Study Protocol C3-001

3rd September 2023

Version 4.1

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DOCUMENT HISTORY

Version	Date	Description
V1.0	19/12/2022	**Final submission to EMA**
V2.0	21/12/2022	**Revision following comments from EMA**
V3.0	19/01/2023	**Revision following comments from EMA**
V4.0	12/03/2023	**Updating study team**
V4.1	03/09/2023	**Updating study period, details on stratified analysis, update on timelines, smoking as exclusion criteria implies current or past smoking at start of follow-up, specification of disease codes for comorbidity**

Study Title	DARWIN EU® - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.
Protocol version identifier	V4.1
Date of last version of protocol	12th March 2023
EU PAS register number	EUPAS103936
Active Substance	N/A
Medicinal product	N/A
Research question and objectives	**Research question:** During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, more information is required. Therefore a real-world non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma. The present study is to produce background information on the occurrence of the health outcomes listed below (see Study Objectives) in adolescent and adult patients with severe asthma using recent data. **The objectives of this study are:** (i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (ii) To estimate the rate of mortality due to infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022. (iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022
Country(-ies) of study	The Netherlands, Spain (2 data sources), Estonia and the UK.
Author	Katia Verhamme Maria de Ridder

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body Mass Index
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real World Interrogation Network
EBB	Estonian Biobank
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
IMASIS	Institut Municipal Assistència Sanitària Information System
ICS	Inhaled Corticosteroids
IPCI	Integrated Primary Care Information Project
LABA	Long acting B2 agonists
LAMA	Long acting muscarinic antagonists
LOINC	Logical Observation Identifiers Names and Codes
LTRA	Leukotriene receptor antagonist
MI	Myocardial Infarction
N/A	Not applicable
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PSMAR	Parc de Salut Mar
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
TBC	To be confirmed
UTartu	University of Tartu

1. TITLE

DARWIN EU® - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.

2. MARKETING AUTHORISATION HOLDER

N/A

3. RESPONSIBLE PARTIES – STUDY TEAM

Table 1 shows a description of the Study team by role, name and organization.

Table 1: Description of Study Team

Study team Role	Names	Organisation
Study Project Manager/Principal Investigator	Katia Verhamme Maria de Ridder	Erasmus MC
Data Scientist	Katia Verhamme	Erasmus MC
Epidemiologist	Katia Verhamme Ed Burn John Arinze	Erasmus MC University of Oxford Erasmus MC
Statistician	Maria de Ridder	Erasmus MC
Data Manager	Mees Mosseveld	Erasmus MC
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Antonella Delmestri Mees Mosseveld Miguel-Angel Mayer Angela Leis JuanManuel Ramirez Raivo Koldo Talita Duarte Salles	University of Oxford – CPRD data Erasmus MC – IPCI data PSMAR - IMASIS PSMAR - IMASIS PSMAR - IMASIS University Tartu IDIAPJGol – SIDIAP data

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

4. ABSTRACT (STANDALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.

Rationale and Background

During the evaluation of the safety results of a clinical trial in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, a non-interventional study was requested to generate background rates of selected health outcomes in patients with severe asthma, with a disease definition that follows recently conducted clinical trials. The results of this study may inform future drug-related safety assessments in severe asthma population.

The present study is to produce background information on the occurrence of the health outcomes listed below (see Objectives) in adolescent and adult patients with severe asthma using recent data.

Research question and Objectives

The objectives of this study are:

(i) To estimate the rate of mortality due to any cause stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(ii) To estimate the rate of mortality due to fatal infections stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iii) To estimate the rate of mortality due to cardiovascular events stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022.

(iv) To estimate the incidence rate of serious cardiovascular events (but not necessarily leading to death) stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic (2020-2022), sex, age and country/database during the study period 2015-2022

Research Methods

Study design

Retrospective cohort studies will be conducted using routinely-collected health data from 5 databases. Based on the application of the respective inclusion and exclusion criteria, 3 retrospective cohorts will be defined (see 9.2.3 for inclusion and exclusion criteria).

The incidence rate of the outcomes of interest will be assessed using Population Level Disease Epidemiology analytical pipelines from the DARWIN EU Complete Catalogue of Standard Data Analyses.

Population

All individuals present in the database in the period between 01/01/2015 and 31/12/2022, with at least 1 year of prior history, being diagnosed with severe asthma and fulfilling inclusion and exclusion criteria (see 9.2.3).

Variables

Variables of interest will consist of outcomes, comorbidity, lifestyle factors, measurements and drug exposure data.

Outcomes of interest are overall mortality and cause-specific mortality (infection-related mortality, cardiovascular-related mortality) and serious cardiovascular events (acute myocardial infarction, acute coronary syndrome/ischemic heart disease, stroke and hospitalisation for heart failure)

Comorbidity namely asthma (including asthma exacerbations), other respiratory conditions (COPD, bronchiectasis, pulmonary fibrosis, lung cancer, upper and lower respiratory tract infection), other comorbidity (cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity), cancer, anaphylaxis, tuberculosis (TBC), human immunodeficiency virus (HIV), acute liver disease and hepatitis B or hepatitis C and conditions frequently associated with asthma (atopic dermatitis, nasal polyposis, chronic rhinosinusitis, chronic idiopathic urticaria, rhinitis)

Lifestyle factors namely alcohol, smoking or drug abuse

Measurements namely aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) bilirubin, blood eosinophils, weight and body mass index (BMI).

Drug exposure namely inhaled corticosteroids (ICS); systemic corticosteroids; other asthma controller medication; i.e. long acting B2 agonists (LABA), Leukotriene Receptor antagonists (LTRA), theophylline, long-acting muscarinic antagonists (LAMA), cromones; Antibiotics and antiviral therapy; Cyclosporine and Methotrexate

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Parc Salut Mar Barcelona (PSMAR), Hospital del Mar (IMIM) (hospital database), Spain
5. University of Tartu - Estonian Biobank, Estonia

Sample size

No sample size has been calculated.

Data analyses

Population-level disease epidemiology: Annual incidence rate of the outcomes of interest will be calculated stratified by country/database, calendar year, age and sex, within the cohort of severe asthma patients.

For the calculation of the incidence rate, the numerator will be the number of patients newly diagnosed with the respective outcomes of interest and the denominator will consist of the number of person-years of the severe asthma patients fulfilling the inclusion and exclusion criteria at risk.

In addition, survival time to all-cause mortality will be estimated using Kaplan Meier analysis.

Based on the application of the respective inclusion and exclusion criteria (see 9.2.3 for inclusion and exclusion criteria), these analyses will be conducted in 3 retrospective cohorts i.e. i) cohort of patients with severe asthma fulfilling inclusion criteria, ii) cohort of patients with severe asthma fulfilling inclusion and exclusion criteria and iii) a cohort of patients fulfilling inclusion criteria and with at least 1 of the exclusion criteria.

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
V2.0	21/12/2022	All	Update	Response to review from EMA
V3.0	19/01/2023	All	Update	Revision following comments from EMA
V4.0	12/03/2023	Study Team	Update	Clarify role of database partners and addition of additional members in study team
V4.1	03/09/2023	All	Updated	Study period is now 2015-2022 (and not 2015-2021) + clarification on stratified analysis (as numbers might be low) + update on timelines + specification of disease codes for certain comorbidities (CV, infection and musculoskeletal diseases)

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	19th December 2022
Final Study Protocol	January 2023
Creation of Analytical code	January 2023
Execution of Analytical Code on the data	February 2023
Interim Study Report (if applicable)	Not applicable
Draft Study Report	15th September 2023
Final Study Report	30 October 2023

7. RATIONALE AND BACKGROUND

Asthma is a highly prevalent condition with an overall prevalence of 9.8%, according to a recent systematic review. [1] Although asthma cannot yet be cured, symptoms can be controlled by the use of asthma controller therapy such as Inhaled Corticosteroids. [2] The majority of patients have mild to moderate asthma but a small proportion of patients (3-10%) have severe uncontrolled asthma and are in need of new medicines. [3]

During the evaluation of the safety results of a clinical trial of an investigational product in patients with severe asthma, differences in rates of serious adverse events were observed in the experimental treatment arm compared to the control arm. In order to contextualise these differences, a non-interventional study was required to generate background rates of selected health outcomes in patients with severe asthma. The disease definition used in the present study follows from recently conducted clinical trials in severe asthma. The results of this study may inform future drug-related safety assessments in the same population.

This present study is designed to produce background information on the occurrence of the health outcomes listed below (see Study Objectives) in adolescent and adult patients with severe asthma using recent data.

8. RESEARCH QUESTION AND OBJECTIVES

Table 2: Primary and secondary research questions and objective

A. **Primary research question and objective**

Objective:	To estimate the i) rate of mortality due to any cause, ii) rate of mortality due to fatal infections, iii) rate of mortality due to cardiovascular events and iv) incidence rate of serious cardiovascular events, stratified by calendar year as well as pre-pandemic (2015-2019) and pandemic

	(2020-2022), sex, age and country/database during the study period 2015-2022.
Hypothesis:	N/A
Population ***(mention key inclusion-exclusion criteria):***	The study cohort will comprise all individuals present in the database in the period between 01/01/2015 and 31/12/2022, with at least 1 year of prior history, and being diagnosed with severe asthma . The rates of the respective outcomes of interest will be estimated in 3 cohorts namely: Cohort 1: Patients with severe asthma fulfilling inclusion criteria. Cohort 2: patients with severe asthma fulfilling inclusion and exclusion criteria Cohort 3: Patients with severe asthma fulfilling inclusion criteria and with at least 1 of the exclusion criteria. See 9.2.3 for inclusion and exclusion criteria.
Exposure:	Not applicable
Comparator:	Not applicable
Outcome:	Mortality (all-cause mortality, mortality due to fatal infections, mortality due to cardiovascular events) and incidence of serious cardiovascular events
Time ***(when follow up begins and ends):***	Follow-up will start on the respective date of the latest of the following: 1) study start date (1st January 2015), 2) date at which a patient first has sufficient prior history (365 days), 3) date on which a patient first fulfils the respective inclusion criteria. Follow-up will end at the earliest date of the following: 1) end date of observation period of a patient in the database, 2) date 52 and 104 weeks following cohort start for the main analyses, 3) date of death or 4) end of study period (31st December 2022). Follow-up for the analysis on the incidence of serious cardiovascular events will end when a patient develops the outcome of interest or is censored due to loss to follow-up.
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (NL), SIDIAP (Spain), PSMAR (Spain), Estonian Biobank – via UTartu (Estonia) and CPRD GOLD (UK)
Main measure of effect:	Incidence of the respective outcomes of interest (mortality (all-cause and cause specific)) and serious cardiovascular events)

9. RESEARCH METHODS

9.1 Study Design

Retrospective cohort studies will be conducted using routinely collected health data from 5 databases. Based on the application of the respective inclusion and exclusion criteria, 3 retrospective cohorts will be defined (see 9.2.3 for a description of inclusion and exclusion criteria).

The incidence rate of mortality and the outcomes of interest will be assessed using Population Level Disease Epidemiology analytical pipelines. (from the DARWIN EU Complete Catalogue of Standard Data Analyses).

9.2 Study Setting

9.2.1 Study population

The study population will comprise severe asthma patients fulfilling the inclusion criteria and present in the database during the study period (2015-2022) and with at least 365 days of data availability before the day they become eligible for study inclusion. Within this study population, 3 cohorts will be identified namely cohort 1: Patients with severe asthma fulfilling inclusion criteria; cohort 2: Patients with severe asthma fulfilling inclusion criteria and not having any of the exclusion criteria and cohort 3: Patients with severe asthma fulfilling inclusion criteria and with at least 1 of the exclusion criteria.

Cohort 1 is the disjoint union of cohort 2 and cohort 3.

9.2.2 Study period and follow-up

The study period will start on 1st January 2015 and end on 31st December 2022. The study period is categorised into a pre-pandemic period (01/01/2015-31/12/2019) and a pandemic period (01/01/2020-31/12/2022).

Table 3: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type	Diagnosis position	Measurement characteristics / validation	Source of algorithm
All patients with severe asthma from the database eligible for the study and fulfilling all inclusion criteria	Patient present in the database during the study period (2015-2022), with at least 1 year of valid database history and fulfilling inclusion criteria (cohort 1). Patients present in the database during the study period (2015-2022), with at least 1 year of valid database history and fulfilling inclusion criteria and not having any of the exclusion criteria (cohort 2). Patient present in the database during the study period (2015-2022), with at least 1 year of valid database history and fulfilling inclusion criteria and having at least one of the exclusion criteria (cohort 3).	Multiple as patients might appear in 3 different cohorts	Prevalent and Incident.#	None	IP and OP	SNOMED codes (see appendix)	N/A	N/A	N/A

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

prevalent means patients with severe asthma prior to the study start – these patients will be included if they fulfil inclusion criteria (and not having any of the exclusion criteria) at start of the study period.

incident means patients diagnosed with severe asthma during study period.

Study participants will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2015), 2) date at which they have sufficient prior history (365 days), 3) date on which they fulfil the respective inclusion criteria. (see figure 1). For a description of inclusion and exclusion criteria, see 9.2.3.

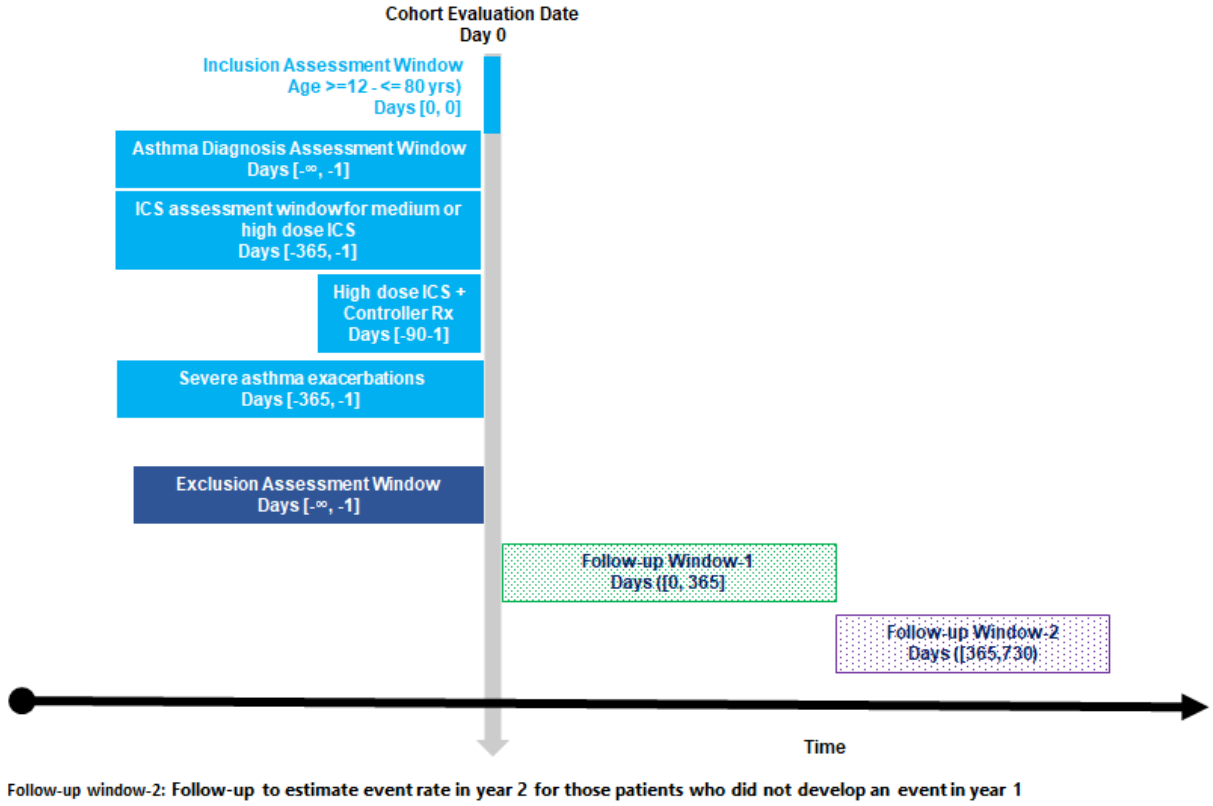

Figure 1: Included observation time for the denominator population

Participants will stop contributing person time at the earliest date of the following: 1) end date of observation period of patient in the database , 2) end of study follow-up period (365 and 730 days following cohort start), 3) date of death or 4) end of study period (31st December 2022). Follow-up for the analysis on the incidence of serious cardiovascular events will end when patients develop the outcome of interest. Only for the Kaplan-Meier estimates, follow-up will not end after 730 days.

Follow-up will start either on the 1st January 2015 or following the date in which the patient fulfils inclusion criteria during the study period for those entering the cohort after 1st January 2015 (see Figure 2)

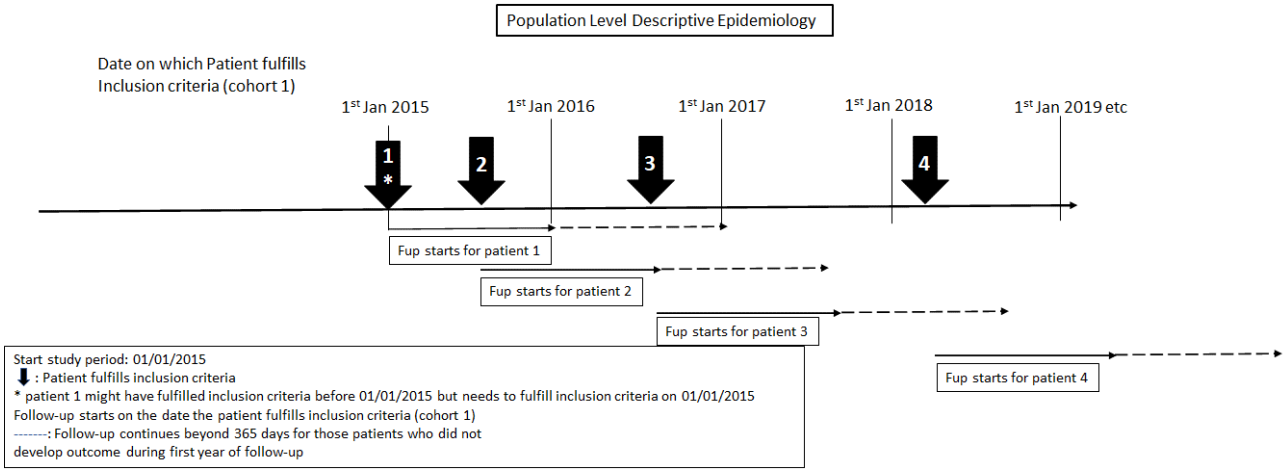

Figure 2: Start of follow-up following fulfilment of inclusion criteria

As an additional analysis, the incidence of the outcomes of interest will be carried out in a long term extension (LTE) period of 52 weeks for those in the cohort who did not experience the health outcome of interest in the first 52 weeks. (Figure 3)

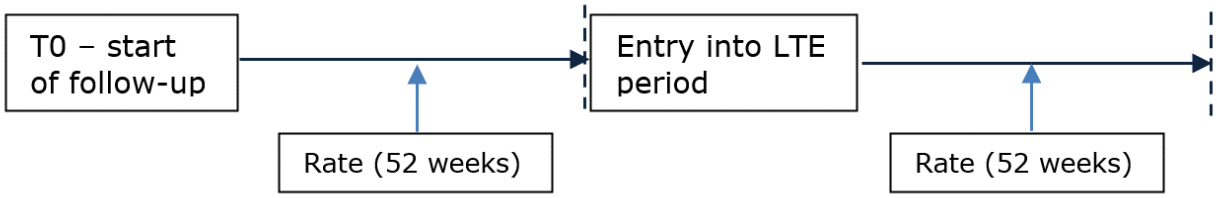

Figure 3: Start of follow-up for the long term extension study (LTE)

9.2.3 Inclusion and exclusion criteria

For this study, **all** of the following **inclusion criteria** at the time of cohort entry will be applied:

- Patients with observation time during the study period and at least 1 year of prior history observed before contributing observation time.
- Patients 12 to 80 years of age at time of cohort entry
- Physician-diagnosed asthma for at least 12 months. Diagnosis of asthma will be based on SNOMED disease codes for asthma and date of diagnosis can be before 1 st January 2015
- Patients treated with medium or high-dose ICS (⩾ 250 µg fluticasone propionate dry powder formulation equivalent total daily dose) as per GINA guideline – GINA 2022) for at least 12 months. (see table 1 in appendix for GINA classification on low, medium or high dose ICS)[2]
- Patients treated with high dose ICS (⩾ 500 µg fluticasone propionate dry powder formulation equivalent total daily dose) (as per GINA guidelines – GINA 2022) for at least 12 weeks. (see table 2 in appendix for GINA classification on low, medium or high dose ICS)[2]
- Use of at least one additional maintenance asthma controller medication; e.g., LABA, LTRA, theophylline, long-acting muscarinic antagonists (LAMA), cromones, etc for at least 12 weeks.

- Documented history of at least 2 asthma exacerbation events in the previous 12 months. Asthma exacerbations are defined as any of the following:

  - a. an asthma exacerbation, requiring treatment with systemic corticosteroids for at least 3 consecutive days (a single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids).
  - b. an ER visit for reason of asthma
  - c. hospitalisation due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for $\geqslant$ 24 hours).
  - d. SNOMED code for "acute asthma exacerbation"

The date on which the patient fulfils all of these inclusion criteria is called the "cohort evaluation date". (see also figure 2)

For this study, 3 cohorts will be generated namely (Figure 4):

Cohort 1: Patients fulfilling inclusion criteria.

Cohort 2: Patients fulfilling inclusion criteria and not having any of the exclusion criteria. Cohort 2 is a subset of cohort 1

Cohort 3: Patients fulfilling inclusion criteria and with at least 1 of the exclusion criteria. Patients from cohort 3 are those in cohort 1 who are not in cohort 2.

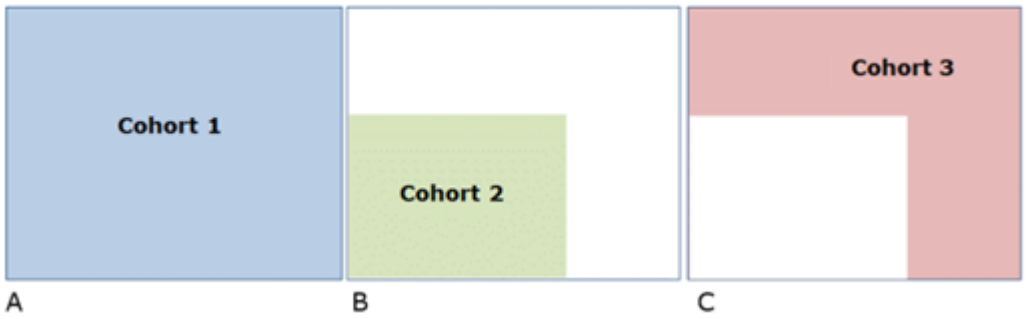

Figure 4: Describing potential cohort size of cohort 1, cohort 2 and cohort 3. A) Patients who meet the inclusion criteria (Cohort 1). B) Patients who meet the inclusion criteria and have no exclusion criteria (Cohort 2). C) Patients who meet the inclusion criteria but have one or more exclusion criteria (Cohort 3).

For this study, the following **patients will be excluded:**

- Patients with any clinically important pulmonary disease other than asthma, in particular exclusion of patients with a medical history of COPD, lung cancer, bronchiectasis or pulmonary fibrosis prior to start of follow-up
- Patients with a SNOMED disease code of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity in the 12 months prior to start of follow-up
- Patients with cancer as comorbidity (current or history of) (except for basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix)

- Patients with a SNOMED disease code of upper or lower respiratory tract infection, requiring treatment with antibiotics or antiviral medications within 2 weeks prior to start of follow-up
- Current/past smokers
- Patients with alcohol or drug abuse in the 12 months prior to start of follow-up
- Patients with SNOMED disease code of TBC in the 12 months prior to start of follow-up
- Patients with SNOMED disease code of HIV prior to start of follow-up
- Patients who have used cyclosporine or methotrexate in the 12 weeks prior to start of follow-up
- Patients with a medical history of anaphylaxis
- Evidence of active liver disease or aspartate transaminase, alanine transaminase, alkaline phosphatase or bilirubin > 2 times the upper limit of normal (ULN) in the 12 months prior to start of follow-up
- Patients with a SNOMED disease code of Hepatitis B or Hepatitis C prior to start of follow-up.

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2015-2022 (or the latest available)	See under inclusion criterion	Before	N/A	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	Before	1 year	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	N/A	N/A	All individuals within the selected databases	N/A	N/A
Age	Patients 12 to 80 years of age	Before	N/A	Depending on the database: Primary care, Secondary care	N/A	N/A	All individuals within the selected databases	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	inclusive at start of follow-up			or combination of primary and secondary care for Estonian Biobank					
Asthma	Physician-diagnosed asthma for at least 12 months. Date of diagnosis can be before the start of study period	Before	12 months or more	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	SNOMED	N/A	All individuals within the selected databases	N/A	N/A
ICS exposure	Patients treated with medium or high-dose ICS for at least 12 months	Before	12 months	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
ICS exposure	Patients treated with high-dose ICS for at least 12 weeks	Before	12 weeks	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma and treated with medium or high dose ICS for at least 12 months	N/A	N/A
Asthma controller therapy	At least one additional maintenance asthma controller medication; e.g., LABA, LTRA, theophylline, long-acting muscarinic antagonists (LAMA), cromones) for at least 12 weeks	Before	12 weeks	Depending on the database: Primary care, Secondary care or combination of primary and secondary care for Estonian Biobank	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma and treated with medium or high dose ICS for at least 12 months and treated with high dose ICS for at least 12 weeks	N/A	N/A
Asthma exacerbations	Documented history of at least 2 asthma	Before	12 months	Depending on the database: Primary care,	SNOMED	N/A	All individuals within the selected databases and	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	exacerbation events within 12 months.			Secondary care or combination of primary and secondary care for Estonian Biobank			diagnosed with asthma and treated with medium or high dose ICS for at least 12 months and treated with high dose ICS for at least 12 weeks and on additional asthma controller therapy for at least 12 weeks		

* A patient is eligible for entry in the study cohort at the date all inclusion criteria are fulfilled

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Other pulmonary conditions	Patients with a medical history of COPD, lung cancer, bronchiectasis or pulmonary fibrosis prior to start of follow-up	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Other Comorbidity	Evidence of cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric comorbidity; TBC; Hepatitis B or Hepatitis C	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Cancer	Evidence of cancer	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Upper or lower respiratory tract infection	Evidence of upper or lower respiratory tract infection requiring treatment with antiviral therapy/antibiotics within 12 weeks prior to start of follow-up	After	2 weeks prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED and RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Current Smoker	Evidence of current smoker	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care	SNOMED		All individuals within the selected databases and	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
				for Estonian Biobank - UTartu			diagnosed with asthma		
Alcohol or drug abuse	Evidence of alcohol or drug abuse	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
HIV	Evidence of HIV	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
cyclosporine or methotrexate	Exposure to any of these drugs	After	2 weeks prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	RxNorm	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Anaphylaxis	Evidence of anaphylaxis	After	∞ prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care for Estonian Biobank - UTartu	SNOMED	N/A	All individuals within the selected databases and diagnosed with asthma	N/A	N/A
Acute liver disease	Evidence of active liver disease or aspartate transaminase, alanine transaminase, alkaline phosphatase or bilirubin > 2 times the upper limit of	After	12 months prior to start of follow-up	Primary care, Secondary care and combination of primary and secondary care	SNOMED	N/A	All individuals within the selected databases and	N/A	N/A

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	normal (ULN) in the 12 months prior to start of follow-up			for Estonian Biobank - UTartu			diagnosed with asthma		

* After, as first inclusion criteria are checked and next it is evaluated if exclusion criteria occur.

9.3 Variables

9.3.1 Exposure

For this study, drug exposure is important as part of the inclusion and exclusion criteria.

The calculation of duration of the exposures is described in section 9.7.3- drug exposure calculations.

This list of drug classes (with respective ATC code) is described in Table 6. Details of drug exposure are described in the appendix

Table 6: Exposure of interest to assess inclusion and exclusion criteria.

Drug Class	Ingredient	ATC code
ICS	Beclomethasone	R03BA01
	Budesonide	R03BA02
	Flunisolide	R03BA03
	Betamethasone	R03BA04
	Fluticasone	R03BA05
	Triamcinolone	R03BA06
	Mometasone	R03BA07
	Ciclesonide	R03BA08
	Fluticasone furoate	R03BA09
ICS+LABA	Salmeterol+fluticasone	R03AK06
	Formoterol+budesonide	R03AK07
	Formoterol+beclomethasone	R03AK08
	Formoterol+mometasone	R03AK09
	Vilanterol+fluticasone furoate	R03AK10
	Formoterol+fluticasone	R03AK11
	Salmeterol + budesonide	R03AK12
	Salbutamol+beclomethasone	R03AK13
	Indacaterol and mometasone	R03AK14
ICS+LABA+LAMA	Vilanterol, umeclidinium bromide, and fluticasone furoate	R03AL08
	Formoterol, glycopyrronium bromide and beclometasone	R03AL09
	Formoterol, glycopyrronium bromide, and budesonide	R03AL11
	Indacaterol, glycopyrronium bromide and mometasone	R03AL12
LABA	Salmeterol	R03AC12
	Formoterol	R03AC13
	Reproterol	R03AC15
	Procaterol	R03AC16
	Bitolterol	R03AC17
	Indacaterol	R03AC18

Drug Class	Ingredient	ATC code
	Olodaterol	R03AC19
LAMA	Tiotropium bromide	R03BB04
	Aclidinium bromide	R03BB05
	Glycopyrronium bromide	R03BB06
	Umeclidinium bromide	R03BB07
	Revefenacin	R03BB08
LABA+LAMA	Vilanterol and umeclidinium bromide	R03AL03
	Indacaterol and glycopyrronium bromide	R03AL04
	Formoterol and aclidinium bromide	R03AL05
	Olodaterol and tiotropium bromide	R03AL06
	Formoterol and glycopyrronium bromide	R03AL07
	Formoterol and tiotropium bromide	R03AL10
Leukotriene receptor antagonists (LTRA)		R03DC
Xanthines		R03DA
Cromones		A07EB
Biologics	Omalizumab	R03DX05
	Reslizumab	R03DX08
	Mepolizumab	R03DX09
	Benralizumab	R03DX10
	Dupilumab	D11AH05
Systemic steroids		H02AB
Antbiotics		J01
Antivirals		J05
Ciclosporin		L04AD01
Methotrexate		L04AX03

Details of exposure are described in Table 7.

Table 7: Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
ICS	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 months prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	Medium or high dose ICS	N/A
ICS	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	High dose ICS	N/A
Other asthma controller therapy	Preliminary code lists provided in Table 2 of Appendix I	N/A	12 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A
Antibiotics and/or Antiviral Drugs	Preliminary code lists provided in Table 2 of Appendix I	N/A	2 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A
Ciclosporine or methotrexate	Preliminary code lists provided in Table 2 of Appendix I	N/A	2 weeks prior to start of follow-up	Primary and secondary care	RxNorm	N/A	All individuals with asthma present in the database	N/A	N/A	N/A

9.3.2 Outcomes

- All-cause mortality
- Fatal infections
- Fatal cardiovascular events
- Serious cardiovascular events (see details below).

As cause of death is not documented within OMOP CDM, additional cohorts will be generated beside the mortality cohort. If the date of infection or cardiovascular events occurred within a window of 14 days prior to the date of mortality, cause of death will be assumed to be related to these respective conditions (i.e. mortality related to infections or mortality related to cardiovascular events)

These additional cohorts will consist of an infectious cohort (covering all types of infections) and a cardiovascular event cohort (covering all types of cardiovascular events). The concept list with SNOMED codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

Serious cardiovascular events are defined as acute myocardial infarction, acute coronary syndrome/ischemic heart disease, stroke and hospitalisation for heart failure. The incidence of the serious cardiovascular events as outcome will be studied overall but also by subgroup namely i) myocardial infarction - ACS/ischemic heart disease, ii) stroke and iii) hospitalisation for heart failure separately.

The concept list with SNOMED codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.3.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

9.3.3.1 Covariates for stratification in population-level incidence study

- Age: 12-17, 18-64, 65-74, 75-80.
- Calendar year (by calendar year(s) which refers to the year in which the follow-up period falls)
- Pre- and pandemic period
- Sex

9.3.3.2 Comorbidities to assess inclusion and exclusion criteria

- Asthma
- Other respiratory conditions, namely COPD, bronchiectasis, pulmonary fibrosis, lung cancer, upper and lower respiratory tract infection
- Comorbidity: cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity
- Cancer
- Anaphylaxis
- TBC (tuberculosis)
- HIV
- Acute Liver Disease
- Hepatitis B and Hepatitis C

The list with SNOMED concept codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.3.3.3 Comorbidities at the time of cohort entry

The prevalence of the following comorbidities will be described at start of follow-up:

- Arterial hypertension
- Number of asthma exacerbations in previous 12 months (which in principle should be minimum 2 in order to fulfil inclusion criteria)
- Gastro-esophageal reflux disease
- Atopic Dermatitis
- Nasal Polyposis
- Chronic Sinusitis
- Chronic spontaneous urticaria
- Rhinitis
- Diabetes mellitus
- Osteoporosis
- Comorbidities that form exclusion criteria (i.e. other respiratory conditions: COPD, lung cancer, bronchiectasis or pulmonary fibrosis; comorbidities (cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological and psychiatric comorbidity); cancer; upper or lower respiratory tract infection, requiring treatment with antibiotics or antiviral medications; smoking (current or past); alcohol; drug use; TBC, HIV, use of methotrexate; use of ciclosporin; anaphylaxis, acute liver disease, abnormal liver enzymes)

The list with SNOMED and LOINC (Logical Observation Identifiers Names and Codes) concept codes for these conditions of interest are described in Appendix I – Table 1: List with concept definitions.

9.3.3.4 Lifestyle factors

- Smoking status (current/past)
- Alcohol and drug abuse

The list with SNOMED and LOINC concept codes for these conditions are described inAppendix I – Table 4: List with concept codes for Lifestyle Factors.

9.3.3.5 Measurements

- aspartate transaminase, alanine transaminase, alkaline phosphatase and bilirubin with values and information on upper limit of normal
- blood eosinophils
- BMI

The list with SNOMED and LOINC concept codes for these conditions are described in Appendix I – Table 3: List with concept codes for measurements .

Table 8: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Comorbidity	Check for conditions of interest at start of follow-up	Binary	All history	Primary and secondary care	SNOMED	N/A	Patients with severe asthma	N/A	N/A
Lifestyle factors	Check for lifestyle factors at start of follow-up	Binary	[- 12 months, 0]	Primary care and secondary care	SNOMED and LOINC	N/A	Patients with severe asthma	N/A	N/A
Measurements	Check for measurements factors at start of follow-up	Continuous	[- 12 months, 0]	Primary and secondary care	SNOMED and LOINC	N/A	Patients with severe asthma	N/A	N/A

9.4 Data sources

This study will be conducted using routinely collected data from 5 databases in 4 countries (3 EU countries and United Kingdom). All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Parc Salut Mar Barcelona (PSMAR), Hospital del Mar (IMIM) (hospital database), Spain
5. University of Tartu - Estonian Biobank, Estonia

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 9**.

Table 9: Description of data sources

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g., primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Data lock for the last update
NL	IPCI	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	1.39 million	1st January 2022
ES	SIDIAP	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	5.8 million	31st March 2022
UK	CPRD GOLD	Covers primary care setting and this database has been used for previous research in patients with asthma.	Primary care	EHR	3 million	1st July 2022
ES	IMASIS	Covers secondary care setting, database has information on treatment of patients with asthma in the in- and outpatient setting and information on mortality and other outcomes for in-house patients	Secondary care (in and outpatients)	EHR	0.6 million	9th July 2022
Estonia	Estonian Biobank – University of Tartu	This database has been used for other studies in patients with asthma	Biobank	Claims data	0.2 million	March 2022

NL = The Netherlands, ES = Spain, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS= Institut Municipal Assistencia Sanitaria Information System, CPRD GOLD = Clinical Practice Research Datalink GOLD, , EHR = Electronic Heath record.
Nap= Not applicable

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands. The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.[5] The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.[5]

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[6]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry. [7]

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[8] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases.

Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants ("gene donors" >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor. [9, 10]

9.5 Study size

No sample size has been calculated.

9.6 Data Management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org. This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.7 Data Analysis

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the Complete Catalogue of Data Analysis of DARWIN EU, which describes the type of analysis for common study designs.

The analysis will include calculation of population based incidence rates, as described in section 9.7.5.1 – Population-level Incidence Study,

9.7.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment and the Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

9.7.2 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts < 5 will be clouded.

9.7.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "PatientProfiles" to extract patient characteristics and exclusion criteria, "IncidencePrevalence"r the population-level estimation of the outcomes of interest and "survival" for the Kaplan-Meier and Aalen-Johansen curves.

Drug exposure calculations

Drug eras will be defined as follows:. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications.

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 5**, first row.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 5: Gap era joint mode

If two eras start at the same date, the overlapping period will be considered exposed by both. We will not consider repetitive exposure.

9.7.4 Methods to derive parameters of interest

Calendar time

Incidence will be calculated in the COVID-19 pre-pandemic and pandemic period. (Fig 6) Calculation of the incidence of the outcomes by period is based on the period the follow-up period at risk of a person falls. This means that the 1 year time at risk can fall into two different periods.

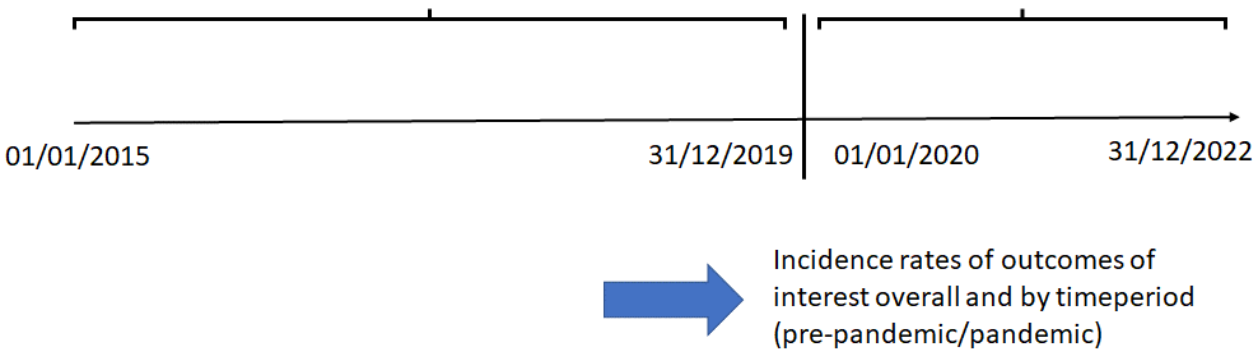

Figure 6: Incidence rate by timeperiod

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: 12-17, 18-64, 65-74, and 75-80. Also, an overall rate for all ages combined will be provided.

Sex

Results will be presented stratified by sex and overall

9.7.5 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

9.7.5.1 Population-level Incidence study

Incidence calculations will be conducted separately for each outcome of interest.

Incidence calculations

Annual incidence rates of the outcome of interest will be calculated as the number of patients with the outcome of interest per 100,000 person-years of the population at risk of developing the outcome during the period. Those study participants who enter the denominator population will then contribute time at risk up to their first outcome during the study period. Or if they do not have an outcome they will contribute time at risk up as described above in section 9.2.2 (study period and end of study follow-up). Incidence rates will be given together with 95% Poisson exact confidence intervals.

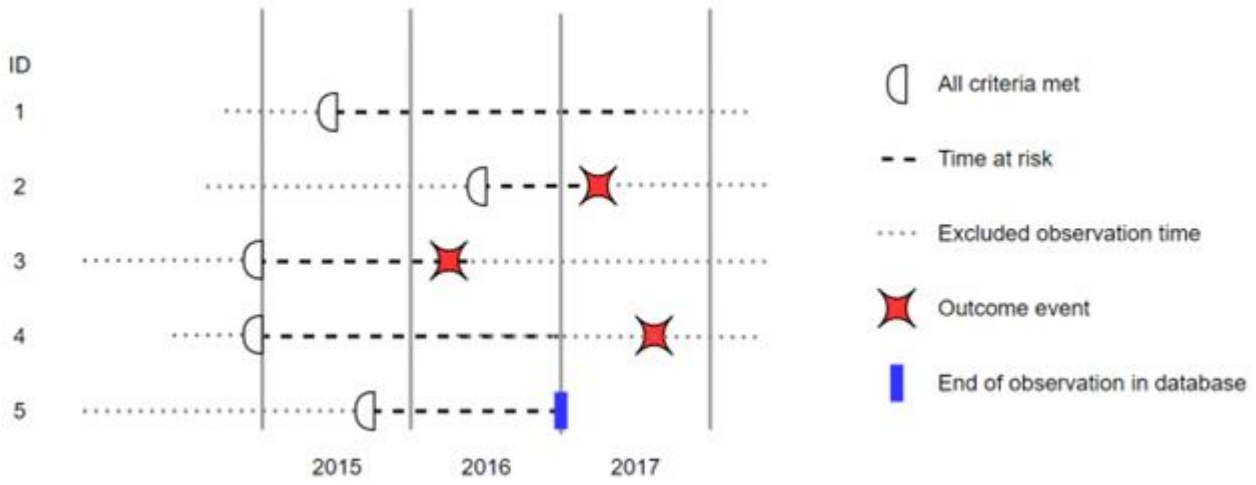

Figure 7: Incidence example for the outcome of interest

An illustration of the calculation of incidence of the outcomes is shown in **Figure 7**.

Patient ID 1 enters the study at a specific moment in time in 2015 when all inclusion and exclusion criteria are fulfilled. From that point in time he/she is at risk and as no event occurred this patient contributes time at risk during 2015, 2016 and 2017. Patient ID 2 enters the study during 2016. An outcome event occurs within a year after follow-up and in particular during 2017. This patient contributes time during 2016 and 2017. Patient ID 3 had severe asthma already before January 1, 2015. Entry in the study is at January 1, 2015. An outcome event occurs in 2016. Patient ID 4 also enters the study at January 1, 2015. An outcome event only occurs during 2017. This is beyond the 2 years follow-up time, so this event is not counted. The patient contributes time in 2015 and 2016. Patient ID 5 enters during 2015. At the end of 2016, observation time in the database ends, e.g. because the patient moves and is no longer in the GP practise. Time at risk stops at this point.

Incidence rates for the pre-pandemic and pandemic periods will be provided, for the first 52 weeks after inclusion as well as for the second 52 weeks after inclusion for those who survived the first 52 weeks.

For these incidence rates, estimates over all databases will be given, using meta-analysis.

9.7.5.2 Kaplan Meier

Kaplan Meier curves with 95% confidence intervals (Greenwood) will be provided showing survival probabilities for overall mortality starting at study entry and ongoing during the available observation time of the patients within the study period. For the other outcomes Aalen-Johansen estimators will be used. All these curves will be reported for the pre- and pandemic periods.

9.7.6 Description of sensitivity analyses.

The proportion of patients with prevalent severe asthma (patients who were already the necessary period on medium or high dose ICS) prior to entry in the study is likely to be different in 2015 compared to later years. During 2015, the proportion of patients with prevalent severe asthma might be considerable however during the following years this proportion will be lower as the only prevalent severe asthma cases will be those entering because their observation in the database started later. As patients with prevalent severe asthma might be more severe (as longer time since date of diagnosis of severe asthma) compared to patients with incident severe asthma, a stratified analysis in incident and prevalent severe asthma will be conducted.

If counts however are too low, it will not be possible to conduct these sensitivity analyses.

9.8 Quality Control

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

A pharmacist will review the codes of the drugs of interest. To obtain information on how detailed drug use is available within the database, the DrugExposure Diagnostics R package will run on the different datasources. Results of this run will indicate whether additional mapping for a specific drug (e.g. for a specific ICS of interest) might be needed.

When defining cohorts for asthma, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.

The study code will be based on the R package IncidencePrevalence which has been developed to estimate incidence and prevalence of conditions and drug use. This package includes numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

9.9 Limitation of the research methods

The study will be informed by routinely collected health care data and so data quality issues must be considered. Severe asthma is based on daily use of medium or high dose ICS as described in recent GINA guidelines. [(2)] To categorise ICS use, information on type of device, strength and dosing will be needed which is not always available for all patients within the different datasources. With regard to drug exposure, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable.

In addition, the recording of events (comorbidity, measurements and lifestyle factors (e.g. smoking status)) may vary across databases and may be incomplete. Although asthma is a highly prevalent condition with published prevalences around 10%, numbers might drop substantially when applying the inclusion and exclusion criteria. [(1)]

9.10 Evidence synthesis

Results from analyses described in Section 9.7 will be presented separately for each database. No pooling of data will be conducted. Estimates over all databases will be provided using meta-analysis for the following mortality and incidence rates: i) rate in first 52 weeks following start of follow-up, during the pre-pandemic period, ii) rate in first 52 weeks following start of follow-up, during the pandemic period, iii) rate in second 52 weeks following start of follow-up for those who did not experience the event in the first 52 weeks, during the pre-pandemic period and iv) rate in the second 52 weeks for those who did not experience the event in the first 52 weeks, during the pandemic period. .

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from various EU member states as well as the UK will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Study Report

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the pdf report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

13. REFERENCES

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14. ANNEXES

Appendix I: List of Stand-Alone documents (e.g., lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

Appendix III: Additional Information

APPENDIX I

APPENDIX I – TABLE 1: LIST WITH CONCEPT DEFINITIONS

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Infections	132736, 256451, 432250, 42597240, 4280729, 37395594, 255848, 132797, 4270490	437474
Asthma	317009, 4293734, 4308356, 46287068, 4279553	4029337, 4312524
COLD	255573, 256448, 36685451, 36685452, 36685453, 36685454, 36685455, 36685456, 36685457, 36685458, 44782563, 44788819	
Bronchiectasis	256449	
Pulmonary fibrosis	4197819	
Lung cancer	443388, 35610239, 4201621	
Upper respiratory tract infection	4110027, 4181583	
Lower respiratory tract infection	255848, 256451, 4270490	
Cardiovascular comorbidity (hypertension, ischemic heart diseases, heart failure, cardiac valve disorders, cardiac arrhythmia, pulmonary embolism, atherosclerosis,	381316, 373503, 321318, 312327, 319844, 316866, 316139, 44784217, 314054, 319843, 316993, 319845, 4133004, 440417, 40479625	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
deep venous thrombosis, stroke, TIA		
Gastrointestinal comorbidity	4000610	443568, 4244495, 36715498
Hepatic comorbidity	4093333	4115573, 4243887, , 4246127, 4130519
Renal comorbidity	4091056	4217308, 196653, 4243885
Neurological comorbidity	376337	4157331
Musculoskeletal comorbidity	80180, 80809, 4046660, 372409, 440674, 80502	
Infectious comorbidity (LRTI and URTI excluded)	4099350, 132797, 378143, 435785, 3739614, 440448, 192956, 195856, 4291005, 196152, 314383, 4138837, 441589, 140480, 435613, 439840, 4291025, 434557, 4267414	
Endocrine comorbidity	31821	
Metabolic comorbidity	436670	
Haematological comorbidity	317248	
Psychiatric comorbidity	432586	4244690
Cancer	443392	4112752, 4111921, 4116082

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Anaphylaxis	441202	
Tuberculosis	434557	
HIV-infection	439727, 4013106, 4083350, 4186235, 4221489, 4298853, 40484507, 44783623	
Acute liver disease	201343, 4049298, 37396531, 4184847, 4243475, 36715006, 36676901, 4058676, 4250743, 4331678, 196455	
Hepatitis B	200031, 439673, 4013553, 4014007, 4244873, 4247369, 4281232, 42537336, 44792587, 45772057, 46286608	
Hepatitis C	197494, 439672, 4132902, 4153375, 4196134, 4227247, 4340380, 43531723, 44789328, 44792611, 44806379, 44813294, 45757360, 45757396, 46273598, 46286609	
Arterial hypertension	316866	4071202
Severe asthma exacerbations	4152913	
Gastro-oesophageal reflux disease	36717641, 36713494, 4175650, 318800, 30437	
Atopic dermatitis	133834	
Nasal polyposis	42537251	
Chronic sinusitis	257012	
Chronic idiopathic urticaria	4199697	
Rhinitis	257007	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Diabetes mellitus	201820, 442793, 604741, 760977, 760978, 760979, 760980, 760989, 761050, 761063, 765375, 4019513, 4034961, 4055679, 4060085, 4065354, 4129379, 4130165, 4144221, 4146514, 4175440, 4182243, 4219466, 4220981, 4242853, 4305491, 4307799, 37018224, 40482801, 40484648, 40484649, 40485020, 42536400, 42689695, 43020791, 45766963, 45768456	
Osteoporosis	80502, 36716194, 4109181, 44783850, 37204244	
Smoking (current or past)	619068, 437264	
Alcohol abuse	436607, 4322643, 4030588, 195300, 4106575, 378421, 4214950, 4302744, 4176651, 4202330, 46269816, 46269817, 37016176, 45757494, 318773, 36714559, 619608, 45757783, 35610532, 46269818, 3655834, 44782445	
Drug abuse	606210, 436954, 4127868, 4022666, 40480941, 40482269, 4295481	
Drug abuse	42529475, 4168205, 4239438, 4206984, 4219142, 3022196, 36031658, 36031249, 4017177, 4229859, 42529480, 4036792, 4038240, 4037138, 42539778, 1616455	
Alcohol abuse	4116983, 4053784, 45766930, 4080065, 36674487, 45772695, 44793164, 37206970, 4207141, 44792459, 3036878, 762596, 4145860, 4042872, 4027638, 44786671, 432456, 44786700, 40481082, 4038704, 3027199, 608490, 44812667	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Smoking (current or past)	44788975, 44788976, 762499, 3012697, 4052948, 600776, 44786669, 762498, 4131520, 37395605, 1616974, 42528924, 44804450, 4206526, 4203874, 4046886, 4141787, 44809281	

Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor.

Before finalizing the concept sets, CohortDiagnostics will run on cohorts created using the initial concept sets to check code counts and patient characteristics which might give indications to adjust the concept sets.

APPENDIX I – TABLE 2: LIST WITH CONCEPT CODES FOR EXPOSURE

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list except for respiratory drugs given via inhalation.

Drug Classes	Include plus descendants	Exclude plus descendants
ICS	21085349, 40152662, 40734060, 40830728, 40143708, 35885804, 35887474, 36035528, 36036727, 36894464, 40143326, 40223712, 40892816, 44817882, 2910652, 42615152, 783228, 1356140, 1356143, 1830424, 1970732, 2069097, 35133500, 35135829, 35831802, 35898300, 36787269, 37002305, 40142910, 40142920, 42479684, 43291282, 44120753, 44120754, 21090035, 21158944, 35130061, 36421291, 36787954, 36812530, 36883710, 36894458, 40142784, 40745353, 42480194, 42483138, 792484, 2070676, 2070686, 2070702, 2071140, 21089505, 35147990, 35149212, 36882733, 37592046, 40144020, 40144024, 40144035, 40144037, 40754973, 40755794, 41048760, 41267401, 42482744, 42925104, 43291091, 43532281, 40156382, 41174011	

Drug Classes	Include plus descendants	Exclude plus descendants
Systemic corticosteroids	36894465, 36894466, 40001300, 40085175, 40085179, 40085513, 40085516, 40085517, 40141448, 40830330, 40830543, 40861538, 40861617, 40861848, 40861854, 40892891, 40986496, 41017247, 41048603, 41080565, 41174426, 41236863, 41298307, 42629017, 43618522, 43733331, 43764799, 2069519, 35151839, 35161377, 35831814, 36277138, 36891530, 40018136, 40018148, 40018149, 40018160, 40018161, 40018167, 40018168, 40018860, 40018864, 40018865, 40019090, 40019099, 40019100, 40145461, 40862057, 40986723, 41080439, 41298715, 41298716, 42479030, 43133389, 43271284, 43697442, 44120815, 21104723, 21110192, 21149460, 35152433, 35604729, 36810746, 37003051, 40036255, 40049686, 40049691, 40049693, 40049698, 40049700, 40049728, 40052988, 40053001, 40097635, 40115558, 40831001, 40861708, 40862260, 40892978, 40893427, 40924493, 40924574, 40955710, 40986444, 41111782, 41112007, 41142946, 41143298, 41205490, 41205491, 41236653, 41236930, 41236997, 41267929, 42481321, 42482500, 42483100, 43213290, 43715288, 44042956, 44081562, 44094631, 44107536, 44187021, 41079961, 41079962, 21158588, 35606532, 40012593, 40060701, 40060705, 40060728, 40923904, 41111375, 42479078, 42480795, 42901434, 43697439, 44068805, 21089621, 21099519, 21099520, 40026665, 40026666, 40026668, 40831106, 44179592, 1719010, 1719021, 2055931, 35147323, 40010223, 40010224, 40022479, 40022480, 40027148, 40027149, 40027150, 40027151, 40027452, 40027453, 40027454, 40027455, 40027461, 40028260, 40028569, 40028598, 40028599, 40028601, 40028607, 40028865, 40028866, 40030154, 40160933, 40823867, 40830638, 40830658, 40830659, 40830660, 40861836, 40861855, 40861856, 40861857, 40861858, 40893020, 40893023, 40893042, 40893426, 40924090, 40924091, 40924102, 40924103, 40924182, 40955308, 40955309, 40955310, 40955331, 40955332, 40955398, 40986509, 41017529, 41017530, 41017544, 41017696, 41017899, 41048833, 41049172, 41049240, 41080245, 41080249, 41080264, 41080265, 41111559, 41111560, 41111561, 41111897, 41143081, 41143082, 41143086, 41143105, 41174078, 41174080, 41174083, 41174102,	

Drug Classes	Include plus descendants	Exclude plus descendants
	41205893, 41236558, 41236559, 41236579, 41236783, 41267495, 41267497, 41267514, 41298498, 41298520, 41298595, 42479771, 42479772, 43157462, 43180508, 43180854, 43202833, 43690608, 43781012, 43853864, 44025603, 44030023, 44042956, 44042957, 44120595, 44120597, 44158898, 35149489, 40013687, 40036261, 40066473, 40072752, 40073185, 40073190, 40073191, 40073197, 40073454, 40073458, 40073467, 40149642, 40171266, 40823867, 40823871, 40825736, 40830847, 40831053, 40861608, 40861791, 40861841, 40861857, 40861923, 40892759, 40892776, 40893002, 40893035, 40893385, 40893498, 40893499, 40923843, 40924167, 40924178, 40924286, 40955209, 40955250, 40955563, 40955667, 40955675, 40986252, 40986383, 40986507, 40986733, 40986947, 41017481, 41017529, 41017544, 41017801, 41018007, 41048618, 41048739, 41049165, 41049240, 41080242, 41080245, 41080264, 41080455, 41080456, 41080489, 41111346, 41111549, 41111718, 41111738, 41174314, 41174498, 41205402, 41205735, 41206037, 41236314, 41236784, 41236873, 41236907, 41267314, 41267407, 41267498, 41267512, 41267632, 41267870, 41298184, 41298208, 41298265, 41298519, 41298573, 41298965, 42482154, 42970587, 43168161, 43661632, 43805225, 44120678, 40073529, 40073531, 40073813, 40077886, 40077887, 40077888, 40143531, 40830453, 40892984, 40924346, 40924453, 40955250, 41049173, 41173847, 42482157, 42873418, 44029985, 40055571, 40055572, 40102083, 40955045, 40070931, 40070932, 40955071, 41267259, 40095885, 21031784, 40041462, 40041493, 41143003, 41236629, 41267406, 41267579, 40059478, 43148942, 1592256, 40054909	
Inhalant long acting B2 agonists (LABA)	1137529, 1196677, 19043191, 19097824, 40240664, 43532539, 45775116	2069155, 35132439, 35142595, 35155079, 35853184, 35853185, 35855413, 35870190, 40008351, 40008352, 40030511, 40030512, 40100370, 40100371, 42926217, 42927690, 42931195, 42931201, 42931239, 42931241, 42935429, 42935522, 42943288, 42956253, 42958521, 42963137, 42963186, 42966617, 42967026, 44042713

Drug Classes	Include plus descendants	Exclude plus descendants
Oral leukotriene Receptor antagonists (LTRA)	43009091, 1154161, 43009065, 1111706	35161116
Systemic theophylline	1237049	41048814, 41080205, 41205733
Inhalant long-acting muscarinic antagonists (LAMA)	42873639, 45775571, 1106776, 44785907	42963186, 42935429, 42935434, 42967026, 42967030, 1758690, 35200237, 35201370, 35605660, 36274577, 40046883, 40046884, 40047197, 40047199, 40224968, 40745498, 40745499, 40745500, 40745501, 40745502, 40745505, 42963137, 42963144
Systemic cromones	1114620, 19008867	35151945, 40071499, 40071501, 40924115, 40955339, 41205665, 41298258, 41298531, 43257911, 43279669, 43821122, 44164517

Drug Classes	Include plus descendants	Exclude plus descendants
Systemic antibiotics	792531, 901845, 902722, 904356, 915175, 915981, 920293, 923081, 925952, 948582, 956653, 986864, 990069, 997496, 997881, 1036425, 1036475, 1036487, 1361385, 1560047, 1592954, 1701651, 1702364, 1702559, 1702911, 1705674, 1707164, 1707687, 1707800, 1708100, 1708880, 1709170, 1712549, 1713332, 1713905, 1713930, 1714527, 1715117, 1716721, 1716903, 1717327, 1717963, 1721543, 1724666, 1724703, 1728416, 1729720, 1733765, 1734104, 1734205, 1736887, 1738366, 1738521, 1740546, 1741122, 1742253, 1742432, 1743222, 1746114, 1746940, 1747005, 1747032, 1748975, 1749008, 1749083, 1750500, 1759842, 1768849, 1769535, 1771162, 1773402, 1774470, 1774932, 1775741, 1776684, 1777254, 1777806, 1778162, 1778262, 1784749, 1786617, 1786621, 1786842, 1789276, 1789515, 1790024, 1790692, 1790868, 1796435, 1796458, 1797513, 1800835, 1836191, 1836241, 1836391, 1836430, 1836503, 1836948, 19000817, 19000818, 19000820, 19000821, 19001904, 19002077, 19003644, 19006043, 19007701, 19008870, 19009138, 19010400, 19010564, 19015123, 19015464, 19017585, 19018516, 19018742, 19023254, 19023508, 19024197, 19027679, 19028241, 19028286, 19028288, 19036545, 19040624, 19041153, 19047071, 19047240, 19047265, 19050750, 19051271, 19051345, 19052683, 19054936, 19063874, 19064329, 19069006, 19070174, 19070251, 19070680, 19072054, 19072122, 19072255, 19072857, 19078399, 19086759, 19086790, 19088223, 19088795, 19092353, 19095043, 19096054, 19100438, 19101402, 19102105, 19123240, 19123877, 19125201, 19126622, 19129642, 19136024, 19136044, 19136210, 19136423, 19136426, 19136429, 19136481, 19136493, 19137362, 35197853, 35197897, 35197938, 35197975, 35197989, 35198003, 35198093, 35198107, 35198137, 35198144, 35198145, 35198165, 35198192, 35200469, 35200881, 35200953, 35834909, 35884386, 36878831, 37496518, 37498010, 40166675, 40798700, 40798704, 40798709, 40798981, 40799027, 40799118, 40799120, 40799121, 40799124, 43008993, 43008994, 43009009, 43009011, 43009022, 43009030, 43009044,	702514, 782669, 1127224, 1127226, 1355743, 1356134, 1356252, 1356265, 1356342, 1356348, 1356350, 1356387, 1356388, 1356390, 1361355, 1592220, 1592227, 1594364, 1594376, 1594381, 1594394, 1594403, 1594495, 1594502, 1594661, 1594690, 1594693, 1831782, 1970313, 1971418, 2035392, 2047724, 2052920, 2052922, 2052955, 2059681, 2068131, 2074040, 2918158, 2934751, 21032191, 21032837, 21034617, 21062030, 21069852, 21070276, 21071756, 21072254, 21081480, 21081483, 21084208, 21091714, 21096152, 21099998, 21105903, 21111150, 21130349, 21132307, 21139721, 21140439, 21140538, 21145117, 21155060, 21159759, 21160318, 21160640, 21164972, 21168381, 35129269, 35129793, 35130946, 35133340, 35134453, 35136033, 35138368, 35141028, 35141912, 35142897, 35143240, 35144130, 35144660, 35146037, 35146548, 35147967, 35153174, 35154779, 35156452, 35156547, 35157195, 35158419, 35158846, 35158972, 35159437, 35159764, 35160132, 35201849, 35605255, 35770401, 35830217, 35830590, 35832008, 35851018, 35851383, 35851392, 35851400, 35851598, 35851732, 35852004, 35852136, 35852549, 35852869, 35852870, 35853726, 35853889, 35856292, 35856522, 35856524, 35857086, 35857832, 35857838, 35857844, 35857993, 35858117, 35858133, 35858134, 35858521, 35858522, 35858524, 35858630, 35858631, 35858962, 35859790, 35860600, 35860696, 35860698, 35860990, 35861002, 35861018, 35861664, 35861723, 35861725, 35861925, 35862078, 35862084, 35862169, 35862341, 35862351, 35862353, 35862688, 35862748, 35863069, 35872071, 35873672, 35873678, 35874205, 36118706, 36259244, 36261799, 36264349, 36266909, 36269500, 36274602, 36406497,

Drug Classes	Include plus descendants	Exclude plus descendants
	43009045, 43009067, 43009082, 43009083, 43009087, 43012398, 44012563, 45774861, 45775686, 45776147, 45892419, 45892599, 46221507, 46274210	36408024, 36408036, 36408764, 36408767, 36408768, 36409570, 36421232, 36888521, 37497505, 37499288, 40000267, 40001157, 40001285, 40001286, 40001295, 40001926, 40007220, 40007222, 40007237, 40008577, 40009804, 40009805, 40010078, 40013471, 40013952, 40013956, 40013957, 40013958, 40013960, 40013961, 40013962, 40013966, 40013972, 40013973, 40013982, 40013984, 40013990, 40013994, 40013996, 40014634, 40014637, 40014639, 40015664, 40015668, 40018152, 40018153, 40018154, 40018155, 40018156, 40020954, 40022926, 40022927, 40022928, 40022930, 40022931, 40022932, 40022933, 40022934, 40022935, 40022936, 40022937, 40022938, 40022939, 40022940, 40022941, 40022942, 40022943, 40022944, 40022945, 40023482, 40023487, 40023500, 40023504, 40023505, 40023878, 40025388, 40027153, 40027161, 40027162, 40027168, 40027170, 40027174, 40027175, 40027448, 40027449, 40027450, 40027456, 40027458, 40027636, 40028359, 40028361, 40028718, 40028720, 40030803, 40030804, 40030826, 40030831, 40030833, 40030884, 40030885, 40030886, 40030890, 40030894, 40030899, 40031315, 40036245, 40037356, 40037357, 40040110, 40040112, 40040113, 40040114, 40040115, 40041049, 40041050, 40041238, 40041241, 40041269, 40041274, 40041276, 40041279, 40041418, 40041911, 40041912, 40046035, 40046787, 40046788, 40046789, 40046790, 40046791, 40047938, 40052932, 40052947, 40052961, 40052963, 40052964, 40052965, 40052966, 40052967, 40052968, 40052969, 40052971, 40052972, 40052974, 40052975, 40052977, 40053580, 40053581, 40054813, 40057263, 40057265, 40057467, 40059318,

Drug Classes	Include plus descendants	Exclude plus descendants
		40059607, 40062637, 40062641, 40062646, 40062648, 40062649, 40063382, 40063556, 40064154, 40064525, 40064526, 40066583, 40066585, 40066772, 40066892, 40066893, 40067028, 40067031, 40067033, 40067405, 40069651, 40069655, 40069978, 40071896, 40071898, 40071899, 40071901, 40071902, 40071903, 40071904, 40071905, 40071906, 40071907, 40071908, 40071909, 40071910, 40072290, 40072291, 40072292, 40072301, 40072303, 40072305, 40072307, 40072308, 40072626, 40073113, 40073114, 40073115, 40081806, 40082165, 40082190, 40082191, 40087787, 40087790, 40088148, 40088149, 40088151, 40088728, 40088730, 40088738, 40093197, 40093198, 40095894, 40095895, 40101806, 40101854, 40101856, 40101857, 40105920, 40105923, 40105936, 40119085, 40123985, 40131262, 40131263, 40131789, 40131790, 40131791, 40131820, 40131827, 40131829, 40131831, 40133137, 40135906, 40136212, 40136419, 40139853, 40140235, 40144501, 40150582, 40151082, 40160496, 40170022, 40180925, 40224235, 40225755, 40235501, 40235511, 40237657, 40241740, 40721707, 40737589, 40752961, 40753319, 40754848, 40754915, 40755236, 40823553, 40824184, 40830335, 40830342, 40830430, 40830471, 40830574, 40830870, 40830871, 40830895, 40830896, 40831103, 40861595, 40861596, 40861622, 40861623, 40861624, 40861733, 40861837, 40861838, 40861880, 40861896, 40861940, 40861941, 40861942, 40861943, 40861944, 40862000, 40862094, 40862190, 40862308, 40892732, 40892823, 40893009, 40893086, 40893136, 40893137, 40893138, 40893141, 40893232, 40893250, 40893273, 40893274, 40893384, 40893386, 40923891,

Drug Classes	Include plus descendants	Exclude plus descendants
		40923892, 40923905, 40923946, 40923968, 40923969, 40924017, 40924059, 40924077, 40924174, 40924183, 40924225, 40924452, 40955003, 40955004, 40955083, 40955147, 40955185, 40955186, 40955411, 40955414, 40955415, 40955792, 40986220, 40986223, 40986283, 40986284, 40986285, 40986300, 40986301, 40986390, 40986405, 40986491, 40986578, 40986586, 40986587, 40986588, 40986752, 40986889, 40986923, 40986998, 41017237, 41017296, 41017318, 41017319, 41017414, 41017417, 41017489, 41017579, 41017627, 41017631, 41017632, 41017640, 41017720, 41017766, 41017789, 41017904, 41048539, 41048551, 41048552, 41048553, 41048701, 41048729, 41048730, 41048831, 41048883, 41048884, 41048918, 41048926, 41048927, 41048946, 41049021, 41049022, 41049034, 41049065, 41049155, 41049166, 41049167, 41079933, 41079934, 41079935, 41080028, 41080029, 41080047, 41080100, 41080123, 41080141, 41080154, 41080161, 41080164, 41080198, 41080200, 41080229, 41080247, 41080248, 41080303, 41080328, 41080334, 41080342, 41080343, 41080473, 41080587, 41080616, 41111338, 41111435, 41111460, 41111587, 41111752, 41111768, 41111889, 41142765, 41142774, 41142874, 41142987, 41143036, 41143065, 41143083, 41143088, 41143146, 41143171, 41143173, 41143179, 41143180, 41143181, 41143182, 41143350, 41143481, 41173786, 41173824, 41173853, 41173877, 41173888, 41173962, 41173980, 41173995, 41174008, 41174010, 41174081, 41174135, 41174177, 41174178, 41174272, 41174277, 41174329, 41174455, 41205371, 41205492, 41205632, 41205884, 41205895, 41205896, 41236280, 41236318, 41236340,

Drug Classes	Include plus descendants	Exclude plus descendants
		41236344, 41236359, 41236438, 41236463, 41236476, 41236492, 41236634, 41236640, 41236641, 41236666, 41236771, 41236880, 41267185, 41267266, 41267344, 41267345, 41267381, 41267385, 41267438, 41267494, 41267536, 41267591, 41267603, 41267731, 41267746, 41267869, 41267996, 41298215, 41298216, 41298226, 41298257, 41298373, 41298399, 41298404, 41298596, 41298736, 41298737, 41298857, 42479089, 42479696, 42479725, 42479727, 42480133, 42480780, 42481931, 42482512, 42483110, 42483137, 42613529, 42614500, 42620715, 42629035, 42873748, 42948109, 42961482, 42963090, 42963093, 42965658, 42970795, 43013733, 43023710, 43030076, 43135095, 43135467, 43146339, 43146353, 43157270, 43158691, 43173476, 43177386, 43177613, 43179753, 43180605, 43199938, 43200492, 43201503, 43201691, 43210737, 43214695, 43258666, 43266736, 43278414, 43283021, 43600599, 43603372, 43605428, 43606620, 43617892, 43622866, 43674454, 43678347, 43678432, 43695029, 43709206, 43709550, 43726548, 43727748, 43743995, 43744478, 43745005, 43761831, 43815878, 43816976, 43836922, 43853162, 43858131, 44029805, 44029898, 44030232, 44030233, 44030339, 44042662, 44042765, 44042892, 44042898, 44042948, 44043303, 44043415, 44043416, 44055876, 44055989, 44056269, 44056275, 44056388, 44056444, 44068862, 44068863, 44081628, 44094488, 44094575, 44094887, 44094935, 44094969, 44094970, 44095070, 44107434, 44107456, 44107535, 44107858, 44120279, 44120402, 44120448, 44120477, 44120495, 44120651, 44120903, 44121002, 44160698, 44160702, 44175740, 44175753, 44183238, 44183242,

Drug Classes	Include plus descendants	Exclude plus descendants
		44187011, 45774469, 45774589, 45892421, 45892681, 46221668
Systemic antivirals	32764, 32765, 739588, 792929, 793843, 908126, 981654, 1146410, 1703063, 1703069, 1703603, 1703687, 1704183, 1708748, 1710281, 1710612, 1711246, 1711523, 1712889, 1715472, 1717002, 1717704, 1724700, 1724827, 1724869, 1727223, 1729323, 1736829, 1736971, 1736999, 1738135, 1738170, 1745072, 1746244, 1747157, 1748921, 1756831, 1757803, 1758392, 1758536, 1762711, 1763339, 1769389, 1781406, 1787101, 1789428, 1799139, 19010924, 19078156, 19083285, 19101679, 19122130, 35198023, 35198210, 35200354, 35200446, 35201105, 35605546, 35606465, 35606467, 36042920, 37499271, 40167569, 40238770, 40238930, 40239330, 42544019, 42874212, 43009047, 43532424,	1356184, 2042290, 2935753, 21022861, 21102304, 35131215, 35153292, 35156005, 35157549, 35161740, 35829278, 35857252, 35858570, 35859531, 35859532, 35859533, 35859534, 35859544, 35859800, 35860190, 35862028, 35862196, 35862840, 36404954, 36881801, 36882754, 36891506, 40006507, 40006509, 40006520, 40006526, 40012442, 40012443, 40021923, 40022935, 40047166, 40048619, 40048641, 40048643, 40048645, 40048646, 40048647, 40079438, 40088497, 40088499, 40098632, 40100094, 40100095, 40147465, 40223217, 40830620, 40830621,

Drug Classes	Include plus descendants	Exclude plus descendants
	43560385, 44785086, 44785094, 45892552, 45892558, 46221696, 46233931	40861701, 40893266, 40923795, 40955222, 41017406, 41017631, 41205307, 42480751, 42482730, 42613396, 42706878, 42966785, 43147470, 43290988, 43714284
Systemic cyclosporine	19010482	35200336, 40028532, 40236657
Systemic methotrexate	1305058	
Biologics	1110942, 35606631, 35603983, 792993, 1593467	

This is a preliminary list of conceptcodes. Codes will be reviewed and might be amended following the execution of the “DrugExposureDiagnostics” R package developed for DARWIN EU.

APPENDIX I – TABLE 3: LIST WITH CONCEPT CODES FOR MEASUREMENTS

Measurements	Include plus descendants	Exclude plus descendants
Aspartate transaminase	3013721, 3042781, 3052577, 37392189, 37398463, 4197974, 37394375, 37208565, 37208512, 4263457, 44810795	
Alanine transaminase	3017537, 3006923, 3052018, 46236949, 37393142, 4190899, 44810789, 37208490, 44788835, 4146380, 37393531, 37208513	
Alkaline phosphatase	3005090, 3001110, 37208509, 37208510, 37393131, 3035995, 37398460, 4156813, 44810790, 4193028	
Blood eosinophils	3013115, 3006504, 3004123, 3015956, 3028615, 3009932, 3010457, 43055367, 43055372, 37393857, 37399255, 44805924, 4216098, 40484040, 37208633, 37208634	
BMI, weight, height	3038553, 4245997, 44783982, 1616652, 36304833, 44807883, 3036277, 607590, 3035463, 4177340, 3023540, 3015514, 3019171, 3030674, 3044852, 4030731, 4093975, 4268280, 3025315, 4099154, 46234683, 3026600, 4178502, 3013762, 3009617, 3015644, 3019336, 3005422, 3023166, 21492642, 4310154, 4175354, 37205098, 37206608, 40759189	
Bilirubin (total)	3006140, 3024128, 3024733, 3028833, 40757494, 46235782, 1175191, 1175183, 1616780, 37394117, 37208618, 37208619, 4041529, 4195338, 4118986, 4210860, 4230543, 37398233, 37399653, 37398424	
Bilirubin (direct)	3028638, 3019676, 3005772, 3027597, 3035521, 3044599, 3043347, 37394191, 37392379, 37208552, 37208553, 4195339, 4198887, 4216632, 44805650, 37398232, 37398235, 37398377	

APPENDIX I – TABLE 4: LIST WITH CONCEPT CODES FOR LIFESTYLE FACTORS

Conditions	Include plus descendants	Exclude plus descendants
Drug abuse	42529475, 4168205, 4239438, 4206984, 4219142, 3022196, 36031658, 36031249, 4017177, 4229859, 42529480, 4036792, 4038240, 4037138, 42539778, 1616455	
Alcohol abuse	4116983, 4053784, 45766930, 4080065, 36674487, 45772695, 44793164, 37206970, 4207141, 44792459, 3036878, 762596, 4145860, 4042872, 4027638, 44786671, 432456, 44786700, 40481082, 4038704, 3027199, 608490, 44812667	
Smoking (current or past)	44788975, 44788976, 762499, 3012697, 4052948, 600776, 44786669, 762498, 4131520, 37395605, 1616974, 42528924, 44804450, 4206526, 4203874, 4046886, 4141787, 44809281	

APPENDIX I – TABLE 5: CATEGORISATION INTO MODERATE AND SEVERE ASTHMA BASED ON ICS DOSING (BASED ON GINA GUIDELINES) [2]

Asthma Therapy	**Total Daily Dose (ug)**	
ICS	Medium	High
Beclomethasone dipropionate (non HFA)	>=500-1000	>1000
Beclomethasone dipropionate (HFA)	>=200 <=400	>400
Ciclesonide	>=160-320	>320
Triamcinolone acetonide	>=1000-2000	>2000
Flunisolide	>=1000-2000	>2000
Fluticasone furoate	>= 92 - <= 199	>199
Fluticasone propionate	>=250 - <=500	>500
Fluticasone propionate HFA	>=250 - <=500	>500
Budesonide	>=320 - <=800	>800
Mometasone furoate	>=200 - <=440	>440

Use of these daily dose cut-off points will be reviewed following the execution of the "DrugExposureDiagnostics" R package developed for DARWIN EU.

APPENDIX II – ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:

DARWIN EU - Background rates of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with severe asthma.

EU PAS Register® 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 - milestones
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[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 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8 – Research questions and objectives
	2.1.2 The objective(s) of the study?	☒	☐	☐	
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
	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? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1 and 9.7.5.1
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				9.2.1
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Table 7
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?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Appendix I – Table 1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. 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? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.2 and 9.3.3.1

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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
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? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4 and appendix
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4, 9.3.2 and appendix
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4, 9.3.3 and appendix
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4 and appendix
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4, 9.3.2 and appendix
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4 and appendix
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

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

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

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. 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? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

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

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 19th January 2023

Date of protocol amendment: 3rd September 2023

Signature: