NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden
Protocol number	B7981102
Protocol version identifier	1.0
Date	01 March 2024
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Ritlecitinib ATC code L04AF08
Medicinal product	Litfulo®
Product reference	EU/1/23/1755/001, EU/1/23/1755/002, EU/1/23/1755/003
Procedure number	EMEA/H/C/006025
Marketing Authorization Holders	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
Joint PASS	No
Research question and objectives	Research Question: To what extent do routinely collected data indicate health care professional's (HCP) adherence to the recommendations for the use of ritlecitinib described in the Summary of Product Characteristics (SmPC), HCP guide, and Patient Card? The study objectives are to: 1. Evaluate, to the extent measurable in the available routinely collected data, indicators of HCP's adherence to the risk minimization measures (RMMs) in accordance with the ritlecitinib SmPC, HCP guide, and Patient Card, specifically:

	• Performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to initiation of ritlecitinib treatment • Performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment • Avoiding live attenuated vaccines shortly before and during treatment with ritlecitinib • No use during pregnancy • No use in patients aged < 12 years • No use during serious infections 2. Describe the characteristics of patients before initiation of ritlecitinib treatment, in terms of: • Risk factors for thromboembolic events (including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis) • Risk factors for malignancy • Risk factors for cardiovascular disease (CVD)
Countries of study	Denmark, France, and Sweden
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	alopecia areata
AE	adverse event
ATC	Anatomical Therapeutic Chemical
ATE	arterial thromboembolism
aRMMs	additional Risk Minimization Measures
AT	alopecia totalis
ATE	arterial thromboembolism
AU	alopecia universalis
BCG	Bacille Calmette-Guérin
CABG	coronary artery bypass graft
CCAM	Classification commune des actes médicaux
CESREES	Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé
CI(s)	confidence interval(s)
CIOMS	Council for International Organizations of Medical Sciences
CIP	Code Identifiant de Présentation
CNIL	Commission Nationale de l'Informatique et des Libertés
CPR	Central Personal Registry
CVD	cardiovascular disease
DNPR	Danish National Prescription Registry
DVT	deep vein thrombosis
EC	ethics committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
HMA	Heads of Medicines Agencies
ICD	International Statistical Classification of Diseases
ICD-10	International Classification of Disease, Tenth Revision
ICD-11	International Classification of Disease, Eleventh Revision
IRB(s)	Institutional Review Board(s)
ISPE	International Society for Pharmacoepidemiology
JAK	Janus Kinase
KVÅ	Klassifikation av vårdåtgärder
MAH	Marketing Authorization Holder
MMR	measles, mumps, rubella
NI	non-interventional
NIS	non-interventional study

Abbreviation	Definition
NMSC	nonmelanoma skin cancer
NOMESCO	Nordic Medico-Statistical Committee
NPU	Nomenclature, Properties and Units
PAS	Post-authorization studies
PASS	Post-authorization safety study
PCI	Percutaneous intervention
PE	pulmonary embolism
PY(s)	person-year(s)
RMMs	Risk Minimization Measures
RWD	real world data
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SNDS	Système National des Données de Santé
TB	tuberculosis
UCD	Unité Commune de Dispensation
US	United States
VTE	venous thromboembolism
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden

Protocol B7981102; Version 1.0; 01 March 2024

Main author: Vera Ehrenstein, Aarhus University

Rationale and background Alopecia areata (AA) is an autoimmune disease that has an underlying immuno-inflammatory pathogenesis and is characterized by nonscarring hair loss ranging from small patches to complete scalp, face, and/or body hair loss. Ritlecitinib was authorized by the European Medicines Agency (EMA), on 15 September 2023, for the treatment of severe AA in adults and adolescents 12 years of age and older. To mitigate the risks associated with ritlecitinib use, required routine risk minimization measures (RMMs), including the Summary of Product Characteristics (SmPC) and package leaflet, are being employed. This noninterventional study (NIS) is designated as a post-authorization safety study (PASS) and is a commitment to the EMA.

Research question and objectives
Research Question: To what extent do routinely collected data indicate health care professional's (HCP) adherence to the recommendations for the use of ritlecitinib described in the Summary of Product Characteristics (SmPC), HCP guide, and Patient Card?

The study objectives are to:
1. Evaluate, to the extent measurable in the available routinely collected data, indicators of HCP's adherence to the risk minimization measures (RMMs) in accordance with the ritlecitinib SmPC, HCP guide, and Patient Card, specifically:

- Performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to initiation of ritlecitinib treatment
- Performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment
- Avoiding live attenuated vaccines shortly before and during treatment with ritlecitinib
- No use during pregnancy
- No use in patients aged < 12 years
- No use during serious infections

2. Describe the characteristics of patients before initiation of ritlecitinib treatment, in terms of:
- Risk factors for thromboembolic events (including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis)
- Risk factors for malignancy
- Risk factors for cardiovascular disease (CVD)

Study design This is a descriptive drug utilization study using secondary data from healthcare databases in Denmark, France, and Sweden. These countries have universal healthcare.
Population The study population will include patients identified in each data source with a record of treatment with ritlecitinib from 15 September 2023 through 14 September 2028. Patients will not be required to have a recorded diagnosis of AA.

Variables The study will collect relevant data including patient demographics, co-morbidities, prescription medications, vaccine administrations, and laboratory testing prior to the initiation of ritlecitinib and during treatment with ritlecitinib to address the study objectives.

Data sources This study will utilize routinely collected electronic healthcare data from national or regional population-based electronic healthcare registers in Denmark, France, and Sweden.

Study size All patients initiating ritlecitinib during the study period will be included.

Data analysis Data will be analysed in each country separately using a common protocol, database-specific definitions of the study variables, and a common analysis strategy. The main measures will be proportions of ritlecitinib users with a given indicator of RMM adherence.

Milestones Data collection will start in September 2027 and end in September 2030. Results will be summarized in a September 2028 interim report and a March 2031 final report.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date[a]	Comments
Registration in the EU PAS register	August 2027	Prior to initiating data collection.
Draft protocol submission	March 2024	Within 6 months from approval of ritlecitinib in the European Union (EU).
Start of data collection[b]	September 2027	Within 4 years from approval of ritlecitinib in the EU.
End of data collection[c]	September 2030	Within 2 years after the end of study period, considering the lag in data availability in the respective data sources.
Interim Report	September 2028	Interim study report planned for submission within 5 years of approval of ritlecitinib in the EU, considering the lag in data availability in the respective data sources.
Final study report	March 2031	Final study report is planned for submission within 6 months from the end of data collection.

a EU approval 15 September 2023.
b Defined as the date from which data extraction starts.
c Defined as the date from which the analytical dataset is completely available, i.e., clean and coded data from all participating countries/databases.

7. RATIONALE AND BACKGROUND

Alopecia areata (AA) is an autoimmune disease that has an underlying immuno-inflammatory pathogenesis and is characterized by nonscarring hair loss ranging from small patches to complete scalp, face, and/or body hair loss. AA may present as: limited patchy hair loss (patchy alopecia areata), complete loss of hair on the scalp (alopecia totalis [AT]), or complete loss of hair on the scalp and the body (alopecia universalis [AU]). The affected skin usually does not have signs of inflammation.

Both males and females of all ages and races can be affected. AA is the second most common cause of hair loss, affecting approximately 147 million individuals worldwide, with a lifetime risk of all subtypes of approximately 2% (1, 2). Incidence rates of AA range from 20 to 200 per 100,000 person-years [PY(s)], and the global lifetime prevalence worldwide is estimated at 2% (2-8). A meta-analysis including articles published up to 01 September, 2018 estimated the overall pooled incidence proportion of AA in Europe as 4.92% (95% confidence interval [CI] 2.41-8.25%), and the pooled prevalence as 0.58% (95% CI 0.49-0.66%) (9). AA is associated with inflammatory diseases including asthma, allergic rhinitis, atopic dermatitis, and autoimmune diseases such as thyroiditis and vitiligo (10). The natural history and prognosis of AA are unpredictable and can be marked by remission, progression, or persistence (11, 12).

Ritlecitinib was authorized by the European Medicines Agency (EMA), on 15 September 2023, for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (13). Ritlecitinib is flagged by the Danish authorities as a medication being subject to heightened monitoring (14).

To mitigate the risks associated with ritlecitinib use, required routine risk minimization measures (RMMs), including the Summary of Product Characteristics (SmPC) and package leaflet, are being employed. In addition to the routine RMMs, Pfizer has agreed to implement additional risk minimization measures (aRMMs) following ritlecitinib approval in the EU, including an educational program intended to enhance the communication of the risks and risk minimization practices to healthcare professionals (HCPs) via an “HCP Guide” and to patients via a “Patient Card”. The patient card is a tool that reminds the patient of certain action(s) to take for risk minimization or aims to ensure that information regarding the patient’s current treatment with the medicinal product and its risks is held by the patient at all times and used as a communication aid with healthcare professionals. The overall objective of the agreed aRMMs is to provide appropriate tools designed to enhance the awareness and knowledge of HCPs and patients about the safety risks and to ensure the optimal use of ritlecitinib.

An evaluation of the database-measurable indicators of adherence of HCPs with the RMMs will help understand whether the program objectives have been met and if further amendments to the program may be needed. Therefore, Pfizer aims to evaluate indicators of adherence to the routine and additional RMMs for ritlecitinib in three EU countries: Denmark, France, and Sweden.

This noninterventional study (NIS) is designated as a post-authorization safety study (PASS) and is a commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

The research question is: to what extent do routinely collected data indicate health care professional's (HCP) adherence to the recommendations for the use of ritlecitinib described in the Summary of Product Characteristics (SmPC), HCP guide, and Patient Card?

8.2. Study Objectives

The study objectives are to:
1. Evaluate, to the extent measurable in the available routinely collected data, indicators of HCP's adherence to the risk minimization measures (RMMs) in accordance with the ritlecitinib SmPC, HCP guide, and Patient Card, specifically:

- Performing laboratory tests of lymphocyte count, platelet count, hepatitis B/C, and tuberculosis (TB) screening prior to initiation of ritlecitinib treatment
- Performing laboratory tests of lymphocyte count and platelet count at week 4 (± 2 weeks) from initiation of ritlecitinib treatment
- Avoiding live attenuated vaccines shortly before and during treatment with ritlecitinib
- No use during pregnancy
- No use in patients aged < 12 years
- No use during serious infections

2. Describe the characteristics of patients before initiation of ritlecitinib treatment, in terms of:
- Risk factors for thromboembolic events (including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis)
- Risk factors for malignancy
- Risk factors for cardiovascular disease (CVD)

9. RESEARCH METHODS

9.1. Study Design

This will be a descriptive drug utilization study using data from healthcare databases in Denmark, France, and Sweden.

9.1.1. Study Population and Study Period

The study population will include patients identified in each data source with a record of treatment with ritlecitinib during the study period. The study period will be 5 years following product launch: from 15 September 2023 through 14 September 2028.

9.1.2. Index Date

The date of the first dispensing or administration of ritlecitinib during the study period will be the index date.

9.2. Setting

Denmark, France, and Sweden have universal healthcare, whereby routinely collected data continuously accrue in the participating nationwide databases (described in Section 9.4). The use of the three population-based data sources will contribute to generalisability of the study results to AA patients in the EU. Data sources have been selected given adequate capture of some or all key study variables and relatively large underlying population sizes of patients across the regions. Indeed, the Danish, French, and Swedish databases capture information from nearly the entire populations of their residents. These large real-world data sources are assumed to be representative of patient and physician populations in their respective countries and will provide invaluable data to evaluate measurable indicators of HCP's adherence to the RMMs.

9.2.1. Inclusion Criteria

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

1. Have at least one dispensing of ritlecitinib during the study period
2. Have at least 12 months of continuous history in a participating data source before the index date

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

Variables will include patient demographics (age and sex), comorbidities (measured by diagnoses from specialist health care at hospital encounters or treatment proxies), medication dispensings, procedures, and laboratory tests (Denmark and France only) prior to initiating ritlecitinib and monitoring tests during follow-up after treatment initiation. The maximum

lookback period for ascertaining characteristics before ritlecitinib initiation will be 12 months (365 days), but will vary for a given RMM measure, per SmPC.

9.3.1. Exposure

The date of the first dispensing of ritlecitinib during the study period will be the index date. The exposure will continue until the end of a 90-day grace period following the estimated discontinuation of the index treatment. Duration of each dispensing will be computed based on days supplied, estimated based on assumed daily dose, package size, and number of packages in each dispensing. Only the first continuous treatment episode will be considered in this study.

9.3.2. Indicators of Adherence to RMMs

The RMMs are described in the Risk Management Plan (13). Briefly, the RMMs recommend performing laboratory screening tests prior to ritlecitinib initiation, including lymphocyte count, platelet count, hepatitis B/C, and TB; performing laboratory tests of lymphocyte count and platelet count 4 weeks after initiation, avoiding live attenuated vaccines shortly before and during treatment, and avoiding use in pregnancy and during serious infections. Ritlecitinib is currently only indicated for those age 12 years or older.

- Lymphocyte count
- Platelet count
- Screening for TB
- Screening for viral hepatitis B and C
- Live attenuated vaccines
    - Measles
    - Mumps
    - Rubella
    - Others as available in data sources
- Pregnancy
- Serious infections

9.3.3. Risk Factors for Thromboembolic Events

Risk factors for thromboembolic events will be identified during the 12 months prior to and including index date:

- Age >65 years
- History of VTE
- History of arterial thromboembolism (ATE)
- Major surgery within 90 days before the index date
- Combined hormonal contraceptives
- Hormone replacement therapy
- Pregnancy
- Malignancy
- CVD

9.3.4. Risk Factors for Malignancy

Risk factors for malignancy will be identified during the 12 months prior to and including index date:

- Age >65 years
- History of malignancy
- History of NMSC
- Obesity
- Alcohol-related conditions
- Tobacco-related conditions

9.3.5. Risk Factors for CVD

Risk factors for CVD will be identified during the 12 months prior to and including index date:

- Age >65 years
- Diabetes
- Obesity
- Hypertension
- Hyperlipidaemia
- Chronic kidney disease
- Alcohol-related conditions
- Tobacco-related conditions

9.3.6. Other Variables

Demographics

- Age at index date
- Sex
- Calendar year of index date

9.3.7. Preliminary Operational Definitions of the Main Study Variables

Generally, in the participating data sources, disease is identified by diagnoses recorded at hospitalizations (all three countries) or at hospital-based specialist outpatient clinics (Denmark and Sweden). Diagnoses are currently coded using the World Health Organization (WHO) International Classification of Diseases, Tenth Revision (ICD-10). The Danish version of the ICD-10 may have more detailed codes compared with the WHO ICD-10. ICD-11 will be used if introduced during the study period. Treatment records originate, depending on the database, from outpatient dispensings, from hospital administrations, and are coded using the Anatomical Therapeutic Chemical (ATC) classification or local structured vocabularies (e.g., local treatment codes in Denmark). Ritlecitinib and concomitant medications and vaccinations will be identified using ATC codes or hospital treatment codes as appropriate. Data on laboratory tests, available from Denmark and France, will be identified using Nomenclature, Properties and Units (NPU) codes or local codes as appropriate. Surgeries will be defined using country-specific procedure/surgery codes. Age (date of birth) and sex will be used as reported in the databases.

Table 1 summarizes the initial operational definitions and data availability per data source, of the eligibility criteria, the exposure and the endpoints. The refined, country-specific definitions of all study variables as well as the final list of other variables with their operational definitions will be provided in the Statistical Analysis Plan (SAP).

Table 1. Preliminary Definitions of the Main Study Variables

Measure	Availability and initial operational definition		
	Denmark	France	Sweden
Ritlecitinib initiation	ATC code L04AF08		
Indicators of Adherence to RMMs			
Lab: lymphocyte count	Potential candidate example codes (subject to refinement): NPU codes NPU02902 B— Neutrophilocytes; NPU02636 B— Lymphocytes; num.c.	Complete blood count including platelets: TNB code 1104	Not available
Lab: platelet count	NPU03568 B— Thrombocytes	Complete blood count including platelets: TNB code 1104	Not available
Screening for TB	Not available	In/outpatient lab test (no results)	Not available
Screening for viral hepatitis B or C	Not available	In/outpatient lab test (no results)	Not available
Vaccines	Vaccine type as recorded in the Danish Health Service Registry. The registry lists vaccine pathogen e.g., MMR vaccine etc. However, it is possible to identify live vaccine based on what is used according to the Danish Health Authority. This registry records vaccines that are paid by public. Travel vaccines and vaccines paid by employer will not be recorded.	Reimbursed vaccines such as MMR, chickenpox (for patients 12 months and above), BCG, Rotavirus, varicella, Dengue, and Yellow Fever not reimbursed.	Not available

Table 1. Preliminary Definitions of the Main Study Variables

Pregnancy	ICD-10 O chapter codes for pregnancy, NOMESCO codes KMCA for Caesarean and/or linkage to the birth registry Diagnosis codes for pregnancy ICD-10 O chapter (https://icd.who.int/browse10/2019/en#/XV) (Subject to availability check: referral codes of prenatal visits at GP from the Danish Health Services Registry) Linkage to birth registry may be considered	ICD-10 codes: O80xx-O84xx (delivery), Z37xx (result of delivery), O01xx-O07xx (abortion and other abnormal products of conception) CCAM codes (medical acts) : (delivery) JQGD010, JQGD012, JQGD004, JQGD001, JQGD003, JQGD008, JQGD013, JQGD005, JQGD002, JQGD007, JQGA002, JQGA004, JQGA003, JQGA005 (termination) JNJD001, JNJD002, JNJP001 (ectopic pregnancy) JJFA001, JJFC00, JJJA002, JJJC002, JJLJ001, JJPA001, JJPC001, JQGA001 Outpatient healthcare code (PRS_NAT): (medical termination) 2422, 3329, 2415, 2416	ICD-10 O chapter codes for pregnancy (https://icd.who.int/browse10/2019/en#/XV) Linkage to birth registry may be considered
Serious infection	Serious infection: ICD-10 codes as primary diagnosis at a hospital contact with a minimum of 1 overnight stay A00-B99, D73.3, E06.0, 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, J38.3, 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, 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, N10, N11, N12, 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, or N75.1, U071 Denmark only: Z861A (the code list will be refined in the SAP to map ICD-10-CM codes to ICD-10 equivalents whenever feasible)		

Table 1. Preliminary Definitions of the Main Study Variables

Risk factors for thromboembolic events, malignancy or CVD			
Age 65 years or older	per date of birth		
History of thromboembolic events including VTE or ATE	ICD-10 codes I26, I260A I269A, I67.6, I74, I80.1, I80.2, I81, I82.0, I82.2; I82.3, I82.8, I82.9 O22.3, O87.0, O87.1 Denmark only: O882D, O882E, T817D		
Malignancy (any, primary or secondary)	ICD-10 codes chapter C	ICD-10 codes chapter C, treatment codes if relevant	ICD-10 codes chapter C
Major surgery within 90 days of index date	NOMESCO Classification of Operations on the nervous system: KA; Operations on endocrine organs: KB; Operations on the heart and large intrathoracic vessels: KF; Operations on respiratory organs, chest, mediastinum and diaphragm: KG; Breast surgeries: KH; Operations on digestive organs and spleen: KJ; Operations on the urinary tract, male genitalia and retroperitoneal tissue: KK; Operations on female genitalia: KL; Obstetric operations: KM; Operations on the musculoskeletal system: KN	CCAM codes for major surgery	Swedish KVÅ Selected procedure codes starting on N, J, L, G (further refinement to be done in the SAP)
Combined hormonal contraceptives	ATC codes G03A		Not available (not reimbursed)
Hormone replacement therapy	ATC codes G03		
Obesity	ICD-10 codes E65		
Alcohol-related conditions	ICD-10 codes K70, F10		
Tobacco-use related conditions	ICD-10 codes J40-J47		
Diabetes	ICD-10 codes E10-E14, ATC codes A10		

Table 1. Preliminary Definitions of the Main Study Variables

Hypertension	ICD-10 codes I10-I15, treatment proxies		
Hyperlipidaemia	ICD-10 codes E78, treatment proxies, laboratory data (Denmark only)		
Coronary artery disease	ICD-10 codes I21-I25 Nordic Medico-Statistical Committee (NOMESCO) codes for coronary artery bypass graft (CABG) or percutaneous intervention (PCI): FNF, FNG, FNA, FNB, FNC, FND, FNE	ICD-10 codes I21-I25	ICD-10 codes I21-I25 Nordic Medico-Statistical Committee (NOMESCO) codes for coronary artery bypass graft (CABG) or percutaneous intervention (PCI): FNF, FNG, FNA, FNB, FNC, FND, FNE
Chronic kidney disease	ICD-10 codes N18, potentially dialysis procedure codes	ICD-10 codes N18	ICD-10 codes N18, potentially dialysis procedure codes
AA diagnosis	ICD-10 code L63		

Source of ICD-10 codes: Denmark and Sweden, inpatient (hospital) or outpatient (specialist visits); France, inpatient hospital encounters. ICD-10 codes with trailing letters are applicable in Denmark only.

9.4. Data Sources

9.4.1. Denmark

Denmark's population-based registers, linkable by a unique identifier, the central person registration (CPR) number, assigned by the CRP registry to all residents at birth or upon immigration contain routinely collected data for the country's entire population of more than 5.8 million individuals and allow long-term follow-up of individuals for assessment of safety events such as MACE or malignancy (15, 16). The CPR registry contains information on age, sex, migrations and deaths. The Danish National Prescription Registry (DNPR) contains information on all prescription medicines dispensed at Danish community pharmacies with

products recorded via Anatomical Therapeutic Chemical (ATC) codes. Certain drugs administered at specialist hospital-based clinics are captured in the Danish National Patient Register (NPR), and tentatively from 2024, in the Danish Hospital Medicines Register (currently in development and expected to become complete in 2024 (17)). Newly approved drugs, especially expensive treatments, are often first prescribed or administered at the specialist hospital clinics with follow-up with general practitioners. Such treatments (active substance) may be identifiable via treatment codes in the Danish NPR. The Danish NPR records diagnoses (WHO ICD-10/ICD-11 codes) and procedures (NOMESCO codes) during inpatient or outpatient hospital encounters. The Danish Cause of Death Registry records causes of death using ICD-10 code categories. The Danish Health Services Register may be used to ascertain referrals for hearing-loss related procedures as well as administration of reimbursed vaccinations; identification of pregnancy referrals may also be explored. The Danish Laboratory Research Database contains information about laboratory tests and their results from hospital-based laboratories. The Danish Vaccination Registry may be used to obtain data on vaccinations (18). Most of these databases have been used extensively in pharmacovigilance, and multiple algorithms have been validated (19-27).

9.4.2. France

The French nationwide administrative database (Système National des Données de Santé – SNDS; French Administrative Healthcare Database) covers more than 99% of the French population – near 67 million inhabitants – from birth (or immigration) to death (or emigration), even if a subject moves, changes occupation or retires (28, 29). Using a unique pseudonymized identifier, it merges all reimbursed outpatient claims from all French healthcare insurance schemes with hospital-discharge summaries from public and private hospitals, and the national death registry. Thus, all reimbursed medical and paramedical encounters are recorded. SNDS captures general characteristics (e.g., sex, year of birth, affiliation scheme, area of residence); registration for Long Term Disease with the diagnosis code, qualifying for full health insurance coverage; outpatient encounter details (e.g., medical and paramedical visits with practitioner specialty, medical and imaging procedures, laboratory tests, quantity of drugs dispensed, drug strength, medical devices; but no indication, physician prescription directions, drug posology or exam results); inpatient details (e.g., primary and associated hospital discharge diagnoses, procedures and laboratory tests performed, innovative or expensive drugs and medical devices invoiced in addition to the hospitalization, length of the hospital stay). Dates, associated costs, and prescriber and caregiver information are provided for each expenditure. Diagnoses are coded using ICD-10 codes. Drug dispensings are identified and captured through ATC codes, but also at the package level in outpatient settings with the Code Identifiant de Présentation (CIP; Presentation Identification Code), and at the unit of administration level in inpatient settings through the Unité Commune de Dispensation (UCD; Common Dispensing Unit). Procedures are coded according to the Classification Commune des Actes Médicaux (CCAM; Common Classification of Medical Procedures), and laboratory tests follow the Nomenclature des Actes de Biologie Médicale (NABM; Nomenclature of Medical Biology Acts). The SNDS database also includes the French National Death Register (CepiDC) data. Though neither medical indication nor result are recorded, the level of detail of the captured information enables an accurate characterization of patient healthcare journeys (30). SNDS has been used

in multiple completed and ongoing studies that include endpoints (venous thromboembolism (VTE) (31), infections (32), GI bleeding (33-35), CVD validation algorithms (36), malignancies (37) identification of pregnancies and other variables relevant for the current study (JAK inhibitors (38), identification of pregnancies). Access to these data sources is strictly regulated by French law and needs approval from the Committee in Health data research (Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé – CESREES), and from the French data protection commission (Commission Nationale de l'Informatique et des Libertés – CNIL). Four to six months are required to obtain CESREES and CNIL approvals. An agreement between the CNAM and the SNDS research partner then needs to be signed to access data extraction. BPE will oversee requesting access to SNDS data.

9.4.3. Sweden

Similar to Denmark, the Swedish register system is a large, nationwide source of population-based data from the entire Swedish population (10.64 million in 2023). Data from the Total Population Register and the Swedish National Health Registers, including the Swedish National Patient Register, Prescribed Drug Register, Total Population Register, Swedish Cause of Death Register, Swedish Medical Birth Register and Swedish Cancer Register will be used. A unique personal identification number is issued to all residents of Sweden upon birth or immigration and is used throughout life. The personal identification number is used to link patient-level data across the various registers. All citizens, independent of socioeconomic status, have unrestricted access to health services including partial or complete reimbursement of purchased medicines due to the tax-supported public health service with universal coverage. The Swedish NPR includes diagnosis information for inpatients at publicly funded hospitals and outpatient specialists' visits, including primary and secondary diagnoses and surgical procedures. The Prescribed Drug Register includes information on all prescribed drugs dispensed at pharmacies in outpatient settings in Sweden since 01 July 2005. The register contains patient level data on dispensed medicines for the entire Swedish population, including information on the dispensed drug as well as the dates of prescription and dispensing (39-43). The coding systems for diagnoses, procedures, and medications are similar in Denmark and Sweden.

All three research centres and associated data sources are listed in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Register.

9.5. Study Size

This is a descriptive study, and no comparative analyses will be conducted. Thus, the purpose of the sample size calculations provided below is to describe the expected precision of the estimates.

The following formula, based on the normal approximation to the binomial proportion, was used to calculate the sample size for this study:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion of patients with evidence of having performed the recommended RMMs prior to/during treatment with ritlecitinib; e is the margin of error, or half the desired width of the CI; and $Z_{1-\alpha/2}$ is the standard normal Z-score corresponding to a cumulative probability of $1-\alpha/2$.

The proportion of patients with evidence of having performed the recommended RMMs prior to/during treatment with ritlecitinib (p) is not known in advance. Assuming varying proportions, the associated sample size and specified margins of error are provided in Table 2.

Table 2. Required Number of Ritlecitinib Treated Patients by Proportion of Patients With Evidence of Having Performed the Recommended Risk Minimization Measures (RMMs) and 95% Confidence Interval (CI) Width

Proportion of patients with evidence of having performed the recommended RMMs	Width of 95% CI (%)	Required number of patients
25%	10.0	289
	15.0	129
	20.0	73
50%	10.0	385
	15.0	171
	20.0	97
75%	10.0	289
	15.0	129
	20.0	73

Abbreviations: CI = confidence interval; RMM(s) = risk minimization measure(s).

The proportion of 50% yields the most conservative (i.e., the largest) sample size for a specified margin of error. In Table 2, a *minimum* sample size of 385 patients per database would maximize the precision of estimates. With 385 patients, the width of the CI will decrease as the proportion of patients with evidence of having performed the recommended RMMs approaches the extremes (0% and 100%, Table 3).

Table 3. Width of 95% Confidence Interval for a Range of Proportions, Assuming 385 Enrolled Patients

Proportion of patients with evidence of having performed the recommended RMMs	Width of 95% CI (%)
10%	6.0
20%	8.0
30%	9.2
40%	9.8
50%	10.0
60%	9.8
70%	9.1
80%	8.0
90%	6.0

Abbreviations: CI = confidence interval; RMM(s) = risk minimization measure(s).

The study will include all patients identified during the study period who meet the eligibility criteria to maximize the precision of the estimates.

9.6. Data Management

All source data will originate via existing data collection practices of the data custodians in Denmark, France, and Sweden. Linkage across different data banks (e.g., registries) within a database (e.g., Danish registries) will be implemented either by a country investigator or by a data custodian, in accordance with the country-specific practices and rules. The investigators in each country will use the source data to create the analytic dataset.

Details on data management will be provided in the SAP. Briefly, data accruing in the routine databases undergo database-specific quality control, subject to data custodians' internal process in each country, which, as a rule, is a government agency (National Health Data Board in Denmark, SNDS in France, National Board of Health in Sweden). Databases in all three countries have been recently characterized in a EMA-commissioned study titled Strengthening Use of Real-World Data in Medicines Development: Metadata for Data Discoverability and Study Replicability (EUPAS39322, (44)). This study was part of the EMA Big Data Initiative. The specific steps of data management taken by investigators to define the analytic dataset from the source data will vary by country. Generally, this will entail the following main steps:

- Obtaining approvals and completing protocol-specific data applications.
- Retrieval of or access to the protocol-specific source data. Retrieval or access is administered by an appropriate data authority in each country.
- Data management to prepare the analysis dataset according to specifications in the SAP by transforming the original routinely collected data to coded data in order to define analysis populations and study variables.

- Data cleaning and checking for consistency by plausibility ranges, units of measurement, and relevance of clinical information. Implausible values will be set to missing. Imputation of missing values is not planned.

- Generation of aggregate-level country-specific SAP-specified output in a computer readable format according to the data template prepared at the principal investigator institution.

The principal investigator institution (Aarhus University) will use the country-specific aggregate data supplied via the data template (using Microsoft Excel or similar standard software) to generate output as appropriate per planned Tables, Listings and Figures, which will be specified in the SAP. The investigators will use either SAS or R software, in the most recent version available to their organizations at the time of the analyses.

9.7. Data Analysis

This is a descriptive study and the data will be analysed and results presented separately by country. Counts and proportions for categorical variables and mean and median with ranges for continuous variables will be calculated to address the study objectives, as below. All proportions will be reported with 95% CIs.

Data sources vary in collection of laboratory test and vaccine information (data on both laboratory tests and their results are available in Denmark; data on performed laboratory tests, but not results, are available in France; laboratory data are not available in Sweden). Data on vaccines are not available in Sweden.

Counts and proportions will be calculated for:

1. Patients with evidence of having performed the following laboratory tests and screenings within 3 months before index date:

    - Lymphocyte count

    - Platelet count

    - Screening for TB

    - Screening for viral hepatitis B and C

2. Patients with evidence of having performed the following laboratory tests at week 4 (± 2 weeks) after index date:

    - Lymphocyte count

    - Platelet count

3. Patients with evidence of having received live attenuated vaccines within 4 weeks before index date

4. Patients with evidence of having received live attenuated vaccines during treatment with ritlecitinib

5. Females in whom pregnancy, as recorded in the available data sources, overlaps with ritlecitinib use

6. Patients aged <12 years on the index date

7. Patients with a serious infection before index date

8. Patients with evidence of having measured risk factors and the number of measured risk factors for thromboembolic events within 12 months before index date

9. Patients with evidence of having measured risk factors and the number of risk factors for malignancy within 12 months before index date

10. Patients with evidence of having measured risk factors and the number of risk factors for CVD within 6 months before index date

The windows for ascertainment of presence of specific events may be revised to reflect the local data flow.

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

9.7.1. Sensitivity Analyses

A sensitivity analysis will restrict to the subset of patients with an AA diagnosis on or up to 5 years before the index date.

9.8. Quality Control

Investigators in the respective countries will be responsible for following the internal standard operating procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and management.

The Department of Clinical Epidemiology, Aarhus University has implemented a series of internal standard operating procedures for data management and analysis as well as staff training. At a minimum, all study documents are reviewed by a senior epidemiologist and a statistician as well as by the entire research team by the entire research team. A senior epidemiologist will supervise the project and review the output before submission to the MAH and regulator. Clinical expertise is available for appropriate interpretation of results.

All project staff members receive comprehensive orientation training and are regularly trained.

The BPE has implemented a quality management system for all its activities and is certified ISO 9001:v2015 for its activities in pharmaco-epidemiology research. CNAM data extraction will be validated using the expected population size estimated using the SNDS. All statistical logs are kept and can be provided. In the case of interim analyses, the database for the interim analysis is locked and kept for ulterior validation if needed. Independent double programming will be performed for the main criteria and analysis, and the results compared for validation.

The Centre for Pharmacoepidemiology, Karolinska Institutet has implemented a Quality System with the purpose to specify the conditions and responsibilities for the daily operations of research projects. Epidemiologists and statisticians at the centre will execute quality controls at multiple levels of the research process as per internal guidelines. At a minimum, the SAP and the statistical programming and analyses will be reviewed and supervised by a senior statistician and all study documents (protocol, report, and publications) will be reviewed by the entire research team. A senior epidemiologist will supervise the project and review the output before submission to the Sponsor. Clinical expertise is available for appropriate interpretation of results. All project staff members receive comprehensive orientation training and are regularly trained.

9.9. Limitations of the Research Methods

The limitations of the study are included below:

- While ritlecitinib is expected to be well-captured in outpatient dispensing streams, the Swedish national health registers have minimal capture of inpatient hospital administrations and dispensings, and partial capture of outpatient hospital administrations (i.e., medications administered in outpatient clinics located in hospitals) and dispensings. Similarly, in the SNDS, hospital admissions only capture administered medications that are expensive. Thus, most medications that are dispensed or administered primarily through hospital channels will be missed. As ritlecitinib is mainly expected to be dispensed in outpatient settings, this limitation is unlikely to result in a large proportion of missed exposed patients.

- Given the use of data sources from three distinct European countries, there will be variability in capture of indicators of adherence to the RMMs across the data sources. For example, data on laboratory tests and vaccinations are not available in Sweden and may be under recorded in Denmark and France. In France, only reimbursed vaccinations are recorded, meaning some vaccines (e.g., yellow fever vaccination) will be missed. All major variabilities in data elements across data sources will be described in the SAP.

- Other limitations, which are similar across many administrative data sources, include incomplete identification of ongoing pregnancies and pregnancies ending in a

termination (as they are identifiable only by pregnancy end date); underascertainment of lifestyle factors such as smoking status and smoking history; and challenges in identifying screening for TB and hepatitis B and C in all participating countries.

- While the study includes databases from multiple regions within the EU that have adequate data quality, results from the participating countries may not necessarily be generalizable to other countries in the EU.

- The ability to ascertain whether the recommended screenings or monitoring took place is limited when using automated health databases because many of the recommendations are at the discretion of the HCP and/or because they will not be captured in administrative claims or register data. For example, it is not possible to assess whether the physician ensured that the woman was using effective contraception or was not lactating. Additionally, it will not be possible to robustly assess whether HCPs discontinued ritlecitinib in response to a patient developing an infection because, for some infections, it will be challenging to assess severity and, depending on the length of the drug holiday, the databases might not capture a discontinuation in response to an infection (e.g., if it was shorter than the anticipated duration of the prescription). Therefore, the screening and monitoring recommendations proposed for assessment in the current study represent only those which can be objectively captured in automated health databases, such as laboratory tests for key clinical values. Furthermore, in data sources in which ritlecitinib use cannot be ascertained in hospital settings, lack of use during serious infectious cannot be assessed.

- Finally, while a subset of risk factors for thromboembolic events, malignancy, and CVD can be assessed in administrative data, it is not possible to confirm whether the prescribing HCP considered the risks and benefits before initiating ritlecitinib in patients at high risk for these outcomes. Thus, an assessment of risk factors can be used to characterize the exposed population but not confirm whether the recommended screening guidelines were considered. Data on body mass index, diet, and exercise are not captured in the participating data sources and data related to smoking and alcohol use is limited and must be inferred by proxies (e.g., tobacco- and alcohol-related conditions).

9.10. Other Aspects

Participating countries will adhere to all requirements imposed legally or locally by data custodians to avoid reporting personal data. Whenever relevant, to prevent inadvertent identification of individuals from a unique set of characteristics, group (cell) sizes in the aggregate data with counts between 1 and 4 will be masked using an appropriate masking method selected by local investigators. Group (cell) sizes between 1 and 4 that can be recomputed from the surrounding complementary data and counts that allow such computation will also be masked.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in anonymized or pseudonymized structured format. Furthermore, the proposed study is a non-interventional study reusing healthcare data (secondary data collection). Data protection and privacy regulations will be respected in collecting, forwarding, processing, and storing data from study participants. Pfizer will have access only to aggregated patient data.

10.2. Patient Consent

As this study involves secondary data, informed consent is not required for use of these data in the participating countries.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

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 the following documents:

- Guide on Methodological Standards in Pharmacoepidemiology issued by ENCePP (45),
- Module VIII of the EMA's Guideline on good pharmacovigilance practices (GVP) –Post-authorization safety studies (46),
- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (47), and
- International Ethical Guidelines for Health-related Research Involving Humans issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)(48).

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 (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in the HMA-EMA Catalogue of RWD studies https://catalogues.ema.europa.eu/catalogue-rwd-studies prior to the start of data collection. The final study results will be disclosed through the EU PAS Register. One or more manuscript(s) will be prepared for publication in a peer-reviewed journal upon completion of the study.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the 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.

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Drug Utilization Study to Evaluate Indicators of Adherence to the Risk Minimization Measures for Ritlecitinib Using Electronic Healthcare Data in Denmark, France, and Sweden

EU PAS Register® number:
Study reference number (if applicable): Study will be registered before the start of the data collection

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)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
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)	☒	☐	☐	7
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)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg 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? (eg, rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (eg risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

[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.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.1
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☐	☐	☒	
	4.2.5 Duration of follow-up	☐	☐	☒	
4.3	Does the protocol define how the study population will be sampled from the source population? (eg event or inclusion/exclusion criteria)	☒	☐	☐	9.2

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? (eg operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (eg precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4, 9.9
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (eg dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

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?	☐	☐	☒	
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (eg precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4, 9.9
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (eg confounding by indication)	☐	☐	☒	

Section 7: Bias		Yes	No	N/A	Section Number
7.2	Does the protocol address selection bias? (eg healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (eg misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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

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? (eg pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (eg clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (eg date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (eg date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (eg age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (eg International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (eg based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.1

Comments:

Section 11: Data management and quality control		Yes	No	N/A	Section Number
11.1	Does the protocol provide information on data storage? (eg 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?	☒	☐	☐	12

Comments:

Re 11.3 study report or summary thereof will be posted on the ENCePP PAS Register

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?	☒	☐	☐	9.9
	12.1.2 Information bias?	☒	☐	☐	9.9
	12.1.3 Residual/unmeasured confounding? (eg anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2	Does the protocol discuss study feasibility? (eg study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

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?	☐	☐	☒	
13.3	Have data protection requirements been described?	☒	☐	☐	10

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 (eg to regulatory authorities)?	☒	☐	☐	6
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:		Prof. Vera Ehrenstein, MPH, DSc
Date: 23/February/2024		
Signature:		Signature:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.