NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	An Active Surveillance, Post-Authorization Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest Among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) Within the Swedish, Population-based, Anti-Rheumatic Treatment in Sweden (ARTIS) Register
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Active substance	PF-05280586 Rituximab
Medicinal product	Ruxience (rituximab)
Product reference	H0004696
Procedure number	EMEA/H/C/004696/0000
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	**Research Question:** What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis in the ARTIS register who are treated with

	Ruxience? **Objectives:** To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and use during pregnancy among patients with rheumatoid arthritis in the ARTIS register who initiate Ruxience.
Country(-ies) of study	Sweden
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ACS	acute coronary syndrome
ADR	adverse drug reaction
AE	adverse event
ARTIS	Anti-Rheumatic Treatment in Sweden
AS	ankylosing spondylitis
CLL	Chronic lymphocytic leukemia
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DALYS	Daily-adjusted Life Years
DAS-28	Disease Activity Score in 28 joints
DMARD	Disease modifying anti-rheumatic drug
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESR	erythrocyte sedimentation rate
EU	European Union
GEP	Good Epidemiological Practice
GPA	Granulomatosis with polyangiitis
GVP	Good pharmacovigilance practices
HAQ	health Assessment Questionnaire
HRQoL	Health-related Quality of Life
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IT	Information Technology
MA	Market Authorisation
MACE	Major acute cardiovascular event
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MPA	Microscopic polyangiitis
N	number
N/A	Not applicable
NHL	Non-Hodgkin’s lymphoma
NI	Non-interventional
NMSC	non-melanoma skin cancer

Abbreviation	Definition
NNH	number needed to harm
NSAIDs	nonsteroidal anti-inflammatory drugs
PASS	Post-Authorization Safety Study
PPV	positive predictive value
PsA	psoriatic arthritis
PV	Pemphigus Vulgaris
QALY	Quality-adjusted Life Year
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SRQ	Swedish Rheumatology Quality Register
TNF	Tumor necrosis factor
VAS	visual analog scale

3. RESPONSIBLE PARTIES

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Not applicable.

4. ABSTRACT

Title: An Active Surveillance, Post-Authorization Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest Among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) Within the Swedish, Population-based, Anti-Rheumatic Treatment in Sweden (ARTIS) Register.

Version: 1

Date: 14 October 2020

Main Author: Cynthia de Luise, Pfizer, Inc.

Rationale and background:

Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus vulgaris (PV).[1]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy. Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies. Approved in the EU on 01 April 2020, PF-05280586 (Ruxience) has been developed by Pfizer as a biosimilar to the licensed reference product, MabThera. Pfizer proposes the assessment of safety events of special interest based on the Ruxience EU Risk Management Plan (RMP) version 1.0 (infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information).[2] This protocol describes a non-interventional, Post-Authorisation Safety Study (PASS) of Ruxience-exposed patients using actively collected prospective data included in the established Anti-Rheumatic Therapies in Sweden (ARTIS) register.

Research question: What are the incidence rates of safety events of special interest in patients with RA who initiate Ruxience in the ARTIS register?

Objectives: To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and use during pregnancy among all patients with rheumatoid arthritis in the ARTIS register who initiate Ruxience.

Study design: This active surveillance study uses data from the established ARTIS register, an ongoing, prospective, disease-based cohort started in 1999 with the primary aim of evaluating the safety of RA patients who are started on new biologic therapies for RA during routine post-marketed clinical use. This study is a secondary data collection study of anonymised, structured data in ARTIS.

Population: The study population will comprise of all patients with RA enrolled within the ARTIS register who initiate treatment with Ruxience.

Data sources: The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Society of Rheumatology to improve the healthcare and treatment for patients with RA. SRQ followed on regional register initiatives, to enable a national real world documentation of many different aspects of RA and developed over time into a harmonised national register. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases. Initially focusing on early RA, SRQ has gradually come to include other segments. Data entry into SRQ is provided by the patient and the rheumatologist in conjunction with visits. Visits are scheduled according to treatment guidelines and clinical practice, at 0 and 3 to 6 months after the initiation of a new anti-rheumatic therapy, and thereafter in relation to the level of disease activity, according to an overall treat to target paradigm. Data are routinely captured as patients must visit their physician annually to renew prescriptions and must refill prescriptions every three months.

Mandated by the Swedish Society of Rheumatology, ARTIS is a research project hosted by the Karolinska Institutet. Since 1999, ARTIS has conducted a safety surveillance programme for immunomodulators based on SRQ linked to additional registers and includes all presently available biologics used for the treatment of patients with inflammatory rheumatic diseases. It covers around 90% of all biologic initiations in Sweden after 1999.

Variables: This study will use data routinely captured in the ARTIS register, which include baseline patient characteristics (ie, demographic and clinical characteristics, comorbidities and current and past therapies), and safety events of special interest including serious infections, all malignancies, CVD events, and use during pregnancy. Infectious and cardiovascular events will be ascertained through record linkage with the Swedish Patient Register, which collects information on all hospitalised patients, and all visits to non-primary outpatient care. Diagnoses are assigned by the discharging/treating physician, as well as date of discharge/visit, hospital and department. Malignancies will be ascertained through linkage with the Swedish Cancer Register which contains data on date of cancer diagnosis and type of cancer according to the International Classification of Disease (ICD). Use in pregnancy will be assessed through additional linkage with the Medical Birth Register which contains data from antenatal, obstetric, and neonatal records, and covers all live and still births (but not all miscarriages) in Sweden.

Study size: This is a descriptive study. All Ruxience-treated patients in the ARTIS register during the study period will be included in the study.

Study period: The Study Start Date is defined as the date when the first patient diagnosed with RA in ARTIS initiates treatment with Ruxience. The Study End Date is defined as 3 years after the Study Start Date.

Data analysis: Annual reports will contain information on uptake of Ruxience and patient characteristics. Interim and final study reports will consist of descriptive summaries of baseline variables and incidence rates based on data linkage for safety events of interest described above for Ruxience-treated patients. No comparative analyses with other cohorts will be performed.

Milestones: The first annual report describing the number and characteristics of patients initiating Ruxience is expected by 15 July 2021 and annually thereafter through 15 July 2023. An interim report and a final report containing incidence rates of events of special interest will be prepared by 01 July 2023 and 31 December 2024, respectively.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	TBD
Start of data collection (estimated)	01 July 2021^
Date of first annual report (estimated)	15 July 2021
Date of second annual report (estimated)	15 July 2022
Date of interim report	01 July 2023
Date of third annual report (estimated)	15 July 2023
End of data collection (estimated)	31 December 2023[#]
Final study report (estimated)	31 December 2024[x]

^ Start of data collection is the planned date for starting data extraction for the purposes of the study analysis.

[#] End of data collection is the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the study objective(s).

[x] Final report must be prepared within 11 months of end of data collection.

7. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[3] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities.[4] Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma).[5,6,7,8,9,10,11,12,13] These patients are also treated with multiple classes of agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and DMARDs including biologicals, each of which carry significant risks as well as benefits.

Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus Vulgaris (PV).[1]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy.[14] Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Biosimilars and non-originator biologicals of rituximab have been approved in several additional countries as of July 2018, including Turkey, Russia, Argentina, South Korea, Australia, and India.[15] The European Medicines Agency (EMA) approved 2 rituximab biosimilars from 2 MAHs including Rixathon (Sandoz) in June 2017, and Truxima (Celltrion) in November 2018. PF-05280586 (Ruxience) has been developed by Pfizer as a biosimilar to the licensed reference product MabThera and was approved in the EU on 01 April 2020.

The Market Authorisation Holder (MAH) proposes the assessment of safety events of special interest based on the Ruxience EU RMP version 1.0 (infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information).[2]

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer. This study is designated as a "Category 4 Additional Pharmacovigilance Activities" in line with the reference product.

8. RESEARCH QUESTION AND OBJECTIVES

The main research question is to estimate incidence rates of safety events of special interest in patients with RA who are enrolled in ARTIS and initiate treatment with Ruxience.

Objectives:

To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and use during pregnancy among RA patients in the ARTIS register who initiate treatment with Ruxience.

9. RESEARCH METHODS

9.1. Study Design

This active surveillance study uses data from the established ARTIS register, an ongoing, prospective, disease-based cohort started in 1999 with the primary aim of evaluating the safety of RA patients who are started on new biologic therapies for RA during routine post-marketed clinical use. This study is a secondary data collection study of anonymised, structured data in ARTIS.

9.2. Setting

Sweden is a Scandinavian country with almost 10 million inhabitants.[16] The prevalence of RA in Sweden is around 0.7% and the overall incidence is 41/100,000 per year.[17,18]

Swedish health-care is tax-funded and offers universal access. Hospital referral is based on geography rather than insurance-status. Patients with RA are typically treated by rheumatologists, the vast majority of whom work in public and hospital-based clinics.

Health and demographic information are collected in a series of registers with a high degree of completeness resulting from the mandatory and semi-automated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registers is possible.[19] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare (Socialstyrelsen*)* and Statistics Sweden (Statistiska centralbyrån), who may perform data linkages and provide de-identified data for research purposes.

Use of a RA treatment for a particular patient in Sweden has never been subject to a formal approval process (with the exception of a period during 2002-2003, when manufacturing issues led to reduced availability of etanercept), mandatory treatment history, or disease activity indices. Instead, the Swedish Society for Rheumatology has issued guidelines for the use of biologics, which are revised on an annual basis, but the ultimate decision to treat with biologics and which biologic to use have always resided with the treating rheumatologist.

9.2.1. Inclusion Criteria

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

1. Initiation of Ruxience as captured in ARTIS/SRQ.
2. Diagnosis of RA by a consulting rheumatologist.*
3. Age >18 years at the time of cohort entry.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.2.3. The SRQ and ARTIS

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 by the Swedish Society of Rheumatology to improve the healthcare and treatment for patients with RA.[20] SRQ followed on regional register initiatives, to enable a national real-world documentation of many different aspects of RA and developed over time into a harmonised national register. SRQ was started mainly for patients with RA, but over time it has been expanded to cover several other rheumatic diseases. Initially focusing on early RA, SRQ has gradually come to include other segments. Data entry into SRQ is provided by the patient and the rheumatologist in conjunction with visits. Visits are scheduled according to treatment guidelines and clinical practice, at 0 and 3 to 6 months after the initiation of a new anti-rheumatic therapy, and thereafter in relation to the level of disease activity, according to an overall treat to target paradigm. Data are routinely captured as patients must visit their physician annually to renew prescriptions and must refill prescriptions every 3 months.

Mandated by the Swedish Society of Rheumatology, ARTIS is a research project hosted by the Karolinska Institutet. Since 1999, ARTIS has conducted a safety surveillance programme for immunomodulators based on SRQ linked to additional registers and includes all presently available biologics used for the treatment of patients with inflammatory rheumatic diseases. It covers around 90% of all biologic initiations in Sweden after 1999.[21,18]

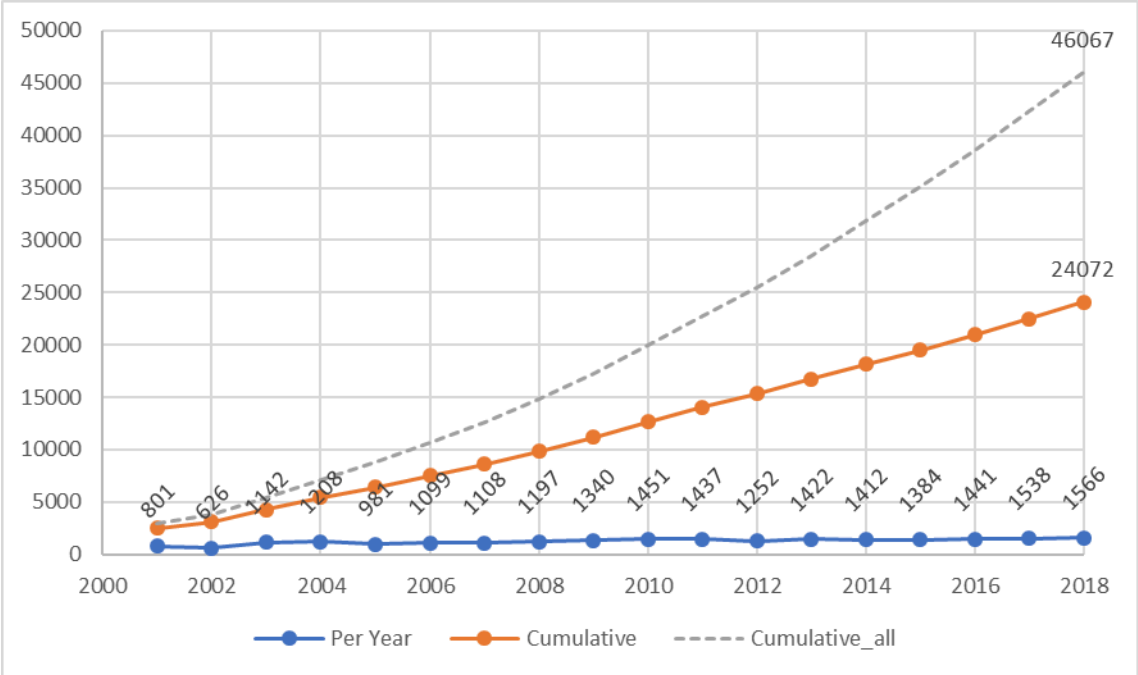
* Diagnosis of RA by a consulting rheumatologist is possible for all patients.

To maintain this high amount of data capture, and to improve completeness of data, the Swedish Society for Rheumatology regularly holds scientific meetings during which the surveillance data are presented. The managers and research nurses of ARTIS regularly visit participating centers to support clinicians in managing the web-based forms and/or entering information. In each of the 6 geographical regions, at least one rheumatologist is assigned as responsible for the registration in SRQ. Similarly, the ARTIS steering committee has geographical representation.

By the end of 2018, the follow-up within ARTIS included over 90,000 biologics treatment initiations among approximately 45,000 individuals. The treatment indication was recorded as RA or polyarthritis in 53% of patients [n=23788], psoriatic arthritis (PsA) in 15% of patients [n=6848], ankylosing spondylitis (AS) in 9% of patients [3914], spondyloarthropathies in 8% of patients [n=3540], juvenile arthritis in 5% of patients [n=2159], and the remainder as other rheumatic diseases.

Figure 1 shows the accumulated number of biologic starts across all rheumatology indications in the SRQ. Figure 2 shows the total number of treatment episodes and their distribution across specific drugs.

Figure 1. Accumulated Number of First Ever Biologics Starts Across All Rheumatology Indications Registered in the Swedish Rheumatology Quality Register and Amenable for Monitoring in the ARTIS Programme



Dashed line = across all rheumatology indications, bold line= RA. Because of sequential discontinuations and switches to a second or third biologic, the total number of biologics treatment initiations is higher (>80,000 treatment starts).

Figure 2. Cumulative Number of Treatment Starts in the Swedish Follow-up on Biologics Treatment Across Patients with Rheumatic Diseases

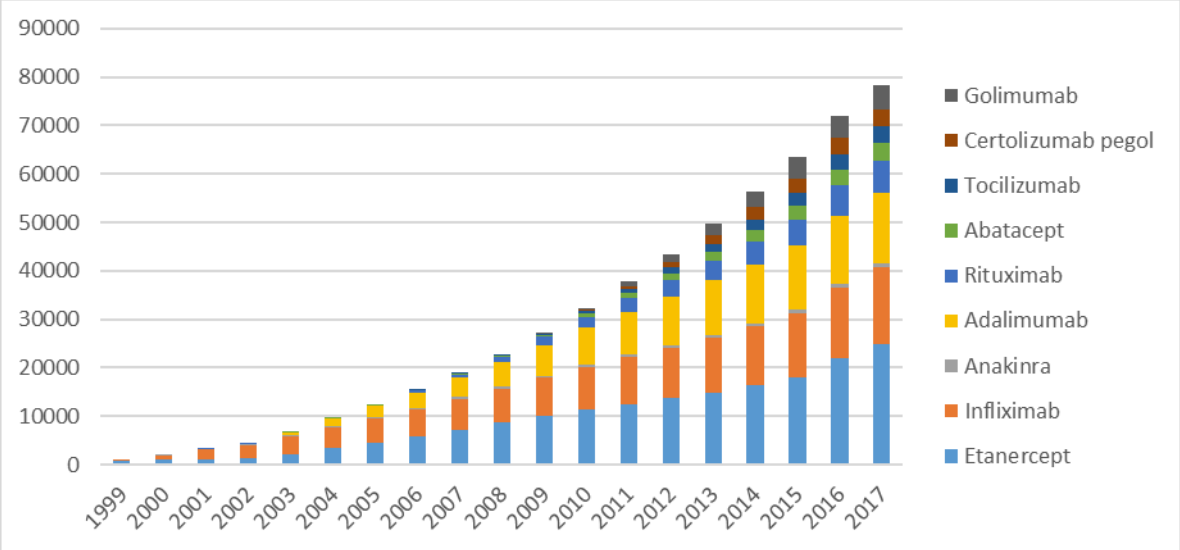


Table 1 below shows the percentage use of biosimilars from 2010 for adalimumab, etanercept, infliximab and rituximab.

Table 1. Temporal Trends in the Percentage Use of Biosimilars in ARTIS

Year	Adalimumab	Etanercept	Infliximab	Rituximab
2010	0	0	0	0
2011	0	0	0	0
2012	0	0	0	0
2013	0	0	0	0
2014	0	0.1%	0	0
2015	0	0.4%	57%	0
2016	0	81%	75%	0
2017	0	74%	92%	0
2018	7%	17%	88%	42%

The treating physicians enter the information into the study data-base via a web-based interface. Optionally, it is possible to send the data to the study secretariat on a pre-designed paper form. Patients can enter his/her data through the internet ahead of the visit, at touch-screens in the waiting room, or on paper. The clinical information can be accessed by the treating physician and has been found to be a very useful tool in the management of individual patients. Currently, the vast majority of the rheumatologist-derived data are entered directly via the internet in direct conjunction with the visit, and over half of the patient-derived data are also entered electronically, ahead of the visit.

Safety outcomes included in ARTIS are derived from 2 sources; spontaneous reports of adverse drug reactions (ADRs), and linkage to the national health care registers of Sweden (Section 9.4.2). This study will only utilise the data describing health outcomes derived from national health care registries.

9.3. Variables

This study will use data routinely captured in the ARTIS register, which include baseline patient characteristics (ie, demographic and clinical characteristics, comorbidities and current and past therapies, and safety events of special interest including serious infections, all malignancies, CVD events, and use during pregnancy. Infectious and cardiovascular events will be ascertained through record linkage with the Swedish Patient Register, which collects information on all hospitalised patients, and all visits to non-primary outpatient care. Diagnoses are assigned by the discharging/treating physician, as well as date of discharge/visit, hospital and department. Malignancies will be ascertained through linkage with the Swedish Cancer Register which contains data on date of cancer diagnosis and type of cancer according to the International Classification of Disease (ICD). classification. Use in pregnancy will be assessed through additional linkage with the Medical Birth Register which contains data from antenatal, obstetric, and neonatal records, and covers all live and still births (but not all miscarriages) in Sweden.

9.3.1. Baseline Data

The data captured include, but are not restricted to, the following: age, sex, years since diagnosis, disease severity, drug history, comorbidities (eg, history of malignancies), current concomitant medications, etc.

9.3.2. Follow-Up and Risk Window

Patients will be followed from treatment start (Index Date) until each outcome of interest, death, emigration from Sweden and end of study follow-up treated as censoring events. The Study End Date is defined as 3 years after the Study Start Date (date when first patient diagnosed with RA in ARTIS initiates treatment with Ruxience).

Some outcomes of interest in this study are thought to potentially occur at a higher rate while on drug, but that increased risk subsides after the drug is discontinued (ie, serious infections, CV events). Those events will be evaluated over a risk window that includes time from drug initiation until 270 days (eg, 9 months) after end of treatment (ie, last dose of Ruxience). The 270-day extension period is implemented to accommodate the very long half-life of Ruxience, and to ensure that any subclinical or undiagnosed illness at time of end of treatment is captured. For non-melanoma skin cancer (NMSC) and other malignancies, the manifestation of which is expected to be delayed relative to the time of exposure, the outcomes will be evaluated from drug initiation until the first event or loss to follow up, reflecting a once-exposed always at-risk paradigm.

9.3.3. Endpoints of Interest

For the interim and final safety reports (which will include information on patients, covariates and incidence rates for pre-specified safety outcomes, from SRQ as well as from the linked Patient/Prescribed Drug and other registers), the following events of interest have been pre-specified.

1. Hospitalised infections overall.
2. NMSC.
3. Malignancies, excluding NMSC.
4. CV events, including but not limited to deep vein thrombosis/pulmonary embolism.
5. Use during pregnancy.

In addition, the final study report will include the number of Ruxience-exposed pregnancies. If data are sufficient, rates of diagnosed malformations can be provided however, the number of Ruxience-exposed pregnancies is expected to be low based on previous data for other biosimilars.

9.4. Data Sources

9.4.1. SRQ

SRQ is the source of disease activity information, measured by C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), health assessment questionnaire (HAQ), number of swollen and tender joints, and patient's global assessment of disease (on a visual analog scale (VAS)) and doctor's evaluation on a Likert type scale. In addition, Disease Activity Score in 28 joints (DAS28), the European league against rheumatism response criteria, and the American College of Rheumatology criterion of improvement (ACR 20 50) can be calculated.

9.4.2. SRQ/ARTIS Linkage

Endpoint information will be derived from the linkage of SRQ/ARTIS to nationwide Swedish health care registers. The register linkage has many advantages in providing data on all comorbidities that have been diagnosed. The drawback is a lag time of between 1 and 2 years from when an event occurs until it can be analysed and reported using the national health care registers. This delay is caused by the annual curation of the Patient and Cancer registers by the National Board of Health and Welfare (ie, data from each year is only made available after internal processing, usually 9 to 12 months later, and the processing of data requests.

9.4.3. The Patient Register and the Prescribed Drug Register

The Swedish Patient Register provides information on all hospitalised (inpatient treated) patients, and all visits to non-primary outpatient care (such as a visit to a rheumatologist). Diagnoses are assigned by the discharging/treating physician, as well as date of discharge/visit, hospital and department. Diagnoses are coded according to the International Classification of Diseases (ICD), with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

The Prescribed Drug Register provides all retrievals of prescribed drugs in Sweden from July 2005 and may be used to aid correct classification of patients by their history of retrieved DMARDs.

9.4.4. The Swedish Cancer Register

The Swedish Cancer Register was established in 1958 and provides data on date of cancer (and some selected pre-cancers) onset, and type of cancer according to the ICD classification and morphology/histology. About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.[22]

9.4.5. The Medical Birth Register

The Medical Birth Register contains prospectively collected data from antenatal, obstetric, and neonatal records since 1973, and covers all live and still births (but not all miscarriages) in Sweden.[23] Among the variables covered are maternal age, parity, smoking and family situation in early pregnancy, and the infant's birth weight and length, gestational age (primarily based on ultrasound dating), and Apgar score. Complications and mother's and infant's morbidities are coded according to the ICD, with version 8 used until 1986, version 9 1987 to 1996 and ICD10 since 1997.

9.4.6. The Cause of Death Register

The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. Although the register was started in 1952, the data is considered complete since 1961.

9.4.7. The Total Population Register

The Total Population Register lists data on residency at a given point in time since it was founded in 1961, and dates of emigration/immigration for all subjects ever resident in Sweden since 1961. This register thus provides information on censoring (death and emigration) of study subjects and can also be used to identify a general population comparison cohort.

9.5. Study Size

All eligible patients in ARTIS who initiate Ruxience during the study period will be included, with no upper limit on the sample size. This is a descriptive study with no apriori hypotheses. Table 2 displays 95% confidence intervals around the incidence proportions for safety events of interests reported in the Ruxience RMP.

Table 2. Precision Estimates Based on Incidence Proportions for Safety Events Reported in the Ruxience RMP

Condition	Incident Count	Population at Risk	Incidence Proportion	Lower Bound of 95% CI	Upper Bound of 95% CI
Any infection (including serious infection)	22	73	0.301	0.199	0.420
Serious infection	3	73	0.041	0.009	0.115
Malignancy (excluding NMSC)	1	73	0.014	0.000	0.074
NMSC	0	73	0.000	0.000	0.049
CV events	3	73	0.041	0.009	0.115

NMSC, non-melanoma skin cancer; CV, cardiovascular; CI, confidence interval.

9.6. Data Management

This study analyses existing data within the ongoing ARTIS register. The ARTIS researchers are responsible for the data management of this study. As previously described, health and demographic information within Sweden is collected in a series of registers with a high degree of completeness resulting from the mandatory and semi-automated registration of their data. Based on each Swedish resident's unique personal identification number, issued to all Swedish residents alive in 1947 or born/immigrated thereafter, linkage of data from different registers is possible.[19] The registers are maintained by governmental bodies (the main registers used in this project are held by the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden (Statiskiska centralbyrån), who may perform data linkages and provide de-identified data for research purposes.

The data warehouses of ARTIS reside on restricted, double backed-up, servers at the Clinical Epidemiology unit at the Karolinska University Hospital Campus. ARTIS data are housed at the Clinical Epidemiology Division and linked to the data received from the National Board of Health and Welfare and/or Statistics Sweden using the unique personal identification number that all Swedish residents receive. Trained staff perform this linkage, in addition to data cleaning and analysis. All work with these data warehouses is done by trained staff in adherence with local guidelines on good programming and data management practices, and on archiving. Data, programs, and documents related to study reports will be maintained for a minimum of ten years.

9.7. Data Analysis

All statistical analyses will be performed by ARTIS using SAS version 9.4 or later. Detailed methodology for all analyses of data included in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by ARTIS and shared with 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.

ARTIS will apply an ICD-code-based algorithm to identify serious infections, malignancies and CV events (MACE), in the Swedish patient register. See Table 3. Endpoint Algorithms and Validation References in ANNEX 1. LIST OF STAND ALONE DOCUMENTS for algorithms and relevant validation references. The specific algorithms for defining those endpoints have not been validated, though the Swedish patient register has been validated several times.[24] The overall positive predictive value (PPV) of the inpatient diagnoses generally ranged from 85% to 95%. A regional validation study of hospitalised acute MI and stroke (components of the MACE endpoint) found PPVs of 96% and 94% respectively, in the period 1977 to 1987.[25] While the ICD algorithms used by ARTIS to define the endpoints of interest may not be validated, their use can be justified given the importance to contextualise the study results with historical findings. ARTIS has previously conducted and published studies of serious infections [26,27,28,29] and MACE [30,31,32,33] events in RA patients.

Per Pfizer's subscription to the ARTIS database, analyses will be conducted by ARTIS researchers and in accordance with ARTIS scientific review policies. The database does not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

9.7.1. Annual Reports

Reports summarising Ruxience uptake and patient characteristics will be provided on an annual basis. These will provide data from SRQ/ARTIS on patients treated with Ruxience.

9.7.2. Interim and Final Study Reports

The interim and final reports will present data on safety events of interest identified through linkages with the patient, cancer, and death registers as appropriate.

For these analyses, the Ruxience cohort will be analysed overall and stratified by previous biologics use. The general analytic approach will be descriptive and include incidence rates of events of interest within the Ruxience cohort. Incidence rates will be calculated by dividing the number of events by the person-time of exposure and will include 95% confidence intervals.

9.8. Quality Control

This study uses data existing within ARTIS. ARTIS works mainly with data from the SRQ, a quality of care register with several guidelines in place to monitor and maintain data quality. Physicians working with the SRQ have access to an online portal in which they can monitor all their patients and their information. Regional representatives encourage/remind the physicians to check the quality of the information by accessing the "Data Quality" section of the "Visit monitoring" tool: in this section a series of questions guide the doctor in checking the quality of the registered information of their patients. Moreover, the data coordinator of SRQ periodically check the quality of the data overall in the region.

9.9. Limitations of the Research Methods

This study is designed to monitor the safety of Ruxience in the clinical practice setting utilising the ARTIS Register, a well-established Swedish-based rheumatology register. Despite the strengths of the register, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of endpoint misclassification, is of concern in interpreting findings.

As a new therapy in the RA treatment armamentarium, it is possible that patients treated with Ruxience 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 events. Biases resulting from channeling may present as increased rates of safety events of interest in the early phases of the study. Stratification on key indicators of disease severity, patient characteristics and past therapies can be done for contextualisation. Trend analyses may be conducted to evaluate rates in Ruxience patients over time.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to patient management. The rates of safety events of interest and their distribution among patient-types may have changed over time.

Endpoint misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While ARTIS has an established system to identify and capture endpoint data, all events cannot be fully verified via source documentation. Instead, linkage to national health care registers allows the register to obtain data on all safety events of interest (regardless of suspected causal relationship to the treatments).

Another limitation of this study design is the absence of a control group which does not allow for comparative analysis of incidence rates with other treatments. This study will follow patients for a period of 3-years from therapy initiation, assuming continued participation and sufficient accrual of Ruxience patients is feasible. This period of follow-up may not be sufficient to adequately evaluate all safety events of interest, specifically malignancies. Conclusions may not be generalisable outside of the 3-year period since initiation of therapy.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves anonymised 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/Independent Ethics Committee

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant Institutional Review Boards (IRB)/International Ethics Committee (IEC). All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

This register-linkage database does not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files. This study has been approved by the Ethics Committee in Stockholm (DNR: 2015/1844-31/2, renewed approval will be sought as needed for the duration of the study).

10.3.1. Ethical Permits

In accordance with Swedish law, non-interventional studies of register-based data (including "quality of care" registers such as SRQ/ARTIS) do not usually require informed consent by the individual study subjects. Instead, regional ethics committees are mandated to provide permission for such studies, after weighing the subjects' potential benefit from the research against the potential risks to the subjects' personal privacy. ARTIS has ethical approval for the studies described in this protocol as outlined above but is subject to strict rules and regulations regarding the maintenance, analysis and reporting of personal data. Patient consent is not required for this study as data already exist within ARTIS register.

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 issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association, the Karolinska Institutet's guidelines on Research Conduct and the European Network of Centres for

Pharmacoepidemiology and Pharmacovigilance (ENCePP). See ANNEX 2. ENCePP checklist for study protocols.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual summary reports will be generated. Analysis using linked register data through 3 years of follow up will be the basis for a final report. Data may be used in regulatory communications external to Sweden for contextualisation purposes. Manuscripts based on specific endpoints of interest may be developed for publication purposes.

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 investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Table 3. Endpoint Algorithms and Validation References

Event	Operationalisation	Validation ICD
Serious infections	Hospitalisations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1	This algorithm has not been specifically validated in ARTIS, but the register itself is subject to strict quality assurance routines and has been validated several times. References: Ludvigsson et al. External Review and Validation of the Swedish National Inpatient Register, BMC Public Health, 2011 (11):450. http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish

Event	Operationalisation	Validation ICD
CV Risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care	'Outcome' was defined as any first-ever ACS event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the underlying cause of death. For discharge diagnoses, the date of admission to hospital was considered the event date. This outcome definition has previously been validated in a Swedish early RA cohort, with a positive predictive value of 95%. In addition, a regional validation study of hospitalised acute MI and stroke found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987. References: https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.39267 Mantel et al. Risk Factors for the Rapid Increase in Risk of Acute Coronary Events in Patients With New-Onset Rheumatoid Arthritis. A Nested Case-Control Study. Arthritis & Rheumatology. 2015; 67(11):2845-2854. Lindblad et al. Validity of register data on acute myocardial infarction and acute stroke. Scandinavian Journal of Public health 1993; 21 (1):3-9.
NMSC	Identified through the Cancer register as all malignancies with ICD-O/2 code C44, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers Alt: all invasive NMSC, identified as non-benign ICD-O/2 code C44, and no basal cell cancers.	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi-automated, resulting in an estimated coverage greater than 95%.

Event	Operationalisation	Validation ICD
Malignancy	All invasive malignancies recorded in the cancer register, excluding NMSC	See NMSC
Abbreviations: ACS= acute coronary syndrome; ARTIS= Anti Rheumatic Treatment in Sweden; ICD= International Classification of Diseases; MACE= major acute cardiovascular events; MI= myocardial infarction; NMSC= non-melanoma skin cancer; RA= rheumatoid arthritis		

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Active Surveillance, Post Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Ruxience for Moderately to Severely Active Rheumatoid Arthritis (RA) within the Swedish, Population based, Anti Rheumatic Treatment in Sweden (ARTIS) register

EU PAS Register® number:
Study reference number (if applicable):B3281013

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	N/A

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.4
4.2.2 Age and sex	☐	☐	☒	N/A

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	9.4
4.2.5 Duration of follow-up	☒	☐	☐	9.4.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2 and 9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 9
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	Section 9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	Section 9
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	N/A

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.3.
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3 and 15.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.8.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	N/A

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	N/A
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	N/A

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	N/A

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.5.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.5
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4.1 and appendices 1 and 2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1 and appendices 1 and 2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	15.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4.1 and appendices 1 and 2
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8.2
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	N/A
10.3 Are descriptive analyses included?	☒	☐	☐	9.8.2
10.4 Are stratified analyses included?	☒	☐	☐	9.8.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	N/A
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	N/A
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	N/A

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	N/A

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	N/A
12.1.2 Information bias?	☒	☐	☐	9.9

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Cynthia de Luise

Date: 25 Sept 2020

Signature: 

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ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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