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NON-INTERVENTIONAL STUDY (NIS) PROTOCOL

PASS information

Title	A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimization Measures (RMMs) for Abrocitinib in the EU Using Electronic Healthcare Data
Protocol number	B7451085
Protocol version identifier	2.0
Date	23 May 2024
EU Post Authorization Study (PAS) register number	To be registered before the start of data collection
Active substance	Abrocitinib (PF-04965842) Anatomical Therapeutic Chemical (ATC) code D11AH08
Medicinal product	Cibinqo
Product reference	*EU/1/21/1593/001; EU/1/21/1593/002; EU/1/21/1593/003; EU/1/21/1593/004; EU/1/21/1593/005; EU/1/21/1593/006; EU/1/21/1593/007; EU/1/21/1593/008; EU/1/21/1593/009; EU/1/21/1593/010; EU/1/21/1593/011; EU/1/21/1593/012; EU/1/21/1593/013; EU/1/21/1593/014; EU/1/21/1593/015.*
Procedure number	EMEA/H/C/005452/0000
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard De La Plaine 17 Brussels, 1050 Belgium
Joint PASS	No
Research objective	The study objectives are to evaluate, to the extent measurable in the available routinely collected data, indicators of healthcare

	professional's (HCP) adherence to the RMMs in accordance with the abrocitinib Summary of Product Characteristics (SmPC) and prescriber's brochure, specifically: • indicators of adherence to performing laboratory tests of complete blood count (CBC), lipid panel, hepatitis B/C and tuberculosis (TB) screening prior to initiation of abrocitinib treatment, • indicators of adherence to performing laboratory tests of CBC and lipid panel at week 4 (± 2 weeks) after initiation of abrocitinib treatment, • indicators of adherence to consideration of risk factors for venous thromboembolism (VTE), major adverse cardiovascular event (MACE), malignancy (excluding non-melanoma skin cancer [NMSC]), NMSC, and serious infection prior to initiation of abrocitinib treatment, • indicators of adherence to avoid live attenuated vaccine immediately prior to and during treatment with abrocitinib, • indicators of adherence to contraindications for use during pregnancy, • indicators of adherence to contraindications for use among patients with severe hepatic impairment, • indicators of adherence to no use in patients aged <12 years, and

	• indicators of adherence to recommended posology (estimated average daily dose)
Country(-ies) of study	Denmark, France, Sweden, Spain, and Hungary
Author	Professor Vera Ehrenstein, MPH, DSc Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard De La Plaine 17 Brussels 1050 Belgium
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Atopic Dermatitis
AE	Adverse Event
aRMM	Additional Risk Minimization Measure
ATC	Anatomical Therapeutic Chemical
CBC	Complete Blood Count
CCAM	Classification Commune des Actes Médicaux
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CIP	Code Identifiant de Présentation
CPR	Central Person Registration
DHPC	Direct healthcare professional communication
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HDL	High-Density Lipoprotein
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
IL	Interleukin
IQR	Interquartile Range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JAK	Janus Kinase
LDL	Low-Density Lipoprotein
MACE	Major Adverse Cardiovascular Event
MAH	Marketing Authorization Holder
NABM	Nomenclature des Actes de Biologie Médicale
NHIFA	National Insurance Fund Administration
NIS	Non-Interventional Study
NOMESCO	Nordic Medico-Statistical Committee
NPU	Nomenclature, Properties and Units
PASS	Post-Authorization Safety Study
RMM	Risk Minimization Measures
SAP	Statistical Analysis Plan
SIDIAP	The Information System for Research in Primary Care
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SNDS	Système National des Données de Santé (French Administrative Healthcare Database)
TB	Tuberculosis
TG	Triglycerides
UCD	Unité Commune de Dispensation
VTE	Venous Thromboembolism
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title A Drug Utilization Study to Evaluate the Effectiveness of RMMs for Abrocitinib in the EU Using Electronic Healthcare Data.

Protocol B7451085; Version 2.0; 23 May 2024

Main author: Vera Ehrenstein, Aarhus University, on behalf of the SIGMA Research Team

Rationale and background Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. Abrocitinib received marketing authorization for the European Union (EU) on 09 December 2021 and is indicated for the treatment of moderate to severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy. To mitigate the risks associated with abrocitinib, required routine RMMs including the SmPC and package leaflet are being employed. In addition to the routine risk minimization measures, additional risk minimization measures (aRMMs) including a prescriber's brochure and patient card, are being implemented in the EU.

Research question and objectives The study objectives are to evaluate, to the extent measurable in the available routinely collected data, indicators of HCPs' adherence to the RMMs in accordance with the abrocitinib SmPC and prescriber's brochure, as measured by:

- indicators of adherence to performing laboratory tests of CBC, lipid panel, hepatitis B/C, and TB screening prior to initiation of abrocitinib treatment,
- indicators of adherence to performing laboratory tests of CBC and lipid panel at week 4 (± 2 weeks) after initiation of abrocitinib treatment,
- indicators of adherence to consideration of risk factors for VTE, MACE, malignancy excluding NMSC, NMSC, and serious infection prior to treatment with abrocitinib,
- indicators of adherence to avoid live attenuated vaccines immediately prior to and during treatment with abrocitinib,
- indicators of adherence to contraindications for use during pregnancy,
- indicators of adherence to contraindications for use among patients with severe hepatic impairment
- indicators of adherence to no use in patients aged < 12 years, and
- indicators of adherence to recommended posology (estimated average daily dose).

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

Population The study population will include patients with a dispensing of abrocitinib as recorded in routinely collected electronic healthcare data in Denmark, France, Sweden, Spain and Hungary during the study period (study start: country-specific aRMM distribution [01

March 2022, Sweden; 09 March 2022, Denmark; 31 July 2022, France; 30 Jan 2023, Spain; 05 April 2024, Hungary]; study end: December 2026). These countries have universal healthcare.

Variables The study will collect all relevant data including patient demographics, co-morbidities, prescription medications, vaccine administration, and laboratory testing prior to the initiation of abrocitinib and during treatment with abrocitinib 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, Sweden, and Spain and an administrative healthcare databases in France and Hungary.

Study size All patients initiating abrocitinib 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 variable, and common analysis strategy. The main indicators will be proportions of abrocitinib users with a given indicator of aRMM adherence.

Milestones

Milestone	Planned date*
Registration in the HMA-EMA Catalogues of RWD Studies	To be registered before the start of data collection
Start of data collection	31 December 2024
End of data collection (the date from which the analytical dataset is completely available, i.e., clean and coded data from all participating countries/databases)	15 May 2028
Interim Report 1	15 November 2025
Interim Report 2	15 May 2027
Final study report	15 November 2028

* Subject to data delivery and application approval timelines by data custodians in participating countries

5. AMENDMENTS AND UPDATES

Amendment number, date	Section	Amendment	Rationale
1.0, 23 May 2024	PASS information; Section 4; Section 8.2; Section 9.7.1	Replaced <18 with <12 as the cut-off for off-label use	< 12 is the correct age for off-label use consistent with adolescent indication (12 years and older) in the EMA
1.0, 23 May 2024	PASS information; Section 4; Section 8.2; Table 2; Section 9.7.1	Separated 'malignancy' into: • malignancy excluding NMSC • NMSC	Consistency with EU RMP important potential risks (v 4.2) published subsequent to V 1.0 B7451085 study protocol
1.0, 23 May 2024	Section 4; Section 7	Include adolescent indication, date of adolescent authorization in the EU, and update the list of potential risks	Consistency with EU RMP updates (v 4.2) published subsequent to V 1.0 B7451085 study protocol
1.0, 23 May 2024	Section 6, Section 12, Annex 2	References to EU PAS Register replaced with HMA-EMA Catalogues of RWD Studies (note, references to 'EU PAS Register Number' remain	Administrative update to reflect changes implemented to EU PAS registration system subsequent to V 1.0 B7451085 study protocol
1.0, 23 May 2024	Section 4, Section 9.2, Section 9.2.1	Updated date of aRMM distribution for Hungary	Data on actual aRMM distribution date, rather than estimated, became available

6. MILESTONES

Milestone	Planned date*
Registration in the HMA-EMA Catalogues of RWD Studies	To be registered before the start of data collection
Start of data collection	31 December 2024
End of data collection (the date from which the analytical dataset is completely available, i.e., clean and coded data from all participating countries/databases)	15 May 2028
Interim Report 1	15 November 2025
Interim Report 2	15 May 2027
Final study report	15 November 2028

* Subject to data delivery and application approval timelines by data custodians in participating countries

7. RATIONALE AND BACKGROUND

AD, also known as atopic eczema, is the most common chronic inflammatory skin disease. AD is characterized by intense itching and recurrent eczematous lesions (1). AD was originally thought to affect primarily preschool children, with prevalence up to 25%, but recent evidence shows that AD in adults has an estimated prevalence of 7–10% (2). AD has a strong genetic component, is associated with atopic co-morbidities including asthma, allergic rhinitis, and food allergies, and coincides with an increased risk of other inflammatory diseases, such as arthritis and inflammatory bowel disease. AD confers a substantial burden to patients and their families, resulting in high healthcare costs. AD has been linked to psychological disturbances and reduced educational attainment (2, 3). Severe and active AD is associated with an increased risk of cardiovascular morbidity (4-6) and with certain types of malignancies (7).

Abrocitinib is a selective Janus Kinase (JAK) 1 inhibitor. The inhibition of JAK1 is thought to modulate multiple cytokines involved in the pathophysiology of AD including interleukin (IL)-4, IL-13, IL-31, IL-22, and interferon gamma. The important identified and potential risks were adopted based on non-clinical and clinical data from abrocitinib development program and from understanding of data from other JAK inhibitors (i.e., tofacitinib, baricitinib, upadacitinib). The important identified risks include VTE and herpes zoster. The important potential risks include serious and opportunistic infections, malignancy major adverse cardiovascular event (MACE), myopathy (including rhabdomyolysis), gastrointestinal perforation, and impaired bone growth and development in patients in patients aged <12 years if used off-label, and fractures. (8). Finally, embryofetal toxicity following exposure in utero is included as a potential risk. Although abrocitinib is contraindicated for use in pregnancy, the patient population will include women of childbearing potential and off-label incidental/unintended exposure during pregnancy could occur (8). Abrocitinib received marketing authorization for EU on 09 December 2021 for the treatment of moderate to severe AD in adults who are candidates for systemic therapy (8). On 21 March 2024, the indication for abrocitinib marketing authorization for the EU was expanded to adolescents 12 years and older.

To mitigate the risks associated with abrocitinib, required routine RMMs including the SmPC and package leaflet are being employed (8). In addition to the routine RMMs, aRMMs are being implemented in the EU. The aRMMs include an educational program intended to enhance the communication of the risks and risk minimization practices to HCPs via a “Prescriber’s Brochure”, a one-time direct healthcare professional communication (DHPC) and to patients via a patient card. The overall objective of the aRMM 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 abrocitinib.

A systematic evaluation of the effectiveness of RMMs helps to understand whether the program objectives have been met or provide evidence that further amendments to the program are needed. This protocol describes the objectives and methods used to assess the effectiveness of the RMMs for abrocitinib in five EU countries: Denmark, France, Sweden, Spain and Hungary (9).

This non-interventional study (NIS) is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research question

Does routinely collected data in the EU indicate adherence to the recommendations for use of abrocitinib described in SmPC, prescriber's brochure and DHPC?

8.2. Research objectives

The study objectives are to evaluate, to the extent measurable in the available routinely collected data, indicators of HCPs' adherence to the RMMs in accordance with the abrocitinib SmPC, prescriber's brochure and DHPC, specifically:

- Indicators of adherence to performing laboratory tests of CBC, lipid panel, hepatitis B/C and TB screening prior to initiation of abrocitinib treatment,
- Indicators of adherence to performing laboratory tests of CBC and lipid panel at week 4 (± 2 week) after initiation of abrocitinib treatment,
- Indicators of adherence to consideration of risk factors for VTE, MACE, malignancy excluding NMSC, NMSC, and serious infection prior to treatment with abrocitinib,
- Indicators of adherence to avoid live attenuated vaccines immediately prior to and during treatment with abrocitinib,
- Indicators of adherence to contraindications for use during pregnancy,
- Indicators of adherence to contraindications for use among patients with severe hepatic impairment,
- Indicators of adherence to no use in patients aged < 12 years, and
- Indicators of adherence to recommended posology (estimated average daily dose).

9. RESEARCH METHODS

9.1. Study design

This will be a descriptive drug utilization study using secondary data from healthcare databases in Denmark, France, Sweden, Spain and Hungary. The study population will comprise patients who are treated with abrocitinib.

9.2. Setting

The study population will include patients with a dispensing of abrocitinib as recorded in routinely collected electronic secondary population data in Denmark, France, Sweden, Spain and Hungary between the study start (country-specific aRMM distribution [01 Mar 2022, Sweden; 09 Mar 2022, Denmark; 31 Jul 2022, France; 30 Jan 2023, Spain; 05 April 2024, Hungary]) and study end (December 2026). Details on the data sources are in Section 9.4). All participating countries have universal health care.

9.2.1. Inclusion criteria

All patients with at least 1 dispensing of abrocitinib between study start (country-specific aRMM distribution [01 Mar 2022, Sweden; 09 Mar 2022, Denmark; 31 Jul 2022, France; 30 Jan 2023, Spain; 05 April 2024, Hungary]) and December 2026 in the participating databases will be eligible for inclusion in this study. The date of the first dispensing of abrocitinib will be the index date. Patients must meet the above inclusion criteria to be eligible for inclusion in the study.

9.2.2. Exclusion criteria

There are no exclusion criteria in this study.

9.3. Variables

The study will collect all relevant data including patient demographics (e.g., age and sex), co-morbidities, prescription medications, vaccinations, procedures, and laboratory tests prior to initiating abrocitinib and while on treatment to address the study objectives. Abrocitinib and concomitant medications and vaccinations will be identified using ATC codes. Diagnoses will be recorded using diagnostic codes. Performance of laboratory tests, available from Denmark, will be identified using Nomenclature, Properties and Units (NPU) codes. Surgeries will be defined using country-specific procedure/surgery codes. Age (date of birth) and sex will be used as reported in the databases. The average daily dose of abrocitinib will be estimated using a combination of information available per country: strength of the prescription dispensed, packet size, World Health Organization (WHO) defined daily dose and duration of therapy (time between prescriptions/dispensings). Availability of specific data types varies by country. There is no information in Hungary available to estimate dose therefore this data source will not be included in analyses of dose.

The maximum lookback period for ascertaining characteristics before abrocitinib initiation will be 12 months (365 days), but will vary for a given RMM measure, per SmPC. Full country-specific algorithms for all study variables, including RMM-specific lookbacks will be specified in the SAP.

Table 1 summarizes the data available by country for analysis of patient co-morbidities, and prior and current medication use. Table 2 summarizes types of RMMs and specificity available by country for analysis. ANNEX 3. ADDITIONAL INFORMATION provides preliminary definitions of the codes to be used to define each element, per country.

Table 1. Availability of patient co-morbidities and concomitant medications in each country

	Denmark	**France**	**Sweden**	**Spain** [1]	**Hungary** [1]
Co-morbidities					
Acne	No	No	No	Yes	Yes
Allergic conjunctivitis	No	No	No	Yes	Yes

Table 1. Availability of patient co-morbidities and concomitant medications in each country

	Denmark	France	Sweden	Spain [1]	Hungary [1]
Allergic rhinitis	No	No	No	Yes	Yes
Anxiety	If treated in specialist care or through medication	No (unless hospitalized)	If treated in specialist care or through medication	Yes	Yes
Asthma	Identification of persisting asthma using hospital records and medication is possible.	Identification of persisting asthma using hospital records and medication is possible.	Yes	Yes	Yes
Attention deficit hyperactivity disorder	If treated in specialist care or through medication	No unless hospitalized	If treated in specialist care or through medication	Yes	Yes
Depression	If treated in specialist care or through medication	Using medication or hospitalization records	If treated in specialist care or through medication	Yes	Yes
Drug hypersensitivity	No	No	No	Yes	No
Gastroesophageal reflux disease	No	No	No	Yes	Yes
Headache	No	No	No	Yes	Yes
Hepatitis B	Yes	Yes	Yes	Yes	Yes
Hepatitis C	Yes	Yes	Yes	Yes	Yes
Hypertension	Via hospital diagnoses and specific treatment proxies	Using algorithm based on antihypertensive drugs and other cardiovascular comorbidities	Via specialist care diagnoses and specific treatment proxies	Yes	Yes
Hypothyroidism	No unless hospitalized	No unless hospitalized	No unless hospitalized	Yes	Yes
Insomnia	No	No	No	Yes	Yes

Table 1. Availability of patient co-morbidities and concomitant medications in each country

	Denmark	France	Sweden	Spain [1]	Hungary [1]
Other allergies (animals, mite, dust, etc)	No	No	No	Yes	Yes (limited)
Other hypersensitivity	No	No	No	Yes	Yes
Rhinitis	No	No	No	Yes	Yes
Seasonal allergy	No	No	No	Yes	Yes (limited)
Tuberculosis	Yes	Active and latent type. Using an algorithm based on drugs, hospital records, imaging and lab tests	Yes	Yes	Yes
Varicella	No	No (unless hospitalized)	No	Yes	Yes (limited)
Concomitant and past medications					
Atopic dermatitis treatments[2]	Yes if used in Denmark	Yes	Yes if used in Sweden	Yes	Yes
CYP2C19/2C9 inducers or inhibitors[3]	Yes if used in Denmark	Yes	Yes, if dispensed in outpatient pharmacies	Yes	Yes
Probenecid	Yes if used in Denmark	Yes	Yes if dispensed in outpatient pharmacies	Yes	Yes
Acid reducing agents	Yes if used in Denmark	Yes	Yes if dispensed in outpatient pharmacies	Yes	Yes
Clopidogrel	Yes if used in Denmark	Yes	Yes if dispensed in	Yes	Yes

Table 1. Availability of patient co-morbidities and concomitant medications in each country

	Denmark	France	Sweden	Spain [1]	Hungary [1]
			outpatient pharmacies		

[1]Information on data availability from Spain and Hungary was collected during the feasibility assessment of these additional data sources. The specific variable definition and additional context on availability will be confirmed in the statistical analysis plan (SAP).
[2]Cyclosporine, azathioprine, methotrexate, mycophenolic acid, mycophenolate mofetil, dupilumab, tralokinumab; other treatments authorized per country at the time of analysis
[3]Arbamazepine, rifabutin, enzalutamide, letermovir, phenytoin, rifampicin, apalutamide, rifamycin, rifaximin, rifapentine, bosentan, alpelisib, dabrafenib, efavirenz, fluconazole, fluoxetine, fluvoxamine, ticlopidine

Table 2. Availability of RMM elements for evaluation in each country

RMM element	Denmark	France	Sweden	Spain[1]	Hungary[1, 2]
Complete blood count: absolute lymphocyte count, absolute neutrophil count, platelet count and haemoglobin level	Yes (date performed, hospital labs)	Yes (in/outpatient lab test, no results)	No	Yes if conducted in primary care	Yes (in/outpatient lab test, no results)
Lipid panel: total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides [TG])	Yes (date performed, hospital labs)	Yes (in/outpatient lab test, no results)	No	Yes if conducted in primary care	Yes (in/outpatient lab test, no results)
Hepatitis B screening	No	Yes (in/outpatient lab test, no results)	No	No	Yes (in/outpatient lab test, no results)
Hepatitis C screening	No	Yes (in/outpatient lab test, no results)	No	No	Yes (in/outpatient lab test, no results)
TB screening	No	Yes (in/outpatient	No	No	Yes (in/outpatient

Table 2. Availability of RMM elements for evaluation in each country

RMM element	Denmark	France	Sweden	Spain[1]	Hungary[1, 2]
		lab test, no results) or ATC codes (tuberculin skin test)			lab test, no results)
Risk factors for VTE, MACE, malignancy excluding NMSC, NMSC, and serious infection:					
History of VTE	Yes, via in/outpatient diagnoses	Yes, via inpatient diagnoses and outpatients algorithm previously used and validated in a PASS study	Yes, via in/outpatient diagnoses	Yes if recorded in primary care	Yes
Age 65 years or older	Yes	Yes	Yes	Yes	Yes
Dose of > 100 mg/day for patients 65 or older	Yes[3]	Yes[3]	Yes[3]	Yes[4]	No
History of atherosclerotic disease	Yes, in/outpatient diagnoses	Yes, via inpatient diagnoses and Long term disease registration	Yes, via in/outpatient diagnoses	Yes if recorded in primary care	Yes
Malignancy excluding NMSC, NMSC	Yes, via Danish Cancer Registry or Danish Cancer Registry	Yes, via Long Term Disease registration status, inpatient diagnosis and outpatients treatments for prostatic cancer	Yes, via Swedish Cancer Register	Yes if recorded in primary care	Yes

Table 2. Availability of RMM elements for evaluation in each country

RMM element	Denmark	France	Sweden	Spain[1]	Hungary[1, 2]
Pregnancy	Yes, completed pregnancies ending in live/still births in medical birth registry and terminations in the patient registry. Use of an algorithm to identify ongoing pregnancies may be applied pending further assessment	Yes, based on an algorithm using pregnancy outcomes (refer to Annex 3 for codes applied)	Yes, completed pregnancies ending in live/still births in medical birth registry	Yes	Yes, completed pregnancies ending in live/still births
Use of combined hormonal contraceptives or hormone replacement therapy	Yes, via dispensed prescriptions in Prescription registry	HRT is reimbursed. Very few hormonal contraceptives are reimbursed in France and are thus not identifiable in the SNDS.	Yes, via dispensed prescriptions in PDR	Partial. Some hormone contraceptives are not reimbursed or are available over the counter.	Hormone replacement therapy data only
Major surgery	Yes, via procedure codes in NPR	Yes, via inpatient procedure codes	Yes, via procedure codes in NPR	Partial. Only if recorded as an ICD-10 procedure.	Yes
Inherited coagulation disorder (Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and Protein S deficiency)	Yes, to the extent identifiable via in/outpatient diagnoses	Yes, to the extent identifiable via inpatient diagnoses	Yes, to the extent identifiable via in/outpatient diagnoses	Yes if recorded in primary care	Yes
Live attenuated vaccines	Publicly-funded vaccine as recorded in the Danish Health Service Registry	Yes for reimbursed vaccines in high risk population (in	No	Yes	To be confirmed

Table 2. Availability of RMM elements for evaluation in each country

RMM element	Denmark	France	Sweden	Spain[1]	Hungary[1, 2]
	(10). Only the pathogen is recorded (e.g., MMR); however, it is possible to identify live vaccine based on what is used according to the Danish Health Authority. A small number of influenza vaccines from Patient Registry.	which it is reimbursed: pregnant women, patients with chronic diseases, patients 65 years or older) such as MMR, DT-Polio and BCG vaccines, not for Rotavirus, chicken Pox, Dengue, Yellow Fever.			
Severe hepatic impairment	Yes[5]	Yes[5]	Yes[5]	To be confirmed[5]	Yes[5]
Diabetes	Yes, in/outpatient diagnoses	Yes, via inpatient diagnoses and Long term disease registration	Yes, via in/outpatient diagnoses	Yes if registered in primary care	Yes
Tuberculosis	Refer to Table 1	Refer to Table 1	Refer to Table 1	Refer to Table 1	Refer to Table 1
Serious or opportunistic infection	Yes, in/outpatient diagnoses	Yes, via inpatient diagnoses	Yes, via in/outpatient diagnoses	Yes if registered in primary care	Yes

[1]Information on data availability from Spain and Hungary was collected during the feasibility assessment of these additional data sources. The specific variable definition and availability will be confirmed in the SAP.
[2]In Hungary, only procedures occurring in the public healthcare setting will be captured.
[3]Average daily dose will be estimated based on the issued prescription strength, packet size, and duration between issued prescriptions. In Denmark, data on the dose administered in hospital (National Hospital Medication Register) may be included as an additional measure of dosage, subject to pending information on data availability, quality and completeness.
[4]Average daily dose in Spain will be estimated based on the WHO defined daily dose for abrocitinib, and duration between issued prescriptions.
[5]Refer to ANNEX 3. ADDITIONAL INFORMATION for further details of variable definition

9.4. Data sources

This study will utilize secondary routinely collected data from population-based electronic registers in Denmark, Sweden and Spain, and a nationwide healthcare databases in France and Hungary. These secondary data sources were selected based on the expected required data elements' availability and projected sample size/number of patients with abrocitinib exposure during the study period. The data sources for this study are described below:

Denmark*:* Denmark's population-based registers, linkable by a unique identifier, the central person registration (CPR) number, assigned to all residents at birth or upon immigration) contain routinely collected data for the country's entire population of 5.8 million individuals (11, 12). The Danish National Prescription Registry contains information on all prescription medicines dispensed at Danish community pharmacies with prescriptions, including vaccinations, recorded via Anatomical Therapeutic Chemical (ATC) codes. Prescriptions administered at specialist hospital-based clinics are captured in the Danish National Patient Register, and tentatively from 2023, in the Danish Hospital Medicines Register (currently in development (13)). 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 National Patient Register. The Danish National Patient Register records diagnoses (WHO International Classification of Diseases (ICD)-10 and ICD-11 codes) and procedures (Nordic Medico-Statistical Committee [NOMESCO] codes) during inpatient or outpatient hospital encounters. Danish Cancer Registry has mandatory reporting of primary malignancies since 1987. Danish Register of Laboratory Results collects information on hospital-performed laboratory tests. Danish Medical Birth Registry will be used to identify pregnancies ending in a live or stillbirth (14-21).

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 an individual moves, changes occupation or retires . 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, medical devices, excluding data on diagnosis); inpatient details (e.g., primary and associated hospital discharge diagnosis, 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 according to the ICD-10 code. Drug dispensing is 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). While neither medical indication nor lab or imaging result are recorded, the level of detail of the captured information enables an accurate characterization of patient healthcare journeys (24).

Sweden*:* Similar to Denmark, the Swedish register system is a large, complete source of population-based data from the entire Swedish population (10.4 million in 2020). Data from the Swedish National Health Registers, including the National Patient Register, Prescribed Drug Register, Total Population Register, Swedish Cause of Death Register, and Swedish Medical Birth Register will be used. A unique personal identity 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 healthcare services including partial or complete reimbursement of purchased medications due to the tax-supported public health service with universal coverage. The Swedish National Patient Register includes diagnosis information for in-patients at public hospitals and outpatient specialists visits, including primary and secondary diagnoses and surgical procedures. The Prescribed Drug Register includes information on outpatient dispensings of all prescribed drugs sold 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 (25-29). The Swedish Medical Birth Register will be used to identify pregnancies ending in live or stillbirth. The coding systems for diagnoses, procedures, and medications are similar in Denmark and Sweden.

Spain: The Information System for Research in Primary Care (SIDIAP) database includes primary care electronic health records for >8 million people in Catalonia dating back to 2006, with 5.8 million people active in June 2021 (30). SIDIAP is representative of the general population living in Catalonia in terms of age, sex and geographic distribution. SIDIAP includes high-quality data on demographics, all-cause mortality, disease diagnoses, prescription and dispensation of drugs, laboratory tests, socio-economic indicators, vaccinations, lifestyle information, parent–child linkage and clinical parameters.

Hungary: Hungary has a single-payer healthcare system with a purchaser-provider split model and output-based payment system. The National Insurance Fund Administration (NHIFA) database contains information on healthcare covered by the state for over 9 million people in Hungary, and has national coverage for reimbursed services (medicine, out- and inpatient services) (31). Data are available for retrospective analyses from 01 January 2004. The NHIFA database includes information on demographics, mortality,

prescribed drug codes, inpatient diagnostic and procedural codes, and outpatient lab, diagnostic services, and diagnostic codes.

There are four NHIFA registers: Demography, Drugs, Inpatient, and Outpatient. The Demography register includes sex, age, and date of death. The Drugs register captures brand information, date, ATC7 codes, volume, ICD codes, and territory. Further, information is collected regarding EU number, invented name, strength, pharmaceutical form, route of administration, packaging, and content. The Inpatient register comprises date (admission, discharge, and length of stay), location, ICD codes, Diagnosis Related Groups (DRG), and International Classification of Procedures in Medicine (ICPM) codes. The Outpatient register captures labs and diagnostic services and specialist visits, including date, location, ICD codes, and ICPM codes.

The research centres affiliated with this study and the associated data sources from Denmark, Sweden, France and Spain are listed in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Register (https://www.encepp.eu/encepp/viewResource.htm?id=42185, https://www.encepp.eu/encepp/viewResource.htm?id=42187, https://www.encepp.eu/encepp/viewResource.htm?id=2291, https://www.encepp.eu/encepp/viewResource.htm?id=41070, https://www.encepp.eu/encepp/viewResource.htm?id=38744)

9.5. Study size

There is no minimum sample size planned in this study. 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 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 laboratory test prior to/during treatment with abrocitinib (e.g., CBC); e is the margin of error, or half the desired width of the confidence interval (CI); and $Z_{1-\alpha/2}$ is the standard normal Z-score corresponding to a cumulative probability of $1-\alpha/2$.

As the proportion of patients with evidence of having performed the recommended laboratory test prior to/during treatment with abrocitinib (p) is not known in advance, it will be set to 50%, which yields the most conservative (i.e., the largest) sample size for a specified margin of error. Therefore, to obtain 95% CIs with a desired width of 10% (half width of 5%) for each laboratory test, the study will require a sample size of at least

385 patients. Note that the proportion of patients with evidence of having performed the laboratory test will vary by test which will affect the precision as well (Table 3).

Table 3. Number of Abrocitinib Treated Patients by Proportion of Patients With Evidence of Having Performed the Recommended Laboratory Test and Width of 95% CI

Proportion of patients with evidence of having performed the recommended laboratory test	Width of 95% CI	Required Number of Patients
25%	0.10	289
	0.15	129
	0.20	73
50%	0.10	385
	0.15	171
	0.20	97
75%	0.10	289
	0.15	129
	0.20	73

Although the sample size identified to meet the aforementioned precision estimate requirements is 385, 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

Full details about the data management will be provided in the SAP. Briefly, all study data will be collected through the routine data collection practices of databases in Denmark, France, Sweden, Spain and Hungary. Data accruing in the routine databases undergo database-specific quality control, subject to data custodians in each country, which, as a rule, is a government agency (National Health Data Board in Denmark, National Board of Health in Sweden, SNDS in France, Catalan Health Institute in Spain, and National Health Insurance Fund (NEAK) in Hungary). Additional details of data collection methods for SIDIAP and NHIFA will be described in the SAP. Databases in Denmark, Sweden, and France have been recently characterised in a EMA-commissioned study titled Strengthening Use of Real-World Data in Medicines Development: Metadata for Data Discoverability and Study Replicability (EUPAS39322, (32)). This study was part of the EMA Big Data Initiative. The specific steps of data management may vary by country, but all will include the following major steps implemented by the investigators at each research institution:

- Obtaining approvals and completing protocol-specific data applications
- Obtaining data permits
- Retrieval or access to the protocol-specific source routinely collected data. Retrieval or access is administered by appropriate data authority in each country.

- Linkage of the national databases by an investigator or by the national data custodian, as specified in country-specific data access procedures and data permits.

- Data management to prepare the analysis dataset according to specifications in the SAP by transforming the original routinely collected data to coded data.

- Data cleaning and checking for consistency by examining range of values, units of measurement, and relevance of clinical information. Frequency tables of variables of interest will be scrutinized for plausibility. Implausible values will be set to missing. Imputation of missing values is not planned.

- Generation of aggregate-level country-specific output in a computer readable format according to the data template prepared at the principal investigator institution. Whenever practical, variable types, lengths, and names may be prespecified in the data template.

The principal investigator institution (Aarhus University) will use the country-specific aggregate data supplied via the data template (using Microsoft Excel) to generate country-specific or combined 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. The investigators will use either SAS or R software, in the most recent version available to their organisations at the time of the analyses.

9.7. Data Analysis

9.7.1. Main analyses

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

Data will be analysed in each country separately using a common protocol, database-specific definitions of the study variable, and common analysis strategies. Only data available in a given country will be analysed and presented (Table 1,Table 2). The results will be presented separately for each country.

For each country, patient baseline characteristics will be reported to the extent measured in each database, including demographics (age and sex), comorbidities (including asthma, food allergies, depression) and prior and current medication use (including treatments for atopic dermatitis and medications noted for interactions in the abrocitinib label as captured in outpatient dispensing data or other available secondary routinely collected data on medication use). Other characteristics frequently diagnosed among patients with atopic dermatitis may be added given acceptable validity and completeness measured via diagnoses or treatment proxies and known in time for inclusion in planned data extractions; existing

ethical and data protection permissions and the associated data applications may need to be amended to enable inclusion of additional variables.

Counts and proportions for categorical variables and mean, median with range or interquartile ranges (IQRs) for continuous variables will be reported to address the study objectives, as follows:

1) The count and proportion of patients with evidence of having performed the following laboratory tests and screenings within 3 months prior to initiation of abrocitinib:

- CBC including absolute lymphocyte count, absolute neutrophil count, platelet count and haemoglobin level
- Lipid panel (ie, total cholesterol, HDL, LDL, and TG)
- Screening for TB, and
- Screening for viral hepatitis B and C

2) The count and proportion of patients with evidence of having performed the following laboratory tests at week 4 (± 2 weeks) after initiation of abrocitinib:

- CBC including absolute lymphocyte count, neutrophil count, platelet count and haemoglobin level
- Lipid panel (i.e., total cholesterol, HDL, LDL, and TG)

3) The proportion of patients with evidence of having risk factors and the number of risk factors for VTE, MACE, malignancy excluding NMSC, NMSC, and serious infection (including age 65 years or older, estimated dose of >100 mg/day for patients ages 65 or older, history of atherosclerotic disease, malignancy, pregnancy, history of VTE, use of combined hormonal contraceptives or hormone replacement therapy, major surgery, inherited coagulation disorder, diabetes, history of serious or opportunistic infection, TB) within 6 months prior to initiation of treatment with abrocitinib

4) The count and proportion of patients with evidence of having received live attenuated vaccines (e.g., measles, mumps, rubella) 4 weeks prior to and during treatment with abrocitinib

5) The count and proportion (among all pregnant women identifiable in a given database) of women in whom pregnancy overlaps with abrocitinib use

6) The count and proportion patients identified with severe hepatic impairment up to 6 months prior to or during treatment with abrocitinib

7) The count and proportion of patients aged <12 years on the index date

8) The count of proportion of patients with an estimated starting dose > 100mg/day, and a description of the duration of use (median and IQR)

All proportions will be reported with 95% CIs.

9.7.2. Sensitivity analyses

The main analyses will be repeated among patients with evidence of AD before abrocitinib initiation. An additional sensitivity analysis will be undertaken in which the date of study period start is aligned with the date of the SmPC issue (09 Dec 2021).

9.8. Quality Control

Investigators in 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 (DCE), Aarhus University has implemented a series of internal Standard Operating Procedures for data management, analysis, and analysis as well as staff training. At a minimum, all study documents are reviewed by a senior epidemiologist and a statistician. All study documents (protocol, report, and publications) are reviewed 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 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 for Pharmacoepidemiology, Karolinska Institutet, 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 MAH. 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. An independent double programming will be performed for main criteria and analysis, and the results compared for validation.

Additional information on the quality control procedures pertaining to data from SIDIAP and NHIFA will be included in the SAP.

9.9. Limitations of the Research Methods

Given the use of data sources from 5 distinct EU countries in this study, there will be variability in data captured across the participating countries. For example, data on laboratory tests and vaccinations are not available in Sweden and may be underrecorded in Denmark and France. If only reimbursed services are recorded (e.g., vaccinations, oral contraceptives), some underascertainment will be associated with absence of data on nonreimbursed services. Given the underrecording, absence of a record of a given RMM metric (e.g., hepatitis B, hepatitis C, or TB screening) cannot be interpreted as an indicator of nonadherence for all metrics, and only databases with high completeness of these data should be used in that assessment (Table 2). Similarly, as vaccines recording is based on reimbursement and data is not expected to be complete, the absence of a record is not necessarily indicative of absence of vaccine receipt. Additionally, prescription strength data serves as a proxy for daily dosage in this study; this approach is supported by the absence of scoring on the abrocitinib 200 mg tablets (which would facilitate splitting into separate 100 mg doses), and by reimbursement in Sweden, Denmark, France and Spain (pending for Hungary) for both the 100 mg and 200 mg tablets (i.e. there is no financial justification for a patient to receive a prescription strength of 100 mg to be taken as 2 tablets to achieve 200 mg daily dosage). However, there may be instances where patient dosage does not correspond to the strength prescribed. Dosage data from SIDIAP can only be derived from a combination of WHO Defined Daily Dose (DDD); data from NHIFA on dosage is not available.

Other limitations include uncertainty about identification of abrocitinib in Denmark (however, most newly approved medicines receive hospital procedure codes); incomplete identification of ongoing pregnancies and pregnancies ending in a termination, as they are identifiable only by pregnancy end date; challenges in identifying screening for TB and hepatitis B and C in all participating countries; and potential underestimation of history of atherosclerotic disease given the likelihood of treatment within a primary care setting in all participating countries. Results from participating countries will not necessarily be generalizable to other countries in the EU.

9.10. Other aspects

None.

10. PROTECTION OF HUMAN SUBJECTS

The study protocol will be submitted to ethics committees or other relevant authorities for approval as required by local law. Approval will also be sought by local authorities as required.

10.1. Patient information

This study involves data that exist in anonymized or pseudonymized structured format and contain no patient personal information. Furthermore, the proposed study is a non-interventional study reusing healthcare data (secondary data collection). All data collected in the study will be deidentified with no breach of confidentiality with regard to personal

identifiers or health information. Data protection and privacy regulations will be respected in collecting, forwarding, processing, and storing data from study participants.

10.2. Patient consent

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

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

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 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 the generally accepted research practices described in the following documents:

- EMA ENCePP Guide on Methodological Standards in Pharmacoepidemiology (33),
- Module VIII of the EMA's Guideline on good pharmacovigilance practices (GVP) –Post-authorisation safety studies (34),
- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the Public Policy Committee, International Society for Pharmacoepidemiology (ISPE) and Drug Safety (35),
- International Ethical Guidelines for for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO (36), and

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a 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 Catalogues of RWD Studiesby the Principal Investigator after the protocol endorsement by the EMA and prior to the start of data collection. The final study report is planned to be submitted to the EMA on 15 November

2028, and the final study results will be disclosed through the HMA-EMA Catalogues of RWD Studies. A manuscript(s) will also 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 investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-22.

2. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers. 2018;4(1):1.

3. Schmidt SAJ, Mailhac A, Darvalics B, Mulick A, Deleuran MS, Sorensen HT, et al. Association Between Atopic Dermatitis and Educational Attainment in Denmark. JAMA Dermatol. 2021;157(6):667-75.

4. Silverwood RJ, Forbes HJ, Abuabara K, Ascott A, Schmidt M, Schmidt SAJ, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ. 2018;361:k1786.

5. Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, et al. Atopic eczema and major cardiovascular outcomes: A systematic review and meta-analysis of population-based studies. J Allergy Clin Immunol. 2019;143(5):1821-9.

6. Schmidt SAJ, Olsen M, Schmidt M, Vestergaard C, Langan SM, Deleuran MS, et al. Atopic dermatitis and risk of atrial fibrillation or flutter: A 35-year follow-up study. J Am Acad Dermatol. 2020;83(6):1616-24.

7. Mansfield KE, Schmidt SAJ, Darvalics B, Mulick A, Abuabara K, Wong AYS, et al. Association Between Atopic Eczema and Cancer in England and Denmark. JAMA Dermatol. 2020;156(10):1086-97.

8. EMA. Cibinqo. Summary of Product Characteristics 2024 [cited 19 APR 2024]. Available from: https://www.ema.europa.eu/en/documents/product-information/cibinqo-epar-product-information_en.pdf

9. Henriksen L, Simonsen J, Haerskjold A, Linder M, Kieler H, Thomsen SF, et al. Incidence rates of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. J Allergy Clin Immunol. 2015;136(2):360-6 e2.

10. Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish National Health Service Register. Scandinavian Journal of Public Health. 2011;39(7 suppl):34-7.

11. 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.

12. 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.

13. Sygehusmedicinregisteret (SMR) [cited 2020 17 December]. Available from: https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/sygehusmedicinregisteret.

14. 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. 2021.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. Recalde M, Rodriguez C, Burn E, Far M, Garcia D, Carrere-Molina J, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022;51(6):e324-e36.

31. Gaal P, Szigeti S, Csere M, Gaskins M, Panteli D. Hungary health system review. Health Syst Transit. 2011;13(5):1-266.

32. Metadata for Data Discoverability and Study Replicability (EUPAS39322) [cited 2022 12 October]. Available from: https://www.encepp.eu/encepp/viewResource.htm?id=39323.

33. 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.

34. 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.

35. 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.

36. 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. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

16. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Drug Utilization Study to Evaluate the Effectiveness of Risk Minimization Measures for Abrocitinib in the EU Using Electronic Healthcare Data

HMA-EMA Catalogues of RWD Studies® number: **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 HMA-EMA Catalogues of RWD Studies®	☒	☐	☐	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)	☒	☐	☐	9.2
	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
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	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
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
5.2	Does the protocol address the validity of the exposure measurement? (eg precision, accuracy, use of validation sub-study)	☒	☐	☐	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?	☒	☐	☐	9.7.1
6.3	Does the protocol address the validity of outcome measurement? (eg precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
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)	☒	☐	☐	9.3
	9.1.2 Outcomes? (eg clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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, 9.4
	9.2.2 Outcomes? (eg date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.4
	9.2.3 Covariates and other characteristics? (eg age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3, 9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3, 9.4
	9.3.2 Outcomes? (eg International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3, 9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3, 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?	☒	☐	☐	9.7.2

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?	☒	☐	☐	10.5

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: 14/Oct/2022		
Signature:		Signature:

17. ANNEX 3. ADDITIONAL INFORMATION

Annex 3 Table A1: Preliminary variable definitions in each database (subject to refinement in the SAP)

Variable definitions for data from Spain (SIDIAP) and Hungary (NHIFA) will be included in the SAP.

RMM element	Denmark	France	Sweden
Complete blood count: absolute lymphocyte count, absolute neutrophil count, platelet count and haemoglobin level	Potential candidate example codes (subject to refinement): NPU codes NPU01960 B— Erythrocytes NPU02902 B— Neutrophilocytes; NPU02636 B— Lymphocytes; num.c. NPU02319 B— Haemoglobin(Fe); NPU02322 P— Haemoglobin(Fe); NPU27411 P— Haemoglobin NPU03568 B— Thrombocytes	Complete blood count including platelets: TNB code 1104	No
Lipid panel total cholesterol, HDL, LDL, and TG	Potential candidate example codes (subject to refinement) NPU codes total cholesterol: NPU01566, NPU18412 High-density lipoprotein: NPU01567, NPU10157, low-density lipoprotein: AAB00101-102, NPU01568, NPU10171, Triglycerides: NPU03620, NPU04094	TNB codes: total cholesterol: 0580, TG: 0590, c-LDL: 2001, exploration of lipid abnormality: 0996 (test only, no result)	No
Hepatitis B screening	No	TNB codes: Hepatitis B screening: 4500, screening IgM anti-HVC: 4501	No
Hepatitis C screening	No	TNB codes: Quantitative genome (RNA) detection: 4124, genotyping HVC: 4125	No
TB screening	No	TNB code: 0243 (test only, no result)	No

RMM element	Denmark	France	Sweden
Risk factors for VTE, MACE, malignancy and serious infection:			
History of VTE	ICD-10 codes I26, I82.0, I82.2; I82.3, I82.8, I82.9	ICD-10 codes I26, I82.0, I82.2; I82.3, I82.8, I82.9	ICD-10 codes I26, I82.0, I82.2; I82.3, I82.8, I82.9
History of atherosclerotic disease	ICD I70.0 – I70.9	ICD10 code I70	ICD10 code I70
Malignancy	ICD-10 codes C00-C75, C81-C96	ICD-10 codes C00-C75, C81-C96; treatment proxy if relevant	ICD-10 codes C00-C75, C81-C96
Pregnancy	ICD-10 codes O, Nomesco codes KMCA for Cesarean and/or linkage to the birth registry	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 codes O + and/or linkage to the birth registry

RMM element	Denmark	France	Sweden
Use of combined hormonal contraceptives or hormone replacement therapy	ATC codes G03 Sex hormones and modulators of the genital system	ATC codes G03 Sex hormones and modulators of the genital system	ATC codes G03 Sex hormones and modulators of the genital system
Major surgery	NOMESCO Classification of Surgical Procedures candidate codes (https://sundhedsdatastyrelsen.dk/-/media/sds/filer/rammer-og-retningslinjer/klassisfikationer/bogudgave-klassifikaiton-operation.pdf?la=da) 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)
Inherited coagulation disorder (Factor V Leyden, Prothrombin gene mutation, Protein C deficiency, and	ICD-10 D68.2 Hereditary deficiency of other clotting factors for Factor V Leyden, Prothrombin gene mutation, Protein C deficiency D68.8 Other specified coagulation defects for	ICD-10 D68.2 Hereditary deficiency of other clotting factors for Factor V Leyden, Prothrombin gene mutation, Protein C deficiency	ICD-10 D68.2 Hereditary deficiency of other clotting factors for Factor V Leyden, Prothrombin gene mutation, Protein C deficiency

RMM element	Denmark	France	Sweden
Protein S deficiency)	others including Protein S deficiency ICD-10 codes (Danish version) D685A Coagulation factor V Leyden mutation, bp 1691 (heterozygous) D685B Coagulation factor V Leyden mutation bp 1691 (homozygous) D685E Prothrombin, mutation bp 20210 (heterozygous) D685F Prothrombin, mutation bp 20210 (homozygous) D685K Protein C deficiency D685L Protein S deficiency	D68.8 Other specified coagulation defects for others including Protein S deficiency	D68.8 Other specified coagulation defects for others including Protein S deficiency
Live attenuated vaccines	Vaccine type as recorded in the Danish Health Service Registry The registry list the vaccine types, only 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.	Yes for reimbursed vaccines such as MMR, DT-Polio and BCG vaccines, not for Rotavirus, chicken Pox, Dengue, Yellow Fever.	No
Diabetes	ICD-10 codes: E10-E14	ICD-10 codes: E10-E14	ICD-10 codes: E10-E14
Tuberculosis	ICD-10 codes: A15-A19	ICD-10 codes: A15-A19	ICD-10 codes: A15-A19
Serious and opportunistic infection	Serious infection: ICD-10 codes[1] 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,	Refer to codes listed for Denmark	Refer to codes listed for Denmark

RMM element	Denmark	France	Sweden
	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) 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,		

RMM element	Denmark	France	Sweden
	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		
Age	Years	Years	Years
Severe hepatic impairment	An algorithm to identify proxies of hepatic impairment with complication (ICD, ATC codes) is being developed in consultation with the local experts[2]	An algorithm to identify proxies of hepatic impairment with complication (ICD, ATC codes) is being developed in consultation with the local experts[2]	An algorithm to identify proxies of hepatic impairment with complication (ICD, ATC codes) is being developed in consultation with the local experts[2]

1 Definition will be updated at the time of SAP writing in consultation with study clinicians
2 Algorithm (per country) to be defined in the SAP.