NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden
Protocol number	B7981101
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: What are the incidence rates (IRs) of the safety events of interest among patients with alopecia areata (AA) receiving ritlecitinib and patients with AA receiving other approved systemic treatments for AA in a real-world setting? Primary objective: to estimate the IRs of safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:

	• Thromboembolic events (including venous thromboembolism [VTE] and arterial thrombosis)
	• Herpes zoster
	• Serious infections
	• Opportunistic infections
	• Malignancy
	  o Malignancy excluding nonmelanoma skin cancer (NMSC)
	  o NMSC
	• Major adverse cardiovascular events (MACE)
	• Neurological events of interest
	  o Peripheral neuropathy
	  o Sensorineural hearing loss
	  o Migraine
	  o Seizures and seizure disorders
	  o Demyelinating disorders including multiple sclerosis
	  o Neurodegenerative disorders
	• Bone fractures
	• Growth metrics in adolescents (Denmark only)
	Exploratory objective: to compare incidence rates of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA, if study size permits.

Countries of study	Denmark, France, and Sweden

Authors	Vera Ehrenstein, MPH, DSc Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark Laure Carcaillon-Bentata, PhD Bordeaux PharmacoEpi (BPE), Bordeaux University, Bordeaux, France Johan Reutfors, MD, PhD Centre for Pharmacoepidemiology (CPE) Karolinska Institutet, Stockholm, Sweden Monica Bertoia, MPH, PhD Safety Surveillance Research, Worldwide Medical and Safety, Pfizer Inc., United States (US)

Marketing Authorization Holder

Marketing Authorization Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
MAH contact person	Monica Bertoia, MPH, PhD Safety Surveillance Research Worldwide Medical and Safety, Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001, US

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	alopecia areata
AE	adverse event
ALS	amyotrophic lateral sclerosis
AT	alopecia totalis
ATC	Anatomical Therapeutic Chemical
ATE	arterial thromboembolism
AU	alopecia universalis
CCAM	Classification commune des actes médicaux
CCI	Charlson Comorbidity Index
CepiDC	French National Death Register
CESREES	Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé
CHMP	Committee for Medicinal Products for Human Use
CI(s)	confidence interval(s)
CIOMS	Council for International Organizations of Medical Sciences
CIP	Code Identifiant de Présentation
COVID-19	coronavirus disease of 2019
CNIL	Commission Nationale de l'Informatique et des Libertés
CPR	Central Personal Registration
CV	cardiovascular
CVD	cardiovascular disease
DLQI	Dermatology Life Quality Index
DVT	deep vein thrombosis
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HIV	human immunodeficiency virus
HR	hazard ratio
HZ	Herpes zoster
IBD	inflammatory bowel disease
ICD	International Statistical Classification of Diseases
ICD-10	International Classification of Disease, 10th Revision
ICD-11	International Classification of Disease, 11th Revision
IQR	interquartile range
IEA	International Epidemiological Association
IEC(s)	Independent Ethics Committee(s)
IPTW	inverse-probability treatment weighting

Abbreviation	Definition
IR(s)	incidence rate(s)
IRB(s)	Institutional Review Board(s)
ISPE	International Society for Pharmacoepidemiology
ITT	Intention-to-treat
JAK	Janus kinase
MACE	major adverse cardiovascular event
MAH	Marketing Authorization Holder
MI	myocardial infarction
NI	non-interventional
NIS	non-interventional study
NMSC	nonmelanoma skin cancer
NOMESCO	Nordic Medico-Statistical Committee
NSAIDs	non-steroidal anti-inflammatory agents
PAS	Post-authorization study
PASS	Post-authorization safety study
PE	pulmonary embolism
PRAC	Pharmacovigilance Risk Assessment Committee
PY(s)	person-year(s)
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SMA	spinal muscular atrophy
SNDS	Système National des Données de Santé
UCD	Unité Commune de Dispensation
US	United States
VTE	venous thromboembolism
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Vera Ehrenstein, MPH, DSc	Professor, Coordinating Investigator, Denmark	Department of Clinical Epidemiology Aarhus University and Aarhus University Hospital	Olof Palmes Allé 43-45 DK-8200 Aarhus N, Denmark
Henrik Toft Sørensen, MD, PhD, DMSc, DSc	Professor, Department Chair, Legally Responsible Investigator	Department of Clinical Epidemiology Aarhus University Hospital	Olof Palmes Allé 43-45 DK-8200 Aarhus N, Denmark
Monica Bertoia, MPH, PhD	Director, Safety Surveillance Research, Worldwide Medical & Safety	Pfizer Inc.	66 Hudson Boulevard East New York, NY 10001, US

Country Coordinating Investigators

Name, degree(s)	Job Title	Affiliation	Address
Cécile Droz-Perroteau, PhD	Director, Coordinating Investigator, France	Bordeaux PharmacoEpi (BPE), Université de Bordeaux	Plateforme de recherche en Pharmaco-épidémiologie CIC Bordeaux CIC1401 Bâtiment du Tondu – case 41 146 rue Léo Saignat 33076 Bordeaux cedex – France
Johan Reutfors, MD, PhD	Coordinating Investigator, Sweden	Centre for Pharmacoepidemiology (CPE) Karolinska Institutet	Centrum för Läkemedelsepidemiologi | Karolinska Institutet Eugeniahemmet T2 | 171 76 Solna, Sweden

4. ABSTRACT

Title An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden

Protocol B7981101; 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 is an orally administered Janus kinase 3 (JAK3) and TEC family kinase inhibitor. 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". This non-interventional (NI) study is designated as a post-authorization safety study (PASS) and is a commitment to the European Medicines Agency (EMA).

Research question and objectives
Research question: what are the incidence rates (IRs) of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting?

Primary objective: to estimate the incidence IRs of safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting.

Exploratory objective: to compare the rates of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA, if study size permits.

Study design Cohort study using routinely collected population-based data.

Population The study population will include patients with AA initiating ritlecitinib, baricitinib or another approved systemic AA treatment as recorded in the participating data sources in Denmark, France, and Sweden during the cohort accrual period. Patients will be included between 15 September 2023 until 14 September 2031 and followed through 14 September 2033.

Variables The safety events of interest are thromboembolic events (including VTE and arterial thrombosis); herpes zoster; serious infections; opportunistic infections; malignancy (including malignancy excluding nonmelanoma skin cancer (NMSC) and NMSC); major adverse cardiovascular events (MACE); neurological events of interest (including peripheral neuropathy, sensorineural hearing loss, migraine, seizures and seizure disorders, demyelinating disorders including multiple sclerosis, and neurodegenerative disorders); bone fractures; and growth metrics in adolescents (Denmark only). In addition, measured

demographic and clinical characteristics (as available in the available routinely collected data) will be described and used in the analysis, including age, sex, and selected co-medications and co-morbidities.

Data sources This study, based on secondary data, will use routinely collected data from population-based registers in Denmark and Sweden, and an administrative healthcare database in France. All participating countries have universal healthcare.

Study size All eligible patients initiating ritlecitinib or comparator treatment during the first 8 years following ritlecitinib approval in the 3 countries will be included.

Data analysis Distributions of the characteristics of patients with AA will be reported separately for ritlecitinib and comparator groups at treatment start, using appropriate summary statistics. IRs and cumulative incidences of the safety events of interest will be computed (primary objectives) and the risks will be compared, if study size permits (exploratory objectives), between initiators of ritlecitinib and initiators of comparator AA treatments. If conducted, measured confounding in the comparative analysis will be controlled using a propensity-score based method; unmeasured confounding will be quantified using the E-value method.

Milestones Data collection will start in September 2027 and end in September 2035. Start of data collection is defined as the date on which the data extraction starts for the first interim report. End of data collection is defined as the date from which the analytical dataset is completely available for the final study report. The analytical dataset is the dataset that contains clean and coded data from all participating countries/databases. Four interim reports will be generated in September 2028, 2030, 2032, and 2034 followed by the final report in March 2036.

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 2035	Within 2 years after the end of study period, considering the lag in data availability in the respective data sources.
Interim analysis reports[d]	September 2028 September 2030 September 2032 September 2034	The 1st interim report is planned to be submitted within 5 years of approval of ritlecitinib in the EU, considering the lag in data availability in the respective data sources. Subsequent interim reports are planned every 2 years thereafter over 6 years (4 interim reports total).
Final study report[d]	March 2036	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 for the first interim report.
c Defined as the date from which the analytical dataset is completely available for the final study report. The analytical dataset is the dataset that contains clean and coded data from all participating countries/databases.
d Interim reports will contain analyses addressing the primary objectives. The final study report will be inclusive of all objectives, conditional on feasibility of the exploratory objective

7. RATIONALE AND BACKGROUND

Alopecia Areata (AA) is an autoimmune disease with immuno-inflammatory pathogenesis characterized by nonscarring 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]). Other clinical variants of AA, such as ophiasis alopecia or diffuse AA, have also been described (1). The affected skin usually does not have signs of inflammation.

AA is the second most common cause of hair loss, affecting approximately 147 million individuals of both sexes and all ethnicities worldwide (2, 3). Incidence rates of AA range from 20 to 200 per 100,000 person-years, and the global lifetime prevalence is estimated at 2% (3-9). A meta-analysis of evidence published up to 1 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%) (10). AA is associated with inflammatory diseases including asthma, allergic rhinitis, atopic dermatitis, and with autoimmune diseases such as thyroiditis and vitiligo (1). The natural history, clinical course and prognosis of AA are unpredictable and can be marked by remission, progression, or persistence (11, 12).

Ritlecitinib is an orally administered Janus kinase (JAK) 3 and TEC family kinase inhibitor. 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 dispensed by prescription only, and in Denmark, currently only in hospital settings. Ritlecitinib is flagged by the Danish authorities as a medication being subject to heightened monitoring (14).

Baricitinib is the only other systemic therapy approved for AA (approved in June 2022). Baricitinib's other indications in the EU are moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs; moderate to severe atopic dermatitis in adult and paediatric patients 2 years of age and older who are candidates for systemic therapy; and active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more specific prior conventional synthetic or biologic disease modifying anti rheumatic drugs (15).

According to the treatment guidelines of the Danish Dermatological Society, updated in July 2023, systemic treatment for AA can be considered in patients meeting all of the following criteria: (1) established AA diagnosis; (2) disease duration >6 months without new lesions, but <8 years if a new lesion has been observed within an 8-year period; (3) severe AA, corresponding to hair loss covering more than 50% of the scalp as measured with the Severity of Alopecia Tool (SALT) score; and (4) Dermatology Life Quality Index (DLQI) ≥10. The 2023 guidelines cite baricitinib, 4 mg daily, as the best documented treatment, following the necessary workup and observing the label restrictions. Baricitinib is indicated for adults, with special caution in patients 65 years of age or older, patients at increased risk of serious cardiovascular disease, patients with a history of smoking and patients at an increased risk of cancer or venous thromboembolism (VTE). The above guidelines require that the effect of systemic treatment be continuously assessed at 3, 6, 9 and 12 months, and

that the treatment be discontinued if both of the following efficacy targets are not achieved after 36 weeks of treatment: (1) SALT score <20% and (2) DLQI <5 (16). However, as of 24 January 2024, the Danish Medical Council (Medicinrådet) no longer recommends baricitinib treatment for severe AA. The Council recommends systemic treatment with combination of methotrexate and prednisolone as the best documented treatment, recommended for patients with long-term widespread disease following a thorough workup (17).

The Swedish Medical Products Agency's guideline on medical treatment of AA, last modified on 06 February 2024, currently cites absence of an effective treatment for AA, however, the guideline is pending an update in early 2024 (18). In France, as of 25 October 2023, baricitinib is the first-line treatment for severe adult alopecia (scalp involvement ≥ 50%), with the importance of monitoring various biological parameters (including haematological and lipid levels) and the contraindication in pregnancy. In accordance with the conclusions of the Pharmacovigilance Risk Assessment Committee (PRAC), patients ages 65 years and older, patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (long-term or former smokers), and patients with risk factors for malignant tumours are advised that baricitinib should only be used in the absence of appropriate therapeutic alternatives. The benefit/risk balance of treatment should be reassessed at regular intervals. Discontinuation of treatment should be considered in patients who show no therapeutic benefit after 36 weeks of treatment (19).

Safety surveillance studies using electronic healthcare databases have been used to successfully monitor real-world safety of newly approved products across a wide spectrum of therapeutic areas and safety events. As part of the ritlecitinib pharmacovigilance plan, this non-interventional study (NIS) based on routinely collected electronic healthcare data from routine clinical practice will be conducted to actively monitor the safety events of interest following exposure to ritlecitinib, baricitinib or other approved systemic treatments for AA following the EU approval of ritlecitinib.

This 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: What are the IRs of the safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting?

8.2. Primary Objective

The primary objective is to estimate the IRs of safety events of interest among patients with AA initiating ritlecitinib and patients with AA initiating baricitinib or other approved systemic treatments for AA in a real-world setting. The following are the primary safety events of interest:

- Thromboembolic events (including VTE and arterial thrombosis)
- Herpes zoster (HZ)
- Serious infections
- Opportunistic infections
- Malignancy
    - Malignancy excluding nonmelanoma skin cancer (NMSC)
    - NMSC
- Major cardiovascular event (MACE)
- Neurological events of interest
    - Peripheral neuropathy
    - Sensorineural hearing loss
    - Migraine
    - Seizures and seizure disorders
    - Demyelinating disorders including multiple sclerosis
    - Neurodegenerative disorders
- Bone fractures
- Growth metrics in adolescents (height and weight, conditional on sufficient data available beyond age 12 years; Denmark only)

8.3. Exploratory Objective

The exploratory objective is to compare the IRs of the safety events of interest among patients with AA receiving ritlecitinib and patients with AA receiving baricitinib or other approved systemic treatments for AA, if study size permits. The decision rule for whether the

comparative analysis can be conducted will be based on the expected number of users and observed number of events and will be specified in the Statistical Analysis Plan (SAP).

9. RESEARCH METHODS

9.1. Study Design

This will be a cohort study based on routinely and prospectively collected electronic healthcare data in Denmark, France, and Sweden. The study population will include a cohort of patients with AA initiating ritlecitinib and, to contextualize the results, cohorts of patients with AA initiating baricitinib or other systemic AA treatments (if approved for the same indication in the EU).

9.1.1. Study Population and Study Period

The study population will include eligible patients (described in Section 9.2) with AA initiating ritlecitinib, baricitinib or other approved systemic AA treatments during the cohort accrual period. The cohort accrual period will include the first 8 years following ritlecitinib approval (15 September 2023 to 14 September 2031). The study period will include follow-up through 14 September 2033, to allow a minimum of 2 years of follow-up for the last patient accrued, given some longer-latency outcomes.

9.1.2. Index Date and Follow-Up

The index date will be the date of the eligible initiation of ritlecitinib, baricitinib or another approved systemic treatment for AA during the cohort accrual period, as recorded in the data sources. Follow-up will start on the date after the index date and continue until the earliest of disenrollment from the data source, an event of interest, or censoring.

9.2. Setting

This study will use population-based secondary data sources from Denmark, France, and Sweden. All three study countries have universal healthcare, whereby routinely collected data continuously accrue in the participating nationwide databases (described in Section 9.4). Loss to follow-up is expected to be minimal and primarily due to emigration, which is expected to be low. Studies based on secondary electronic healthcare data sources are efficient for monitoring rare events and events that require long-term follow-up, when these types of events are well captured in the data source.

These large real-world data sources are expected to allow robust assessment of the safety events of interest. Most proposed safety events of interest are likely to be well captured in the data sources, as the majority of the events require immediate treatment in either a hospital or specialized outpatient setting. Furthermore, safety events such as thromboembolic events have been shown to have high positive predictive values in the Danish and Swedish national registries (20).

9.2.1. Inclusion Criteria

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

1. Have a record of at least one dispensing or hospital administration (hereafter collectively referred to as dispensing) of ritlecitinib, baricitinib, or other approved systemic AA treatment during the cohort accrual period.
2. Have a diagnosis of AA on or up to 5 years before the index date, recorded during a hospital/specialist clinic encounter or by AA noted as the indication on an outpatient pharmacy dispensing record (whenever indication is captured). Treatment proxies may be considered if relevant for a data source and sufficiently specific for AA (21).

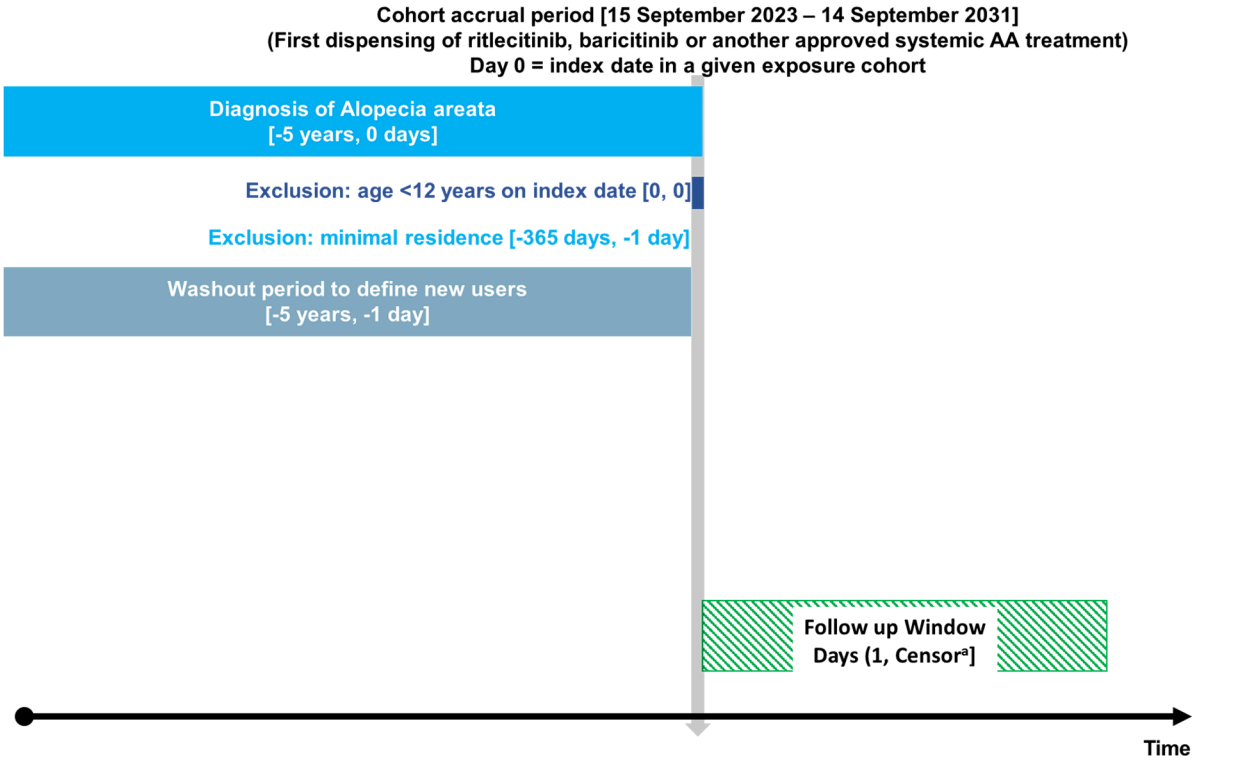
9.2.2. Exclusion Criteria

Patients meeting any of the following criteria, applied in the order listed, will not be included in the study:

1. Age less than full 12 years on the index date
2. Less than 12 months presence in the data source, due to residence in a given country
3. A previous record of the agent dispensed on the index date at any time on or up to 5 years before the index date

Figure 1 shows the study design schema.

Figure 1. Study Design Schema



a. Earliest of: outcome of interest, or censoring by discontinuation/switch, death, disenrollment, end of the study period on 15 September 2033.

9.3. Variables

9.3.1. Exposure

Exposure cohorts will be defined based on the type of treatment dispensed on the index date. The following 3 exposure cohorts will be defined:

1. Ritlecitinib cohort
2. Baricitinib cohort
3. Other approved systemic AA treatment cohort (if used)

The eligible treatment initiated on the index date will be referred to as the index treatment. The exposure will continue until the end of a 90-day grace period following the estimated discontinuation of the index treatment. Discontinuation may result either by stopping the index treatment or initiation (switching to) another study 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. Dispensings less than 90 days apart will represent a continuous treatment period. Definitions, including duration of the grace period, may be slightly modified if otherwise indicated by the data.

9.3.2. Endpoints

The following endpoints (safety events of interest) will be assessed.

- Thromboembolic events, including:
  - VTE (including deep vein thrombosis [DVT] and pulmonary embolism [PE])
  - Arterial thrombosis (includes myocardial infarction [MI] and stroke)
- HZ
- Serious infections
- Opportunistic infections
- Incident primary malignancy, including:
  - Incident primary malignancy excluding nonmelanoma skin cancer (NMSC), overall and by major organ
  - Incident NMSC
- MACE*, including (22):
  - Nonfatal MI
  - Nonfatal stroke
  - Unstable angina
  - Hospitalization due to heart failure

  Coronary revascularization by percutaneous intervention or coronary artery bypass graft
  - Cardiovascular death

  *Other MACE definitions (eg, excluding unstable angina, hospitalized heart failure, revascularization procedure) may be considered.
- Neurological events of interest (including the following events that are captured in at least one of the databases):
  - Peripheral neuropathy
  - Sensorineural hearing loss
  - Migraine
  - Seizures and seizure disorders
  - Demyelinating disorders including multiple sclerosis
  - Neurodegenerative disorders
- Bone fractures

- Growth metrics in adolescents
    - height and weight, conditional on sufficient data available beyond age 12 years (Denmark only)

9.3.3. Other Variables

The following demographic and clinical characteristics (as available in data sources) will be assessed among the members of the study population:

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

AA characteristics
- Duration (to the extent possible to assess, e.g., since first recorded diagnosis in the available data)
- Severity (to the extent measurable in the data sources, e.g., by the intensity of AA-associated health care utilisation)

History of medication use, identified up to 5 years before and including index date
- Therapies for AA
- Potential off-label AA treatments such as corticosteroids (topical, oral, injected), diphencyprone, anthralin, topical minoxidil, methotrexate, dupilumab, other JAK inhibitors
- Medications that may modify risk for the endpoints
    - Low-dose aspirin
    - Non-aspirin non-steroidal anti-inflammatory agents (NSAIDs)
    - Anti-hypertensive medications
    - Lipid-lowering medications
    - Anticoagulants
    - Antiplatelets
    - Combined hormonal contraceptives (except France, no reimbursement)
    - Post-menopausal hormone replacement therapy
    - Anti-diabetic medications
    - Other immunosuppressants or biologics

History of comorbid conditions that are risk factors for the endpoints, identified on or before index date (to the extent measured in the participating data sources). The lookback period will be up to 5 years or as indicated by clinical rationale.
- Thromboembolic events (including VTE and arterial thrombosis)
- Stroke
- Diabetes
- Obesity (hospital diagnoses only, morbid obesity only)

- Hypertension
- Hyperlipidaemia
- Coronary artery disease/ischemic heart disease
- Chronic kidney disease
- Major surgery within 90 days before the index date
- Any malignancy
- NMSC
- HZ
- Human immunodeficiency virus (HIV)
- Serious infection
- Opportunistic infection
- Inflammatory/autoimmune diseases including other indications for the study drugs
  - Asthma
  - Allergic rhinitis
  - Systemic lupus erythematosus
  - Autoimmune thyroiditis
  - Psoriasis
  - Psoriatic arthritis
  - Celiac disease
  - Inflammatory bowel disease (IBD)
  - Vitiligo
  - Multiple sclerosis
  - Sjögren's syndrome
  - Sarcoidosis
  - Other indications for the study drugs
    - Rheumatoid arthritis
    - Atopic dermatitis
    - Juvenile idiopathic arthritis
- Ritlecitinib contraindications (to the extent measured in the databases)
  - Active serious infections including tuberculosis
  - Liver failure
  - Pregnancy
- Bone fractures
- Osteoporosis
- Neurological events
  - Peripheral neuropathy
  - Sensorineural hearing loss
  - Migraine
  - Seizures and seizure disorders
  - Demyelinating disorders including multiple sclerosis
  - Neurodegenerative disorders

- Comorbidity as measured by a population-appropriate comorbidity index, such as Charlson Comorbidity Index (CCI). Use of disease risk scores may be considered for the exploratory objective.

Lifestyle factors, identified during the 12 months prior to and including index date

- Conditions related to alcohol misuse as a proxy for alcohol consumption, which is not recorded in the participating data sources
- Tobacco-related conditions as a proxy for smoking, which is not recorded in the participating data sources

9.3.4. 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).

Table 1 summarizes the initial operational definitions 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 SAP.

Table 1. Preliminary Operational Definitions of the Main Study Variables

Variable	Definition for all countries unless otherwise specified	Role in the analysis
Age	In years	Eligibility criterion, demographic characteristic
Sex	Male, female, other	Demographic characteristic
Ritlecitinib	ATC code L04AF08	Exposure
Baricitinib*	ATC code L04AA37 (through 2023) L04AF02 (2024 onwards) Treatment code BWHP106 (Denmark only)	Exposure
AA	ICD-10 code† L63	Eligibility criterion
Thromboembolic events (including DVT, PE, and arterial thrombosis)	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, O882D, O882E, T817D	Safety event of interest/endpoint
HZ	ICD-10 codes† B01, B02, H031F, H131M, G051M, H190D, H192D, H190J, H220C, B027, B028, B029, G051I, H621B ATC codes J05AB01 (HZ-specific tablet dose 800 mg in package of 35 tablets based on product code) J05AB11 (HZ-specific tablet dose: 500 mg based on product code) J05AB09 (HZ-specific tablet dose: 500 mg based on product code) (23)	Safety event of interest/endpoint
Serious infection	ICD-10 codes† as the primary diagnosis at a hospital contact with a minimum of 1 overnight stay (24) 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, Z861A (the code list will be refined in the SAP to map ICD-10-CM codes to ICD-10 equivalents whenever feasible)	Safety event of interest/endpoint

Table 1. Preliminary Operational Definitions of the Main Study Variables

Variable	Definition for all countries unless otherwise specified	Role in the analysis
Opportunistic infection	ICD-10 codes† A02.1, A02.21, A02.22, A02.23, A02.24, A02.29, A07.2, A07.3, A18.7, A18.59, A18.4, A19.0- A19.9, A18.6, A18.15, A18.4, A18, A17.0, A18.89, A15.0, A18.11, A18.17, A18.85, A18.81, A15.7, A18.12, A18.50- A18.59, A18.1, A15.4, A18.2, A18.11, A15.5, A15.6, A17.0-A17.9, A18.31, A18.84, A18.0- A18.09, A18.83, A18.16- A18.18, A18.14-A18.15, A18.32, A18.83, A17, A17.0-A17.9, A18.0-A18.9, A19.0- A19.9, A18.14, A15.0, A18.17, A18.83, A30, A30.1, A30.2, A30.3, A30.4, A30.5, A31.0-A31.9, A31.1, A31.2, A31.8, A31.9, A32, A32.11, A32.12, A32.7, A43, A43.8, A44.0, A44.1, A44.8, A44.9, A81.2, A92.3, B00.0, B00.3, B00.4, B00.5, B00.7, B02.7, B00.81, B00.82, B02, B02.0, B02.1, B02.3, B02.39, B02.7, B02.8, B02.0, B02.1, B25, B25.0, B25.1, B25.8, B25.9, B27.1, B37.1, B37.5, B37.6, B37.7, B37.8, B37.81, B37.82, B37.89, B38, B38.3, B38.4, B38.7, B39, B39.0, B39.1, B39.3, B39.9, B40, B40.2, B40.80, B40.81, B37.5, B38.4, B40.89, B41, B42, B44.0, B44.7, B44.9, B45.0, B45.2, B45.3, B45.7, B45.8, B45.9, B46.0, B46.1, B46.2, B46.3, B46.4, B46.5, B46.8, B46.9, B48.2, B48.4, B52.2, B55.0, B55.1, B55.2, B57 (all), B57.41, B58.1, B58.2, B59, B60.8, B96.2, H31.8, and H32 Note: codes will be refined in the SAP to map ICD-10-CM codes to ICD-10 equivalents whenever feasible according to the published evidence (25)	Safety event of interest/endpoint
Incident primary malignancy excluding NMSC	Denmark, France Sweden: ICD-10 codes† C00-C43, C45-C75, C81-C96 France: treatment proxy if relevant Only incident primary malignancies will be considered	Safety event of interest/endpoint
NMSC	ICD-10 codes† C44	Safety event of interest/endpoint

Table 1. Preliminary Operational Definitions of the Main Study Variables

Variable	Definition for all countries unless otherwise specified	Role in the analysis
MACE (22)	ICD-10 codes† I20, I21, I60, I50, I11.0, I13.0, I13.2, I61, I62, I63, I64, H34 Denmark and Sweden: 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 I00-I99 as the underlying cause of death in death certificates (cause of death registries) Due to longer lags for death certificate data, CV death may be defined based on death within 30 days of a given diagnosis. France: CCAM procedure codes: For CABG: DDMA030, DDMA031, DDMA032, DDMA033, DDMA034, DDMA035, DDMA036, DDMA037, DDMA038, EPFA006, ENFA003 For PCI: DDAF001, DDAF002, DDAF003, DDAF004, DDAF005, DDAF006, DDAF007, DDAF008, DDAF009, DDAF010, DDAA002, DDFF001, DDFF002, DDLF001, DDPF002, DDSF001, YYYY082	Safety event of interest/endpoint
Bone fractures	ICD-10 codes M48.4, M48.5, M80, M84.3, M84.4, S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2 (26). Additionally, surgery codes may be considered	Safety event of interest/endpoint
Neurological events of interest		
Peripheral neuropathy	ICD-10 codes: G60-G64, M54.1, G90.0	Safety event of interest/endpoint
Sensorineural hearing loss	ICD-10 codes: H90.3-H90.8, associated health services and devises may be considered	Safety event of interest/endpoint
Migraine	ICD-10 codes: G43	Safety event of interest/endpoint
Seizures and seizure disorders	ICD-10 codes: G40, G41, P90, R56	Safety event of interest/endpoint
Demyelinating disorders including multiple sclerosis	ICD-10 codes: G35-G37	Safety event of interest/endpoint
Neurodegenerative disorders: Alzheimer, Parkinson, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), multiple system atrophy	ICD-10 codes: G12, G20, G23, G30	Safety event of interest/endpoint
Growth metrics conditional on sufficient data available beyond age 12 years	Denmark only: height and weight as recorded in the Danish Children's Database. Height and weight measures in adolescents will be benchmarked to geographically appropriate age and sex strata as percentiles in growth curves.	Safety event of interest/endpoint

Table 1. Preliminary Operational Definitions of the Main Study Variables

Variable	Definition for all countries unless otherwise specified	Role in the analysis
Cause-specific mortality (part of MACE)	As recorded in each database: The Danish Civil Registration System, The Danish Cause of Death Registry, The Swedish Cause of Death Register, The French National Death Register (CepiDC)	Safety event of interest/endpoint

*Additional treatments may be defined in the SAP.
†Source of ICD-10 codes: France, inpatient hospital encounters; Denmark, Sweden, inpatient (hospital) or outpatient (specialist visits). ICD-10 codes with trailing letters are applicable in Denmark only.

9.4. Data Sources

This study will utilize routinely collected data from population-based registers in Denmark and Sweden, and an administrative healthcare database in France.

9.4.1. Denmark

Denmark's population-based registers, linkable by a unique identifier, the central person registration (CPR) number, assigned by the CPR 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 (27, 28). The CPR registry contains information on age, sex, migrations and deaths. The Danish National Prescription Registry contains information on all prescription medicines dispensed at Danish community pharmacies with products recorded via ATC codes. Indication may be recorded for certain dispensings (21). Certain drugs administered at specialist hospital-based clinics are captured in the Danish National Patient Register, and tentatively from 2024, in the Danish Hospital Medicines Register (currently in development and expected to become complete in 2024 (29)). 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 procedure/treatment codes in the Danish National Patient Registry. The Danish National Patient Registry records diagnoses (using a Danish version of the WHO ICD-10/ICD-11 codes) and procedures (using the Nordic Medical Statistical Committee 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 National Health Services Register may be used to identify procedures and specialist referrals associated with hearing loss. The Danish Children's Database captures height and weight from routine school examinations and contains data until children reach age 16 years. Most of these databases have been used extensively for pharmacovigilance, and multiple algorithms have been validated (23, 30-37).

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 (38, 39). 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., gender, 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 the WHO 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 (40). SNDS has been used in multiple completed and ongoing studies that include endpoints (VTE (41), infections (42), CVD algorithms (43), malignancies (44)) and other variable definitions relevant for the current study (JAK inhibitors (45)). 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, complete source of population-based data from the entire Swedish population (10.64 million in 2023). Data from the Swedish 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, 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 unchanged 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 National Patient Register includes diagnosis information for inpatients at public hospitals and outpatient specialists' visits, including primary and secondary diagnoses and surgical procedures. The Prescribed Drug Register includes information on all prescribed drugs dispensed 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 (20, 46-49). 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

All ritlecitinib-treated patients meeting study inclusion and exclusion criteria in all data sources during the accrual period will be included in the study. Estimated anticipated group size of the ritlecitinib-exposed population across the three databases is provided in Table 2. Overall, an estimated 835 ritlecitinib-exposed patients are expected to be accrued over 8 years. Of note, these sample size calculations are estimates based on the projected uptake of ritlecitinib in the study countries and are subject to the actual uptake and final study inclusion and exclusion criteria.

Table 2. Estimated Cumulative Number of Ritlecitinib-Exposed Patients by Accrual Year

	Years Post-Approval							
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**
Estimated New Patients Treated Per Year in Denmark, France, and Sweden (based on projected market uptake)	0	148	192	220	255	288	321	247
Estimated 50% Meeting Eligibility Criteria (conservative estimate, true proportion may be higher)	0	74	96	110	127	144	161	123
Estimated Cumulative Number of Patients Exposed to Ritlecitinib	0	74	170	280	**407**	551	712	**835**

Table 3 shows the background age-standardized IRs (number of patients with events per 1,000 person-years (PYs)) of selected safety events of interest in patients with AA obtained from the population-based electronic healthcare registers in Denmark (Pfizer data on file). Number of PYs needed to observe approximately 1 event, given the estimated background rates and a doubling of the background rates is also presented.

Table 3. Age Standardized Incidence Rates (IRs) of Selected Safety Events of Interest in Patients with Alopecia Areata (AA) in Denmark (Pfizer data on file)

Event	IR per 1,000 PYs	PYs Needed to Observe Approximately 1 Event, Given Background IR	PYs Needed to Observe Approximately 1 Event, Given Doubling of Background IR
Any primary malignancy excluding NMSC[a]	1.13	885	442
Thromboembolic events	1.17	855	427
DVT	0.87	1,149	575
PE	1.09	917	459
ATE	2.50	400	200
MACE[b]	1.41	709	355
Herpes zoster infection	1.83	546	273
Serious infections[c,d]	1.89	529	265

a. Incidence rate of malignancy including NMSC in patients with AA not available.
b. Defined by the following outcomes: CV death; acute myocardial infarction; unstable angina; ischemic stroke; haemorrhagic stroke; hospitalization due to heart failure; coronary revascularization by percutaneous intervention or coronary artery bypass graft.
c. Including the following infection types: abscess, bacteraemia, candidiasis and other fungal infections, coronavirus disease of 2019 (COVID-19), female pelvic infections, heart infections (acute rheumatic fever, infectious peri- or myocarditis, endocarditis), human immunodeficiency virus disease, infections of central nervous system, infectious complications of procedures, catheters etc., influenza, intra-abdominal infections, male genital infection, miscellaneous bacterial infection, miscellaneous viral infections, obstetrical infections, other lower-respiratory tract infections, parasitic infections, pneumonia, sepsis, sexually transmitted diseases, skin infections, septic arthritis, osteomyelitis, myositis, upper respiratory tract infection, urinary tract infections, and viral hepatitis.
d. Incidence rate of opportunistic infections in patients with AA not available.

Abbreviations: AA = alopecia areata; ATE = arterial thromboembolism; CV = cardiovascular; DVT = deep vein thrombosis; IR = incidence rate; NMSC = nonmelanoma skin cancer; MACE = major adverse cardiovascular event; PE = pulmonary embolism; PY(s) = person-year(s)

With an estimated 835 ritlecitinib-exposed patients accrued over 8 years (Table 2), and with a 10-year study period, the expected number of observed PYs will be 0*9 + 74*8 + 96*7 + 110*6 + 127*5 + 144*4 + 161*3 + 123*2 = 3,864, assuming no lost to follow-up. A 1:1 ratio of ritlecitinib:comparator patients would yield a total of 7,728 PYs and an expected number of events of 9, 10, and 15 for the endpoints malignancy, thromboembolic events, and serious infections during follow-up. In this setting, there would be sufficient power to detect a minimum HR of 6.7, 6.4, and 4.3 for the endpoints malignancy, thromboembolic events, and serious infections (or other outcomes of similar incidence). However, the analysis will be conducted separately by data source and each individual data source is unlikely to accrue 835 ritlecitinib-exposed patients.

Minimum detectable HRs will be lower for the subgroup analysis of patients with a minimum of 5 years of follow-up (during the 10-year study period). 407 ritlecitinib-exposed patients

accrued over 5 years (Table 2), assuming a 1:1 ratio and no lost to follow-up, would provide sufficient power to detect minimum HRs of 10.3, 9.9, and 6.1 for the endpoints malignancy, thromboembolic events, and serious infections.

Of note, it is possible that the comparator groups may be larger than the ritlecitinib group, given baricitinib's earlier approval date and the potential inclusion of other EU approved systemic treatments. If patients are receiving baricitinib at a substantially higher rate than ritlecitinib (e.g., a ratio of 2:1 or greater), then the minimum detectable hazard ratios could be met with fewer ritlecitinib-exposed patients.

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, (50)). 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.

Approaches to federated analysis (common data models and/or scripts) may be considered if practical. The investigators will use either SAS or R software, in the most recent version available to their organizations at the time of the analyses. Individual-level data will not travel across country borders and will not be pooled.

9.7. Data Analysis

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. Data will be analysed and reported separately in each country. If relevant, meta-analysis of country-specific results for the exploratory objective may be considered.

9.7.1. Descriptive Analysis

Distributions of the descriptive characteristics of patients with AA will be reported by exposure cohort, using appropriate summary statistics: counts and proportions for categorical variables, and means and standard deviations (or median with interquartile range (IQR), where appropriate) for continuous variables.

9.7.2. Analyses of the Primary Objectives

The primary analysis will comprise estimation of IRs with 95% CIs for the safety events of interest using a time-to-event analysis (except the growth metrics, which will be reported using means, medians or percentiles as appropriate). The analyses will include:

- Total number of patients in each exposure cohort
- Number of each new safety event of interest observed during the follow-up time in each exposure cohort
- Crude IRs (and cumulative incidences over selected prespecified periods) of the safety events of interest and 95% CIs in each exposure cohort
- Age- and sex-standardized IRs and 95% CIs in each exposure cohort

The summary of event rates will report time to first event since index date for each exposure cohort with appropriate censoring rules applied for those who do not experience an event by the end of the follow-up period, including those who die and those who emigrate. Rates will be expressed as events/10,000 person-years (PYs) of follow-up or a larger denominator if appropriate.

The index date and follow-up period will be considered separately with respect to acute-onset outcomes (thromboembolic events, all infection endpoints, MACE) versus delayed outcomes (malignancy excluding NMSC, NMSC, fracture, the neurologic events of interest, MACE). IR and cumulative incidence of each endpoint will be computed after excluding patients with a respective prevalent condition. This lookback period to identify prevalent conditions may be shorter for acute-onset outcomes than for delayed outcomes. For events with long induction/latency period (e.g. malignancy, MACE), events during a prespecified post-index date period may be disregarded and considered prevalent, according to the hypothesized induction/latency periods. The endpoint MACE will be analysed using both approaches. Approaches with and without censoring at treatment discontinuation will be considered.

9.7.3. Analyses of the Exploratory Objective

An exploratory comparative analysis estimating hazard ratios of the safety events of interest among AA patients treated with ritlecitinib compared with patients treated with baricitinib or other systemic treatment will be conducted for the final report only, study size permitting. This analysis will use Cox's proportional-hazards regression to estimate HRs and 95% CIs. To account for potential confounding in the comparative analysis, a propensity-score based method, such as inverse-probability treatment weighting (IPTW) will be used to balance measured characteristics of the exposure cohorts being compared (51). The covariate balance between the exposure cohorts (before and after IPTW) will be evaluated using standardized differences for continuous covariates and standardized differences of proportion for each (non-missing) category for categorical covariates. Characteristics with standardized differences greater than 0.10 after weighting will indicate imbalance and will be adjusted for in the comparative analyses. If IPTW is applied, robust variance estimators will be used to address lack of independence between patients induced by weighting. The extent of unmeasured confounding will be assessed using the E-value method (52, 53). Full details of the methods will be provided in the SAP.

9.7.4. Subgroup Analyses

If study size permits, the following analyses will be conducted for the subgroups listed below: descriptive characteristics by exposure cohort, IRs by exposure cohort, and HRs for comparative analyses.

- Sex (male, female)
- Adolescent and adult populations, based on age on index date (12-17 years, 18 years and older)
- Prior systemic therapy
- To allow for sufficient follow-up for outcomes with long induction or latent periods, subgroup analyses will be conducted among the subset of patients with a minimum of 5 years of follow-up, defined as patients initiating the study treatments between 15 September 2023 and 14 September 2028.

- Subgroups may be considered based on ritlecitinib dose and duration

9.7.5. Sensitivity Analyses

A number of sensitivity analyses will be performed as listed below. Each sensitivity analysis will aim to examine the robustness of the findings given certain assumptions about the analysis. Each sensitivity analysis will be performed on the entire study population and, with the exception of the analysis parameter that is being altered, will use all main analysis procedures:

- Re-estimating the IRs and HRs with shorter grace periods for defining treatment discontinuation/switch: e.g., zero days and 30 days

- Re-estimating the IRs and HRs for acute-onset events using an intention-to-treat (ITT)-like approach, whereby follow-up will not be censored by treatment discontinuation

- Re-estimating the IRs and HRs for malignancy excluding NMSC and NMSC, using 6 months instead of 12 months after treatment initiation as the minimum induction period

- Re-estimating the IRs and HRs among patients without a record of rheumatoid arthritis, atopic dermatitis, or juvenile idiopathic arthritis on or before index date

- Re-estimating the IRs and HRs for MACE using an alternative definition

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. A senior epidemiologist will supervise the project and review the output before submission to the MAH and the 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 following are the potential limitations of this study:

- Unknown completeness of indication, as inferred from prior diagnoses, may lead to misclassified identification of the indicated population of patients dispensed ritlecitinib, baricitinib or other systemic AA treatment, by both incomplete capture of the indication of interest (AA) and incomplete exclusion of alternative on-label indications unless recorded at hospital encounters. In Denmark, indication may be recorded in a dispensing record in the Prescription Registry (estimated 82%). Correctness of this indication is close to 100% when compared against corresponding pharmacy records, however, validity against the clinical record has not been assessed (21). Reliance on hospital diagnoses to ascertain AA and other indications may lead to selection bias if unidentified patients with specific conditions differ systematically from those who are identified (54).

- The study will utilise data on dispensing or another administrative treatment record as a measure for intake of the drug. Relying on such records may lead to misclassification of the timing and status of exposure.

- Given the use of data sources from 3 distinct EU countries in this study, there will be variability in the type and completeness of the data captured across the data sources.

- Certain types of variables, such as anthropometrics and lifestyle (smoking, alcohol consumption, weight, height) are either not captured or are incomplete or have unknown completeness in some or all participating data sources. Completeness of recording of lifestyle factors, specifically smoking and alcohol use, is low, and the available proxies identify only persons with sequelae indicative of poor lifestyle. These proxies may also identify persons without a poor lifestyle.

- Several neurological safety events of interest are expected to be underrecorded in hospital encounters (eg, dizziness, headache). Therefore, the analysis is limited to endpoints that are well-captured by the data sources (eg, seizures).

- Some conditions including sensorineural hearing loss, and others that are primarily treated outside settings that contribute to the data sources, are likely to be under recorded

in hospital encounters, which may or may not be possible to compensate by inclusion of specific treatment proxies. The degree of under-recording vary by condition and depend on country-specific referral patterns and treatment settings. There will be a certain degree of misclassification of the outcome definitions, for example, since incidence rates are operationalized as hospitalisation rates or rates of dispensing of a treatment proxy.

- In the SNDS data available, no information is recorded regarding medical diagnosis outside inpatient stays. This may induce non-differential information bias which may lead to an underestimation of the endpoint occurrence. The use of other proxies such as the prescriber's specialty or the diagnosis related to the Long-Term Registration status may help in determining the treatment indication.

- Because NMSC is managed in outpatient care in France, this endpoint cannot be assessed in SNDS. In the other data sources, NMSC is known to be under-recorded, is subject to detection bias, and is associated with the underlying disease. Therefore, data on this endpoint need to be interpreted with caution. In general, NMSC is an endpoint that is very prone to detection bias and does not have the same validity as other malignancy diagnoses.

- The analysis of fractures will reflect data collected on fractures that required hospitalization or visits to specialist clinics, and may therefore underestimate the frequency of this safety event of interest. Fractures treated outside hospital settings or outpatient specialist clinics will not be captured in Denmark and Sweden. In France additional fractures may be captured by of orthopaedic splinting procedure codes from the French medical classification of clinical procedures (55).

- Data on causes of death are lagging 2-3 years in the available data sources and may therefore be incomplete for the ascertainment of the MACE endpoint in the final study report. Alternative definitions to compensate for the incompleteness may be explored, e.g., use of death from hospital records.

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/IECs or other authorities relevant in each country. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC 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 (56)
- Module VIII of the EMA's Guideline on good pharmacovigilance practices (GVP) –Post-authorisation safety studies (57)
- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) (58), 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 WHO (59)

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. 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.

13. REFERENCES

1. Lintzeri DA, Constantinou A, Hillmann K, Ghoreschi K, Vogt A, Blume-Peytavi U. Alopecia areata - Current understanding and management. J Dtsch Dermatol Ges. 2022;20(1):59-90.
2. Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015;8:397-403.
3. Mirzoyev SA, Schrum AG, Davis MDP, Torgerson RR. Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990-2009. J Invest Dermatol. 2014;134(4):1141-2.
4. Lee JH, Kim HJ, Han KD, Han JH, Bang CH, Park YM, et al. Incidence and prevalence of alopecia areata according to subtype: a nationwide, population-based study in South Korea (2006-2015). Br J Dermatol. 2019;181(5):1092-3.
5. Harries M, Macbeth AE, Holmes S, Chiu WS, Gallardo WR, Nijher M, et al. The epidemiology of alopecia areata: a population-based cohort study in UK primary care. Br J Dermatol. 2022;186(2):257-65.
6. Benigno M, Anastassopoulos KP, Mostaghimi A, Udall M, Daniel SR, Cappelleri JC, et al. A Large Cross-Sectional Survey Study of the Prevalence of Alopecia Areata in the United States. Clin Cosmet Investig Dermatol. 2020;13:259-66.
7. Mostaghimi A, Gao W, Ray M, Bartolome L, Wang T, Carley C, et al. Trends in Prevalence and Incidence of Alopecia Areata, Alopecia Totalis, and Alopecia Universalis Among Adults and Children in a US Employer-Sponsored Insured Population. JAMA Dermatol. 2023;159(4):411-8.
8. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. Journal of autoimmunity. 2007;29(1):1-9.
9. Eaton WW, Pedersen MG, Atladottir HO, Gregory PE, Rose NR, Mortensen PB. The prevalence of 30 ICD-10 autoimmune diseases in Denmark. Immunol Res. 2010;47(1-3):228-31.
10. Lee HH, Gwillim E, Patel KR, Hua T, Rastogi S, Ibler E, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. J Am Acad Dermatol. 2020;82(3):675-82.
11. Harries MJ, Sun J, Paus R, King LE, Jr. Management of alopecia areata. BMJ. 2010;341:c3671.
12. Darwin E, Hirt PA, Fertig R, Doliner B, Delcanto G, Jimenez JJ. Alopecia Areata: Review of Epidemiology, Clinical Features, Pathogenesis, and New Treatment Options. Int J Trichology. 2018;10(2):51-60.
13. (EMA) EMA. Litfulo (ritlecitinib) 2023 [cited 2023 05 November]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/litfulo.
14. Medicin.dk. Ritlecitinib 2024 [cited 2024 17 February]. Available from: https://pro.medicin.dk/Medicin/Praeparater/10557.
15. (EMA) EMA. Olumiant (baricitinib) 2023 [cited 2023 05 November]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant.

16. Selskab DD. Retningslinje for behandling af alopecia areata juni 2023 2023 [cited 2023 05 November]. Available from: https://dds.nu/retningslinjer/.
17. Medicinrådet. Baricitinib (Olumiant) 2024 [cited 2024 02 February]. Available from: https://medicinraadet.dk/igangvaerende-vurderinger/laegemidler-og-indikationsudvidelser/baricitinib-olumiant-svaer-alopecia-areata-egen-drift.
18. Läkemedelsverket. Hudsjukdomar 2024 [cited 2024 12 February]. Available from: https://lakemedelsboken.se/kapitel/hud/hudsjukdomar.html?search=alopecia%20areata&iso=false&imo=false&nplId=null&id=f1_110.
19. HAUTE AUTORITÉ DE SANTÉ (HAS). Baricitinib OLUMIANT 2 mg et 4 mg 2023 [cited 2024 04 January]. Available from: https://www.has-sante.fr/upload/docs/evamed/CT-20292_OLUMIANT_pelade_PIC_EI_AvisDef_CT20292.pdf.
20. Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, et al. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clin Epidemiol. 2021;13:533-54.
21. Harbi H, Pottegård A. Validation of the "Indication for Use" (INDO) Variable in the Danish National Prescription Registry. Epidemiology. 2024;35(1):1-6.
22. Gyldenkerne C, Mortensen MB, Kahlert J, Thrane PG, Warnakula Olesen KK, Sorensen HT, et al. 10-Year Cardiovascular Risk in Patients With Newly Diagnosed Type 2 Diabetes Mellitus. J Am Coll Cardiol. 2023;82(16):1583-94.
23. Schmidt SAJ, Vestergaard M, Baggesen LM, Pedersen L, Schonheyder HC, Sorensen HT. Prevaccination epidemiology of herpes zoster in Denmark: Quantification of occurrence and risk factors. Vaccine. 2017;35(42):5589-96.
24. Holland-Bill L, Xu H, Sorensen HT, Acquavella J, Svaerke C, Gammelager H, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. Ann Epidemiol. 2014;24(8):593-7, 7 e1-18.
25. Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-16.
26. Ludvigsson JF, Mahl M, Sachs MC, Björk J, Michaelsson K, Ekbom A, et al. Fracture Risk in Patients With Inflammatory Bowel Disease: A Nationwide Population-Based Cohort Study From 1964 to 2014. Am J Gastroenterol. 2019;114(2):291-304.
27. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. European Journal of Epidemiology. 2014;29(8):541-9.
28. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.
29. Sygehusmedicinregisteret (SMR) [cited 2020 17 December]. Available from: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/sygehusmedicinregisteret.
30. Halvorsen S, Johnsen SP, Madsen M, Linder M, Sulo G, Ghanima W, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in

atrial fibrillation: a Scandinavian population-based cohort study. Eur Heart J Qual Care Clin Outcomes. 2022;8(5):577-87.
31. Fortuny J, von Gersdorff G, Lassalle R, Linder M, Overbeek J, Reinold J, et al. Use of intravenous iron and risk of anaphylaxis: A multinational observational post-authorisation safety study in Europe. Pharmacoepidemiol Drug Saf. 2021;30(10):1447-57.
32. Ehrenstein V, Huang K, Kahlert J, Bahmanyar S, Karlsson P, Lofling L, et al. Outcomes in patients with lung cancer treated with crizotinib and erlotinib in routine clinical practice: A post-authorization safety cohort study conducted in Europe and in the United States. Pharmacoepidemiol Drug Saf. 2021;30(6):758-69.
33. Luhdorf P, Overvad K, Schmidt EB, Johnsen SP, Bach FW. Predictive value of stroke discharge diagnoses in the Danish National Patient Register. Scand J Public Health. 2017;45(6):630-6.
34. Adelborg K, Sundboll J, Munch T, Froslev T, Sorensen HT, Botker HE, et al. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. BMJ Open. 2016;6(12):e012817.
35. Sundboll J, Adelborg K, Munch T, Froslev T, Sorensen HT, Botker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016;6(11):e012832.
36. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.
37. Harbi H, Pottegard A. Validation of the 'indication for use' (INDO) variable in the Danish National Prescription Registry. Epidemiology. 2023.
38. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiology and Drug Safety. 2017;26(8):954-62.
39. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Revue d'Épidémiologie et de Santé Publique. 2017;65:S149-S67.
40. Thurin NH, Bosco-Levy P, Blin P, Rouyer M, Jove J, Lamarque S, et al. Intra-database validation of case-identifying algorithms using reconstituted electronic health records from healthcare claims data. BMC Med Res Methodol. 2021;21(1):95.
41. Blin P, Samama CM, Sautet A, Benichou J, Lignot-Maleyran S, Lamarque S, et al. Comparative effectiveness of direct oral anticoagulants versus low-molecular weight heparins for the prevention of venous thromboembolism after total hip or knee replacement: A nationwide database cohort study. Pharmacol Res. 2019;141:201-7.
42. EUPAS36129. An observational post-authorization safety study to describe the safety of ustekinumab and other treatments of ulcerative colitis in a cohort of patients with ulcerative colitis using the French Nationwide claims database (SNDS) France [cited 2022 15 March]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=41418.

43. Bezin J, Girodet PO, Rambelomanana S, Touya M, Ferreira P, Gilleron V, et al. Choice of ICD-10 codes for the identification of acute coronary syndrome in the French hospitalization database. Fundam Clin Pharmacol. 2015;29(6):586-91.
44. Bosco-Lévy P, Boutmy E, Grelaud A, Sabido M, Diez P, Lacueille C, et al. Risk of malignancies in newly treated patients with disease-modifying drugs for multiple sclerosis: Assessment according tocohort and nested-case control approaches. ISPE Annual Meeting Abstracts. Pharmacoepidemiology and Drug Safety. 2021;30(S1):3-400.
45. EUPAS34204. Official titleComparative assessment of venous thromboembolism and other risks among patients with rheumatoid arthritis treated with baricitinib versus tumor necrosis factor inhibitors - French part of the study program [cited 2022 14 March]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=34205.
46. Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, Norgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. Pharmacoepidemiol Drug Saf. 2013;22(7):691-9.
47. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.
48. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11(1):450.
49. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
50. Metadata for Data Discoverability and Study Replicability (EUPAS39322) [cited 2022 12 October]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=39323.
51. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
52. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.
53. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. JAMA. 2019;321(6):602-3.
54. Chubak J, Dalmat RR, Weiss NS, Doria-Rose VP, Corley DA, Kamineni A. Informative Presence in Electronic Health Record Data: A Challenge in Implementing Study Exclusion Criteria. Epidemiology. 2023;34(1):29-32.
55. Bouyer B, Leroy F, Rudant J, Weill A, Coste J. Burden of fractures in France: incidence and severity by age, gender, and site in 2016. Int Orthop. 2020;44(5):947-55.
56. ENCePP Guide on Methodological Standards in Pharmacoepidemiology [cited 2021 21 March]. Available from: http://www.encepp.eu/standards_and_guidances/methodologicalGuide9_2_1_4.shtml.
57. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies 2017 [cited 2022 10 February]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices.

58. International Society for Phamacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (GPP) 2015 [cited 2023 05 June]. Available from: https://www.pharmacoepi.org/resources/policies/guidelines-08027.
59. CIOMS. International Ethical Guidelines for Health-related Research Involving Humans [cited 2022 28 February]. Available from: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: An Active Surveillance Study to Monitor the Real-World Safety of Ritlecitinib Among Patients with Alopecia Areata in Denmark, France, and Sweden.

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

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? (eg, 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)	☒	☐	☐	9.1.1
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?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	9.7.2
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))	☒	☐	☐	9.7.3

[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 3: Study design	Yes	No	N/A	Section Number
3.5 Does the protocol describe the approach for the collection and reporting of AEs/adverse reactions? (eg, AEs that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.1
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	☒	☐	☐	9.3.3
4.2.3 Country of origin	☒	☐	☐	9.1.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1
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?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.7.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
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

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	9.7.3
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)	☒	☐	☐	9.7.3, 9.7.5

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)	☒	☐	☒	9.7.4

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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				9.4
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4, 9.3.4

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4, 9.3.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4, 9.3.4
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?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.5
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Re 10.6: Outcome misclassification will be addressed when discussing study limitations. Re 10.7: Missing data concept is not applicable for the data used in this study.

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).	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
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/ IRB been described?	☒	☐	☐	10
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, 12
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:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.