be further defined in Statistical Analysis Plan.

9.4. Data Sources

The structured data within Optum COVID testing database will be used to identify populations, exposures, confounders and endpoints of interest as described in Section 9.3.

As of 22 April 2020 the Optum COVID database currently includes 32,000 patients who have either been tested for COVID-19 or diagnosed with COVID-19 (regardless of positive/negative result). Refreshes of this data are delivered on a bi-weekly basis through September 2020 and on a monthly cadence from October 2020 – February 2021. This cohort includes details of a patient's office visit and/or hospital stay, including but not limited to: demographic, diagnosis, procedures performed, vital signs and other biometric measures, laboratory results, and prescriptions written and dispensed. All diagnosis data in this study will be obtained from structured data (via ICD-10-CM codes or ICD-9-CM codes where applicable). All drug treatment data will be pulled from prescription written, medication administration, and procedure tables when appropriate (via ICD-9-CM or ICD-10-CM, NDC, CPT, and HCPCS codes).

9.5. Study Size

Given the descriptive nature of most analyses, there is no minimum sample size. Sample size achieved will depend on the number of patients testing positive for SARS-CoV-2 and the indication-specific rate of infections and will increase over time with subsequent data cuts.

Prior to conducting any post-hoc comparative analyses, the feasibility of robust comparisons given accrued sample size will be assessed as described in the SAP.

9.6. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using SAS (version 9.4, SAS Institute, Cary, NC, USA). As the database will be regularly updated, date and version of the database will be specified in the report of the study, and the intermediate datasets will be archived if the report will be submitted to a regulatory agency or will be published.

9.7. Data Analysis

After selection of the study population, summary statistics of baseline variables will be determined for the baseline period. The index date for each patient is defined as the first date that the study inclusion criteria are satisfied. Baseline variables will be summarized as

appropriate for categorical and continuous variables with 95% CI provided to show precision of the estimate.

Among patients who are included in the study, outcomes will be included that occur during the risk window from index date until the first of death (based on discharge status), 3 months post-SARS-CoV-2 diagnosis, or end of study period/datacut.

The endpoints of interest within each indication, non-indicated subcohort and indication/treatment combination will be summarized as appropriate for categorical and continuous variables with 95% CI provided to show precision of the estimate.

The handling of missing data will be described in the SAP. No variables will be imputed.

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.

9.8. Quality Control

Analyses are programmed according to the specifications in the protocol, and if applicable, the statistical analysis plan, and documented in a programming plan. Final deliverables will be reviewed and verified by a second, independent programmer who may also perform double programming. All quality checks will be documented in the programming plan.

9.9. Limitations of the Research Methods

Limitations that are general to claims database analyses and specific to this study should be noted. Diagnosis of autoimmune conditions will be identified using ICD-10-CM diagnosis codes, which are subject to potential miscoding, though presumably without respect to the treatment or outcomes. Where possible, validated algorithms will be used. The baseline period of this study is of limited duration thus baseline comorbidities and risk factors occurring outside of this baseline period may not be captured, which may lead to misclassification.

SARS-CoV-2 is a new disease with evolving diagnostic mechanisms and care. Diagnosis codes have only been established since after the first cases in the US and the validity of the diagnosis codes are unknown. The spectrum of clinical manifestations of SARS-CoV-2 is unknown. Many infected persons are thought to have mild to unrecognizable symptoms and may not present for care or diagnosis. These infections will not be represented in the datasets thus this study is generalizable with respect to more serious sequelae of infection.

Similarly, patients with chronic diseases or in inpatient setting, the elderly, or other risk groups may be more likely to be under ongoing care or thought to be at higher risk and therefore may be more likely to seek care or be referred for testing. Thus differences

between indicated and non-indicated populations may arise from access to care/health behaviors rather than true differences in risk.

The primary analyses are descriptive in nature and inferences regarding association of treatment or indication are not possible. Feasibility of comparative analyses will depend on the number of infected patients with indications/treatments of interest.

Generalizability may be further limited as SARS-CoV-2 testing patterns and treatment are evolving over time.

9.10. Other Aspects

Not Applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

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

Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review was not required.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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2. The COVID Tracking Project at The Atlantic. https://covidtracking.com/data/us-daily (accessed 22 April 2020).

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	21 June 2023	A Descriptive Retrospective Database Study to Evaluate Serious Clinical Manifestations and Outcomes among SARS-CoV-2 Diagnosed Patients with RA, PsA or UC treated with systemic therapies: A Post-Approval Safety Study of Tofacitinib in the Context of the COVID-19 Pandemic.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

APPENDIX 1. AMERICAN COLLEGE OF RHEUMATOLOGY GUIDELINES

American College of Rheumatology
Empowering Rheumatology Professionals

Empowering rheumatology professionals to excel in their specialty

2200 Lake Boulevard NE, Atlanta, GA 30319
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COVID-19 Clinical Guidance for Adult Patients with Rheumatic Diseases

DEVELOPED BY THE ACR COVID-19 CLINICAL GUIDANCE TASK FORCE

This draft summary was approved by the ACR Board of Directors on April 11, 2020.
A full manuscript is pending journal peer review.

PURPOSE

The purpose of this document is to provide guidance to rheumatology providers on the management of adult rheumatic disease patients in the context of the COVID-19 pandemic. These statements are not intended to replace clinical judgment. Modifications made to treatment plans, particularly in complex rheumatic disease patients, are highly disease-, patient-, geography-, and time-specific and, therefore, must be individualized as part of a shared decision-making process. This guidance is provided as part of a 'living document', recognizing rapidly evolving evidence and the anticipated need for frequent updates as such evidence becomes available.

METHODS

The North American Task Force, including 10 rheumatologists and 4 infectious disease specialists, convened on March 26, 2020. Clinical questions were collated, and an evidence report was generated and disseminated to the panel. Questions and drafted statements were reviewed and assessed using a well-established method of consensus building (modified Delphi process). This included two rounds of asynchronous anonymous voting by email and two webinars including the entire panel. Panel members voted on agreement with draft statements using a numeric scoring system, and consensus was determined to be "low" (L), "moderate" (M) or "high" (H), based on the dispersion in voting results. To be approved as guidance, median votes were required to correlate to pre-defined levels of agreement (with median values interpreted as "agreement", "uncertainty" or "disagreement") with either moderate or high levels of consensus.

RECOMMENDATIONS

General statements for patients with rheumatic disease:

- The risk of poor outcomes from COVID-19 appears to be related primarily to general risk factors such as age and comorbidity (H).
- Patients should be counseled on general preventive measures, eg, social distancing and hand hygiene (H).
- As part of a shared decision-making process between patients and rheumatology providers, select measures to reduce healthcare encounters and potential exposure to SARS-CoV-2 (beyond general preventive measures) may be reasonable, eg, reduced frequency of lab monitoring, optimal use of telehealth, increased dosing intervals between intravenous medications) (M/H).
- If indicated, glucocorticoids should be used at the lowest dose possible to control rheumatic disease, regardless of exposure or infection status (M/H).
- Glucocorticoids should not be abruptly stopped, regardless of exposure or infection status (H).
- If indicated, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be continued in full doses or initiated (M/H).

ONGOING TREATMENT OF STABLE PATIENTS IN THE ABSENCE OF INFECTION OR SARS-COV-2 EXPOSURE:

- Hydroxychloroquine or chloroquine (HCQ/CQ), sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), immunosuppressants (eg, tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine), biologics, Janus kinase (JAK) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) may be continued (this includes patients with giant cell arteritis with an indication, in whom IL-6 inhibitors should be continued, if available) (M/H).
- Denosumab may still be given, extending dosing intervals to no longer than every 8 months, if necessary to minimize healthcare encounters (M).
- For patients with a history of vital organ-threatening rheumatic disease, immunosuppressants should not be dose-reduced (M).

IN PATIENTS WITH SLE:

- In newly diagnosed disease, HCQ/CQ should be started at full dose, when available (H).

- In pregnant women with SLE, HCQ/CQ should be continued at the same dose, when available (H).

- If indicated, belimumab may be initiated (M).

TREATMENT OF NEWLY DIAGNOSED OR ACTIVE RHEUMATIC DISEASES, IN THE ABSENCE OF INFECTION OR SARS-COV-2 EXPOSURE:

Active Inflammatory Arthritis:

- For patients well-controlled on HCQ/CQ, this disease-modifying anti-rheumatic drug (DMARD) should be continued, when available; when unable to access (including in patients with active or newly diagnosed disease), switching to a different conventional synthetic DMARD (either as monotherapy or as part of combination therapy) should be considered (M/H).

- For patients well-controlled on an IL-6 inhibitor, this DMARD should be continued, when available; when unable to access the agent, switching to a different biologic should be considered (M). The panel noted uncertainty regarding the use of JAK inhibitors in this situation.

- For patients with moderate to high disease activity despite optimal conventional synthetic DMARDs, biologics may be started (H). The panel noted uncertainty regarding the use of JAK inhibitors in this situation.

- For active or newly diagnosed inflammatory arthritis, conventional synthetic DMARDs may be started or switched (M).

- If indicated, low-dose glucocorticoids (≤10 mg prednisone equivalent) or NSAIDs may be started (M/H).

Other Rheumatic Diseases:

- In patients with systemic inflammatory or vital organ-threatening disease (eg, lupus nephritis or vasculitis), high-dose glucocorticoids or immunosuppressants may be initiated (M).

- In patients with newly diagnosed Sjögren's, given the paucity of data proving efficacy, HCQ/CQ should not be started (M).

ONGOING TREATMENT OF STABLE PATIENTS FOLLOWING SARS-COV-2 EXPOSURE (WITHOUT SYMPTOMS RELATED TO COVID-19):

- HCQ, SSZ, and NSAIDs may be continued (M/H).

- Immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped temporarily, pending a negative test result for COVID-19 or after 2 weeks of symptom-free observation (M). The panel noted uncertainty re: temporarily stopping MTX or LEF in this situation.

- In select circumstances, as part of a shared decision-making process, IL-6 inhibitors may be continued (M).

RHEUMATIC DISEASE TREATMENT IN THE CONTEXT OF DOCUMENTED OR PRESUMPTIVE COVID-19 INFECTION:

- Regardless of COVID-19 severity, anti-malarial therapies (HCQ/CQ) may be continued, but SSZ, MTX, LEF, immunosuppressants, non-IL-6 biologics, and JAK inhibitors should be stopped or held (M/H).

- For patients with severe respiratory symptoms, NSAIDS should be stopped (M). The panel demonstrated low consensus with regards to stopping NSAIDs in the absence of severe symptoms.

- In select circumstances, as part of a shared decision-making process, IL-6 inhibitors may be continued (M).

Updated April 14, 2020

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