PASS Protocol	
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Study number	H0005588
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TREATY: Tezepelumab Pregnancy Study

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

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PASS INFORMATION

Title	A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab
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Marketing authorisation holder(s)	ASTRAZENECA PHARMACEUTICALS LP, 1800 Concord Pike, Wilmington, Delaware 19803, United States of America.
Joint PASS	No
Research question and objectives	**Primary objectives** 1. To estimate the risk of **major congenital malformations (MCM)** in live and non-live offspring, and termination of pregnancy for foetal anomaly (TOPFA) among women with severe asthma who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with Standard of Care (SOC) for severe asthma) during **first** trimester of pregnancy 2. To estimate the relative risk of **MCM** in live and non-live offspring, and TOPFA among women with severe asthma exposed to tezepelumab during **first** trimester of pregnancy compared to women with severe asthma

	exposed to SOC for severe asthma and unexposed to tezepelumab during **first** trimester of pregnancy **<u>Secondary objectives</u>** 3. To estimate the risk of **foetal death** (a composite of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with SOC for severe asthma) during pregnancy, overall and by trimester of exposure 4. To estimate the risk of **minor congenital malformations (mCM)** in live births of women with severe asthma who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with SOC for severe asthma) during pregnancy, overall and by trimester of exposure 5. To estimate the risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy [TOP], and pre-eclampsia) in pregnancies among women with severe asthma who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with SOC for severe asthma) during pregnancy, overall and by trimester of exposure 6. To estimate the risk of **individual birth outcomes** (emergency caesarean section [EC-section], preterm birth [PTB], small for gestational age [SGA], and low birth weight [LBW]) in pregnancies among women with severe asthma who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with SOC for severe asthma) during pregnancy, overall and by trimester of exposure 7. To estimate the relative risk of **foetal death** (composite outcome of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC

	for severe asthma and unexposed to tezepelumab during pregnancy 8. To estimate the relative risk of **mCM** in live offspring of women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy 9. To estimate the relative risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy 10. To estimate the relative risk of **individual birth outcomes** (EC-section, PTB, SGA, and LBW) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy 11. To describe the **demographic and clinical characteristics** of pregnant women with severe asthma and their live births who were - Exposed to tezepelumab - Unexposed to tezepelumab (treated with SOC for severe asthma) during pregnancy, by study cohort overall, and by trimester of exposure for main study cohort (all pregnancies)

Country (-ies) of study	Denmark, France, Sweden, and United States of America
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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDA	Confidential Disclosure Agreement
CDR	Cause of Death Registry
CI	Confidence interval
CM	Congenital malformations
CPR	Central Person Register
CRO	Contract Research Organisation
DCIR	Données de Consommation Interrégimes
EC-section	Emergency caesarean section
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EoP	End of pregnancy
ERB	Ethics Review Boards
EU	European Union
FDA	US Food and Drug Administration
GINA	Global Initiative for Asthma
GPP	Good pharmacoepidemiology practice
GVP	Good pharmacovigilance practices
HAS	Haute Autorité de Santé
ICD	International Classification of Diseases
ICS	Inhaled corticosteroids
IRB	Institutional Review Board
IVF	In vitro fertilisation
LAMA	Long-acting muscarinic antagonist
LBW	Low birth weight
LMP	Last menstrual period
LTRA	Leukotriene receptor antagonist

Abbreviation or special term	Explanation
MAH	Marketing Authorization Holder
MBR	Medical Birth Registry
MCM	Major congenital malformations
mCM	Minor congenital malformations
NBHW	National Board of Health and Welfare
NHISR	National Health Interview Survey Registry
NPR	National Patient Register
OCS	Oral corticosteroids
PASS	Post-authorisation safety study
PMSI	Programme de médicalisation des systèmes d'information
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity scores
PTB	Preterm birth
QC	Quality Control
RLRR	Register of Laboratory Results for Research
RPS	Register of Pharmaceutical Sales
RR	Risk ratio
SABA	Short-acting β2-agonist
SAP	Statistical analysis plan
SGA	Small for gestational age
SMR	Danish Hospital Medication Register
SNDS	Système National des Données de Santé
SOC	Standard of Care
SPDR	Swedish Prescribed Drug Register
TOP	Termination of pregnancy
TOPFA	Termination of pregnancy for foetal anomaly
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

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		US Feasibility PM	
		Project Manager	
		Epidemiologist	

4. ABSTRACT

Title

A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with Severe Asthma Exposed to Tezepelumab

Protocol version 3.0, 31 October 2023, PPD *(IQVIA) and* PPD *(IQVIA)*

Rationale and background

Asthma is a common chronic condition in pregnancy often requiring medical interventions, with one-third of women with asthma experiencing deterioration of their asthma during pregnancy. In addition to pregnancy itself being a risk factor for asthma exacerbation and severity due to increased oxygen needs, factors such as excessive weight gain in the first trimester of pregnancy is a potential risk factor for exacerbating the disease during pregnancy.

Asthma management during pregnancy is laid out in the general guidelines for adolescent and adult patients and encourages close monitoring during pregnancy. The benefit of optimal asthma control and prevention of acute exacerbations during pregnancy outweighs the potential risk of specific asthma drugs and associated adverse effects of untreated asthma. It is well known that poorly controlled maternal asthma is a risk factor for adverse obstetric and offspring outcomes (e.g., pre-eclampsia, haemorrhage, unplanned caesarean delivery, low birth weight (LBW) and small for gestational age (SGA), among others).

Despite evidence of a generally favourable benefit-risk profile of asthma medications during pregnancy, there is still a knowledge gap on the specific safety of some asthma drugs in pregnancy, especially of biological therapies. Clinical trials of medicines in their development phases typically exclude or include only a small proportion of pregnant women, precluding the assessment of safety of treatment in this specific group before market authorisation. Thus, post-authorisation safety assessments are essential. Secondary use of data from sources such as claims databases and electronic health records can generate real-world evidence on the safety of asthma drugs in pregnancy in a cost-effective and timely manner.

As part of the original marketing authorisation application to the European Medicines Agency (EMA), AstraZeneca included a proposal within the European Union (EU) Risk Management Plan, to conduct a non-interventional multi-country post-authorisation safety study to characterise the use of tezepelumab in women with severe asthma during pregnancies. The study design and objectives describe pregnancy and birth outcomes of pregnant women with severe asthma who receive tezepelumab and compare these estimates to estimates from pregnant women exposed to Standard of Care (SOC) for severe asthma who did not receive tezepelumab during pregnancy.

Research question and objectives

The aim of this study is to describe and compare the potential risk and relative risk of congenital malformations (CM) and adverse pregnancy and birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other SOC treatments for severe asthma during pregnancy

Primary objectives

1. To estimate the risk of **major congenital malformations (MCM)** in live and non-live offspring, and termination of pregnancy for foetal anomaly (TOPFA) among women with severe asthma who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during **first** trimester of pregnancy
2. To estimate the relative risk of **MCM** in live and non-live offspring, and TOPFA among women with severe asthma exposed to tezepelumab during **first** trimester of pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during **first** trimester of pregnancy

Secondary objectives

3. To estimate the risk of **foetal death** (a composite of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
4. To estimate the risk of **minor congenital malformations (mCM)** in live births of women with severe asthma who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
5. To estimate the risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, termination of pregnancy [TOP], and pre-eclampsia) in pregnancies among women with severe asthma who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
6. To estimate the risk of **individual birth outcomes** (emergency caesarean section [EC-section], preterm birth [PTB], SGA, and LBW) in pregnancies among women with severe asthma who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure

7. To estimate the relative risk of **foetal death** (a composite outcome of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
8. To estimate the relative risk of **mCM** in live offspring of women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
9. To estimate the relative risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
10. To estimate the relative risk of **individual birth outcomes** (EC-section, PTB, SGA, and LBW) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
11. To describe the **demographic and clinical characteristics** of pregnant women with severe asthma and their live births who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

    during pregnancy, by study cohort overall, and by trimester of exposure for main cohort (all pregnancies)

Study design

This study is an observational cohort study utilising secondary data from multiple data sources from Denmark, France, Sweden, and the United States of America (USA). The study will describe and compare the following outcomes in pregnancies and offspring from women with severe asthma exposed to tezepelumab and women with severe asthma unexposed to tezepelumab, treated with SOC for severe asthma (with or without other biologics) during pregnancy: MCM and mCM, foetal death (composite of miscarriage, stillbirth, and ectopic pregnancy), individual adverse pregnancy outcomes (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia), and individual adverse birth outcomes (EC-section, PTB, SGA, and LBW). The unit of analysis is individual pregnancies in women with severe asthma (i.e., each woman may contribute multiple pregnancies to the study).

Population

The study period for analysis will be based on the date of market availability for tezepelumab and data lag in each data source at the end of follow-up. The start of the study period will be the market launch date of tezepelumab in each country, which at the time of protocol writing is expected as follows: Denmark (Q2 2023), France (Q3 2022), Sweden (Q2 2023), and USA

(Q1 2022). The end of the study period will depend on data lag in each data source but is planned for Q3-Q4 2031 for the European databases and Q3 2032 for the USA.

To address the research question, eligible cohorts will be identified through a nested selection process. The *source population* will be identified from the existing data sources and comprises women with asthma with at least one end of pregnancy (EoP) record during the study period. Inclusion and exclusion criteria common to pregnancies exposed and unexposed to tezepelumab will be applied to each pregnancy to create the *study population* consisting of pregnancies in women who received treatment for severe asthma during pregnancy, from which the exposed and unexposed cohorts will be identified.

Variables

Exposures

The exposures of interest are tezepelumab and SOC for severe asthma, obtained from existing databases. *In-utero* exposure during specific exposure assessment windows to tezepelumab (either as monotherapy or polytherapy added to SOC for severe asthma) will be compared to non-exposure to tezepelumab (pregnancies exposed to SOC for severe asthma). The exposure window begins at Last menstrual period (LMP) and ends at the end of first trimester for MCM outcomes, or EoP for all other outcomes. In addition, a wash-out period from 130 days prior to conception (LMP + 2 weeks) will be applied to minimise the risk of exposure misclassification. As pre-eclampsia will be assessed prior to EoP or postpartum, the exposure assessment window (for both tezepelumab exposed and unexposed) will be capped at pre-eclampsia record, and patients with a pre-eclampsia record prior to exposure to tezepelumab or SOC for severe asthma will be excluded.

Outcomes

The primary outcome of interest is MCM. MCMs among live and non-live offspring, and TOPFA will be classified according to the Description of the Congenital Anomaly Subgroups in the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) Guide 1.5, and coded using national extensions of the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD10), or adapted to the relevant coding system for each data source.

The secondary outcomes of interest are foetal death, mCM, individual adverse pregnancy outcomes, and individual birth outcomes.

Foetal death will be defined as a composite of at least one of the following pregnancy loss outcomes: miscarriage, stillbirth, or ectopic pregnancy. Miscarriage is defined as foetal loss before 22 weeks of gestation, stillbirth is defined as foetal death occurring at or after 22 weeks of gestation, and ectopic pregnancy is defined as a pregnancy outside the uterine cavity.

mCM among live offspring will be classified according to the Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5, and coded using national extensions of ICD10, or adapted to the relevant coding system for each data source.

The individual adverse pregnancy outcomes include ectopic pregnancy, miscarriage, stillbirth (please see definitions in the section above primary outcomes), TOP, and pre-eclampsia. TOP will include any reason for termination and if captured, TOPFA will be a subset of all TOP. Pre-eclampsia will be identified by ICD10 codes in maternal records from 20 weeks of gestation up to 4 weeks postpartum.

Individual birth outcomes include EC-section, PTB, SGA, and LBW. EC-section will include unplanned procedures either initiated prior to initiated labour or as a complication to ongoing labour. PTB is defined a live birth at less than 37 weeks of gestation (< 37 weeks), SGA is defined as a birth weight lower than the 10^{th} percentile of the distribution of birth weights among live births, by gestational age and sex, using national definitions for foetal weight and birthweight; and LBW is defined as weight at birth less than 2500 grams.

Patient and infant characteristics

Demographic characteristics include maternal age, maternal socioeconomic status, and maternal ethnicity. *Maternal lifestyle characteristics* is often captured at first antenatal visit during first trimester, and will include smoking status, alcohol abuse, substance abuse, maternal weight and height or body mass index (kg/m^2). *Maternal clinical characteristics* at LMP will include comorbid conditions, co-medications, selected autoimmune conditions, pre-pregnancy diabetes, pre-pregnancy hypertension. *Health Care Utilisation* in the last 12 months prior to LMP will be used as proxy of burden of maternal comorbidities and will consider: number of outpatients and primary care visits, use of emergency department, hospitalisations (number of days, number of hospitalisations), type of health care providers visited. *Obstetric history (prior to current pregnancy)* will include gestational diabetes, pre-eclampsia, spontaneous abortion, stillbirth, PTB, and SGA births. *Infant characteristics* at birth will include gender, gestational age, birth weight, Apgar score, and calendar year.

Data sources

Denmark

The National Registers consisting of a multitude of health databases and covering 100% of the country.

France

The French National Health Data System (SNDS) covers approximately 99% of the French population and includes demographic data and extensive data on health encounters including hospitalisations.

Sweden

The National Registers consisting of a multitude of health care databases and covering 100% of the country.

USA

Carelon is a large administrative healthcare database maintained by Carelon Research (previously Health Core) covering approximately 21 million actively enrolled members. It contains a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from one of the largest commercially insured populations in the USA.

Study size

Both sample size and power calculations were carried out for the primary outcome MCM at the meta-analysis level. The following assumptions were made in the sample size and power calculations: prevalence of 8% for MCM; uptake of 0.8 to 11.5% for tezepelumab depending on the year from market launch; non-inferiority margin of a risk ratio (RR) of 2.5; and exposed versus non-exposed patient allocation ratios of 1:2 and 1.3. The probability of observing at least one MCM outcome event during the study period was estimated for each data source to assess their capacity to contribute to the meta-analysis.. For all data sources the estimated probabilities were ≥ 74%, which was considered sufficient to include all data sources in study size calculations at the meta-analysis level.

Based on a matching ratio of 1:2 and 1:3; 190 and 169 tezepelumab exposed pregnancies, respectively, across the data sources would be required to achieve 80% power to rule out an RR of 2.5 or greater for the MCM outcome.

Additionally, the minimum detectable RR that could be ruled out with 80% and expected power to rule out a target RR of 2.5 was computed, given the expected number of 441 live births among women with severe asthma. The minimum detectable RR was at least 1.79 for MCMs under the assumed uptake scenario. The expected power to rule out an RR of 2.5 was ≥ 99% under the assumed uptake scenario.

As the exact uptake of tezepelumab among pregnant women with severe asthma is unknown at this time, these assumptions around tezepelumab uptake will be re-evaluated during the first interim report, and the study milestones will be adjusted as necessary to ensure a sufficient sample is obtained to address the research objectives.

Data analysis

The data analysis for each study objective will be performed separately for each data source.

Confounding will be accounted for separately in each data source using a multiple step adjustment methodology. First, the propensity scores (PS) will be computed for each separate study cohort. After PS computation, individuals will be stratified using a set of three criteria.

In the second part, PS adjustment (matching) will be performed within each of the strata. Exact matching variables will include mother's age, year of pregnancy and timing of the severe asthma treatments during pregnancy. The PS will be obtained using a logistic regression model or other appropriate method (e.g. gradient boosting machines) where the potential confounders will be included as covariates. The number of confounders included in the PS model will depend on available sample size, to avoid unreliable estimates. Additionally, comparative analysis using PS matching will be performed only if the PS model fit is considered appropriate and if the covariate balance in the adjusted cohorts is sufficient. Covariate balance will be assessed by examining the distribution of variables in the study sub-cohorts and estimating standardised differences for each variable between the study sub-cohorts.

Descriptive analyses will be performed in the study sub-cohorts exposed to tezepelumab and unexposed to tezepelumab to estimate the prevalence (i.e., risk), with associated 95% confidence intervals (CIs), of MCM (objective 1), foetal death (objective 3), mCM (objective 4), adverse pregnancy outcomes (objective 5), and adverse birth outcomes (objective 6). Analyses by trimester of exposure will be conducted for secondary objectives 3-6 in addition to the overall analysis. The measures of study outcomes will be estimated before and after application of confounder adjustment (exact matching and PS matching) to obtain crude and adjusted estimates, respectively. Descriptive analyses will also be conducted for study objective 11 to describe the demographic and clinical characteristics of pregnancies and infants in the study sub-cohorts exposed to tezepelumab and unexposed to tezepelumab. For the main study cohort, additional analysis by trimester of exposure will be conducted. For continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1^{st}) and upper (3^{rd}) quartiles, as well as 5^{th} and 95^{th} percentiles will be presented. For categorical variables, the numbers and percentages of observations for each of the categories and numbers and percentages of missing values will be presented in descriptive analyses.

For the comparison of the study sub-cohorts exposed to tezepelumab and unexposed to tezepelumab within the study cohorts, the association metrics of RRs will be estimated. Both crude and adjusted RRs, with associated 95% CIs, will be estimated for the study outcomes of MCM (objective 2), foetal death (objective 7), mCM (objective 8), adverse pregnancy outcomes (objective 9), adverse birth outcomes (objective 10). Crude and adjusted RRs will be estimated before and after PS adjustment (exact and PS matching), respectively. If covariate balance is not achieved through PS adjustment, additional adjustment by using these covariates in the outcome regression model will be considered. Additionally, any other potential confounders (or risk factors) that are not included into the PS model but are hypothesised to be associated with the study outcomes may be used as covariates for the statistical models. The RRs will be estimated if there is at least one outcome event observed per exposure group.

Data source level analyses' results will be combined in a meta-analysis. The meta-analysis for the primary objective will be performed using effect size estimates from all study countries for which RRs will be estimated. Prior to conducting the meta-analyses, heterogeneity across the study countries will be assessed. Results of the meta-analysis will be derived using fixed-effect or random-effects model. The choice of the primary meta-analysis approach will be based on the investigation of the effect heterogeneity between countries. Irrespective of the chosen primary meta-analytic approach, full results from both random-effects and fixed-effect models will be presented. Data source-specific results and the overall combined estimate will be presented in forest plots including effect size and 95% CI for each study country included in the analysis.

Milestones

A progress report is planned for May 2025 which is 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of the protocol which is currently assumed to be Q2 2024. The progress report will provide a status update of database applications and, if applicable, relevant amendments pertaining to database applications.

Two interim reports will be submitted 46 (March 2028) and 82 (March 2031) months after PRAC endorsement of the protocol, and the final study report is planned for March 2034.

The first interim report is planned to monitor the uptake of tezepelumab in the planned study populations, update sample size assumptions, and describe the study outcomes among individuals exposed to tezepelumab in the study populations, using all available data at the time of reporting. The second interim report will similarly provide monitoring of the tezepelumab uptake and describe the study outcomes among individuals exposed and unexposed to tezepelumab in the study populations to form a comparator cohort, as relevant to the descriptive primary and secondary objectives from all available data at the time of reporting. Neither of the interim reports will include analyses related to comparative analyses, meta-analyses, or sensitivity analyses.

The final study report will include all descriptive, comparative, sensitivity, and meta-analyses of all available data at the time of completion of the final study report.

5. AMENDMENTS AND UPDATES

Table 1 Substantial amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	*06 March 2023*	*NA*	*NA*	*NA*
2	*18 July 2023*	*Section 6, Table 2*	*Statistical Analysis Plan date and End of data collection date*	*Updated to include planned date of SAP and End of data collection to include preparation of the analytic dataset.*
2	*18 July 2023*	*Section 8*	*Objective 3-6 & 11 assessment by trimester of exposure*	*Secondary descriptive objectives to be assessed overall and by trimester of exposure.*
2	*18 July 2023*	*9.2.2.2*	*Exclusion criteria and rationale*	*Exclusion criteria has been updated following PRAC comments, and rationale for each criteria has been provided.*
2	*18 July 2023*	*9.2.2.3, throughout*	*Study population names*	*Study population names has defined in section 9.2.2.3 and updated throughout the protocol.*
3	*31 October 2023*	*9.2*	*Setting*	*Description of settings updated with selected data sources*
3	*31 October 2023*	*9.2.1*	*Description of study time period per data source*	*Study time period updated with selected data sources and respective relevant dates*
3	*31 October 2023*	*9.2.5*	*Description of study time frames*	*Description of pregnancy dates and definitions added to section 9.2.5. Description of index date (pregnancy date) updated.*
3	*31 October 2023*	*9.4*	*Data sources updated*	*Feasibility assessment has been completed and results incorporated in the protocol.*
3	*31 October 2023*	*9.3.2*	*Outcome definitions and data source-specific information*	*References to additional information available in Appendix C added throughout section.*
3	*31 October 2023*	*9.3.2.4*	*Adverse birth outcomes*	*Description of adverse birth outcomes updated with termination of pregnancy for foetal anomaly (TOPFA) definition.*
3	*31 October 2023*	*9.3.2.5*	*Individual birth outcomes*	*Distinction between emergency and planned C-section added. Clarification on gestational age and birth weight definitions added.*

Number	Date	Section of study protocol	Amendment or update	Reason
3	*31 October 2023*	*9.4.*	*Data sources*	*Section updated with selected data sources.*
3	*31 October 2023*	*9.4.*	*Study size*	*Sample size and power calculations updated with selected data sources.*
3	*31 October 2023*	*Appendix C*	*Appendix Tables with additional information on selected data sources*	*Additional information provided following PRAC assessment report on Protocol V2.0*

6. MILESTONES

A progress report is planned for approximately May 2025 which is 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of the protocol which is currently assumed to be Q2 2024. The progress report will provide a status update of database applications and, if applicable, relevant amendments pertaining to database applications. Database access may take between 7 to 18 months; therefore, the progress report may not include patient numbers from all data sources.

To monitor the use of tezepelumab among pregnant women, and inform the detection and evaluation of signals, two interim reports and a final report has been planned as detailed below. The two interim reports will be submitted 46 (March 2028) and 82 (March 2031) months after PRAC endorsement of the protocol. The long wait before data extraction is based on previous experience and expected uptake of tezepelumab, and deemed necessary to accrue exposed pregnancies. The first interim report (usage monitoring and initial signal detection) will contain descriptive analyses relevant to primary and secondary objectives, using all ***available data at the time of reporting***. The second interim report (usage monitoring and further signal detection) will inform the timing of the signal evaluation in the final study report by reporting updated descriptive analyses including an evaluation of the unexposed population to form a comparator cohort, as relevant to the primary and secondary objectives from all ***available data at the time of reporting***. Neither of the two interim reports will include analyses related to comparative analyses, sensitivity analyses, or meta-analyses.

The final study report is planned for March 2034. The ability to achieve this milestone (signal evaluation) will be reviewed at each interim report considering the observed uptake of tezepelumab among pregnant women with severe asthma. The assumptions regarding uptake, which were made to justify the required study period to accrue a sufficient sample size, will be evaluated in the interim reports, and the study period will be adjusted based on the sample size achieved. The study milestones are outlined in Table 2 below.

Table 2 Study milestones

Milestone	Planned date
Registration in the EU PAS register	11 May 2024 (1 month after endorsement by EMA)
Statistical Analysis Plan	30 September 2024
Study progress report 1	30 May 2025
Start of data collection	30 June 2027
End of data collection	31 March 2033
Interim report 1	31 March 2028
Interim report 2	31 March 2031
Final report of study results	31 March 2034

7. RATIONALE AND BACKGROUND

7.1 Disease Burden of Severe Asthma

Asthma is a common chronic condition caused by inflammation of airways and bronchial hyperresponsiveness leading to airflow obstruction and characteristic clinical symptoms including intermittent cough, wheezing, chest tightness, and shortness of breath (1).

Asthma intensity varies over time and treatment is based on control of symptoms and frequency of exacerbation, in addition to management and treatment of contributing comorbidities and trigger factors. Some asthma patients require high-intensity treatment and a subset of them experience symptoms or exacerbations despite treatment. Severe asthma is characterised by poor symptoms control and frequent disease exacerbations despite adherence to maximal optimised therapy and treatment of asthma's contributory factors, or worsening when high dose treatment is decreased (2).

Worldwide, the proportion of people diagnosed with asthma is estimated to be around 9.8% (3), with a global estimate of 262 million people being affected by asthma in 2019 (4). Among adults, a survey showed higher prevalence of asthma in females than in males (5). The prevalence of severe asthma ranges from 3% to 10% of adults with an asthma diagnosis and represents a high burden of asthma morbidity and mortality, and higher costs for health care systems (1).

7.2 Current Treatment Paradigm

Recent advances in evidence has highlighted the complex and heterogeneous mechanisms of asthma, considering molecular pathways and clinical presentation of the disease (6). The current treatment paradigm of asthma focuses on the clinical management of disease symptoms, clinical presentation, and the immune components of asthma (7).

The Global Initiative for Asthma (GINA) strategy guidelines recommend asthma therapy in progressive steps, according to severity and frequency of symptoms, with the lowest being for mild asthma and higher steps being for moderate to severe asthma (2). For severe asthma patients, a high-intensity therapy with medium to high dose maintenance inhaled corticosteroids (ICS) plus formoterol (a long-acting β2 agonist [LABA]) is recommended as the preferred baseline treatment. Several add-on therapies including long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), low dose azithromycin, low dose oral corticosteroids (OCS), LABA, if not used yet, may be considered. For patients experiencing symptoms or exacerbations despite high-intensity treatment, the preferred therapy consists of treatment with a high dose ICS concomitant with other controller options and add-on therapies with LAMA or with biologics (2,8,9).

Tezepelumab was recently launched as a first-in-class biologic add-on treatment for patients with severe asthma in the United States of America (USA) and has subsequently received regulatory approval in countries of the European Union (EU) (10). Tezepelumab is an

antibody that reduces airway inflammation and asthma symptoms by preventing the attachment of thymic stromal lymphopoietin (TSLP) to its receptor. Because of its action at the top of the inflammation cascade, tezepelumab is considered a promising alternative treatment to a broader population of patients with severe asthma, fulfilling a high unmet need in asthma control (11).

7.3 Severe Asthma Treatment in Pregnancy

Asthma is a relatively common chronic condition in pregnancy, with high prevalence of asthma exacerbation requiring medical interventions (12). For instance, it is expected that one-third of women with asthma experience deterioration of their asthma during pregnancy (13). In addition to pregnancy itself being a risk factor for asthma exacerbation due to increased oxygen needs, rapid weight gain in the first trimester of pregnancy is another risk factor for asthma exacerbation during pregnancy (14).

For pregnant women, asthma management follows the same guidelines as for overall adolescent and adult patients (2). The treatment of asthma during pregnancy is encouraged by current guidelines (2) since the benefit of optimal asthma control and prevention of acute exacerbations during pregnancy outweighs the potential risks of specific asthma drugs and potential adverse effects of untreated asthma (15). It is well known that poorly controlled maternal asthma is a risk factor for poor obstetric and offspring outcomes (e.g., pre-eclampsia, haemorrhage, unplanned caesarean delivery, low birth weight (LBW) and small for gestational age (SGA), among others) (15).

7.4 Knowledge Gaps

Although there is evidence that the benefits of asthma treatment during pregnancy in general outweigh the risks (16), further evidence is still needed on the safety of specific asthma drugs in pregnancy, especially that of biological therapies (16,17). Clinical trials of medicines in their development phase typically exclude or include only a small proportion of pregnant women, precluding the assessment of safety of treatment in this specific group before market authorisation (17). Thus, post-authorisation evidence generation is essential to inform treatment guidelines for women of reproductive age. Secondary use of data from sources such as claims databases and electronic health records can generate real-world evidence on the safety of asthma drugs in pregnancy in a cost-effective and timely manner.

7.5 Regulatory Commitment

As part of the original marketing authorisation application to the European Medicines Agency (EMA), AstraZeneca included a proposal within the EU Risk Management Plan, to conduct a non-interventional, multi-country post-authorisation safety study (PASS) to characterise the use of tezepelumab in women with severe asthma during pregnancy. The study design and objectives are described in this protocol. The study aims to describe pregnancy and offspring outcomes of women with severe asthma who received tezepelumab; and compare these estimates to pregnancies and offspring of women with severe asthma who received treatment

with Standard of Care (SOC) for severe asthma but did not receive tezepelumab during pregnancy.

7.6 Study Rationale and Main Aims

Considering the knowledge gaps and regulatory commitments, the main aims of this PASS are:

- To estimate the risk of adverse pregnancy and offspring outcomes in a population of women with severe asthma who received tezepelumab during pregnancy, and
- To compare the estimates obtained above to estimates from a comparator group of women with severe asthma unexposed to tezepelumab, who received SOC for severe asthma during pregnancy

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to describe and compare the potential risk and relative risk of congenital malformations (CM) and adverse pregnancy and birth outcomes in pregnancies and offspring of women who received tezepelumab for severe asthma during pregnancy and women who received other SOC treatments for severe asthma during pregnancy.

8.1 Objectives

Primary objectives

1. To estimate the risk of **major congenital malformations (MCM)** in live and non-live offspring, and termination of pregnancy for foetal anomaly (TOPFA) among women with severe asthma who were
   - Exposed to tezepelumab
   - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during **first** trimester of pregnancy
2. To estimate the relative risk of **MCM** in live and non-live offspring, and TOPFA among women with severe asthma exposed to tezepelumab during **first** trimester of pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during **first** trimester of pregnancy

Secondary objectives

3. To estimate the risk of **foetal death** (a composite of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma who were
   - Exposed to tezepelumab
   - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
4. To estimate the risk of **minor congenital malformations (mCM)** in live births of women with severe asthma who were

- Exposed to tezepelumab
- Unexposed to tezepelumab (treated with SOC for severe asthma)

during pregnancy, overall and by trimester of exposure

5. To estimate the risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia) in pregnancies among women with severe asthma who were
   - Exposed to tezepelumab
   - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
6. To estimate the risk of **individual birth outcomes** (emergency caesarean section [EC-section], preterm birth [PTB], SGA, LBW) in pregnancies among women with severe asthma who were
   - Exposed to tezepelumab
   - Unexposed to tezepelumab (treated with SOC for severe asthma)

   during pregnancy, overall and by trimester of exposure
7. To estimate the relative risk of **foetal death** (a composite outcome of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
8. To estimate the relative risk of **mCM** in live offspring of women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
9. To estimate the relative risk of **individual adverse pregnancy outcomes** (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
10. To estimate the relative risk of **individual birth outcomes** (EC-section, PTB, SGA, and LBW) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy
11. To describe the **demographic and clinical characteristics** of pregnant women with severe asthma and their live births who were
    - Exposed to tezepelumab
    - Unexposed to tezepelumab (treated with SOC for severe asthma)

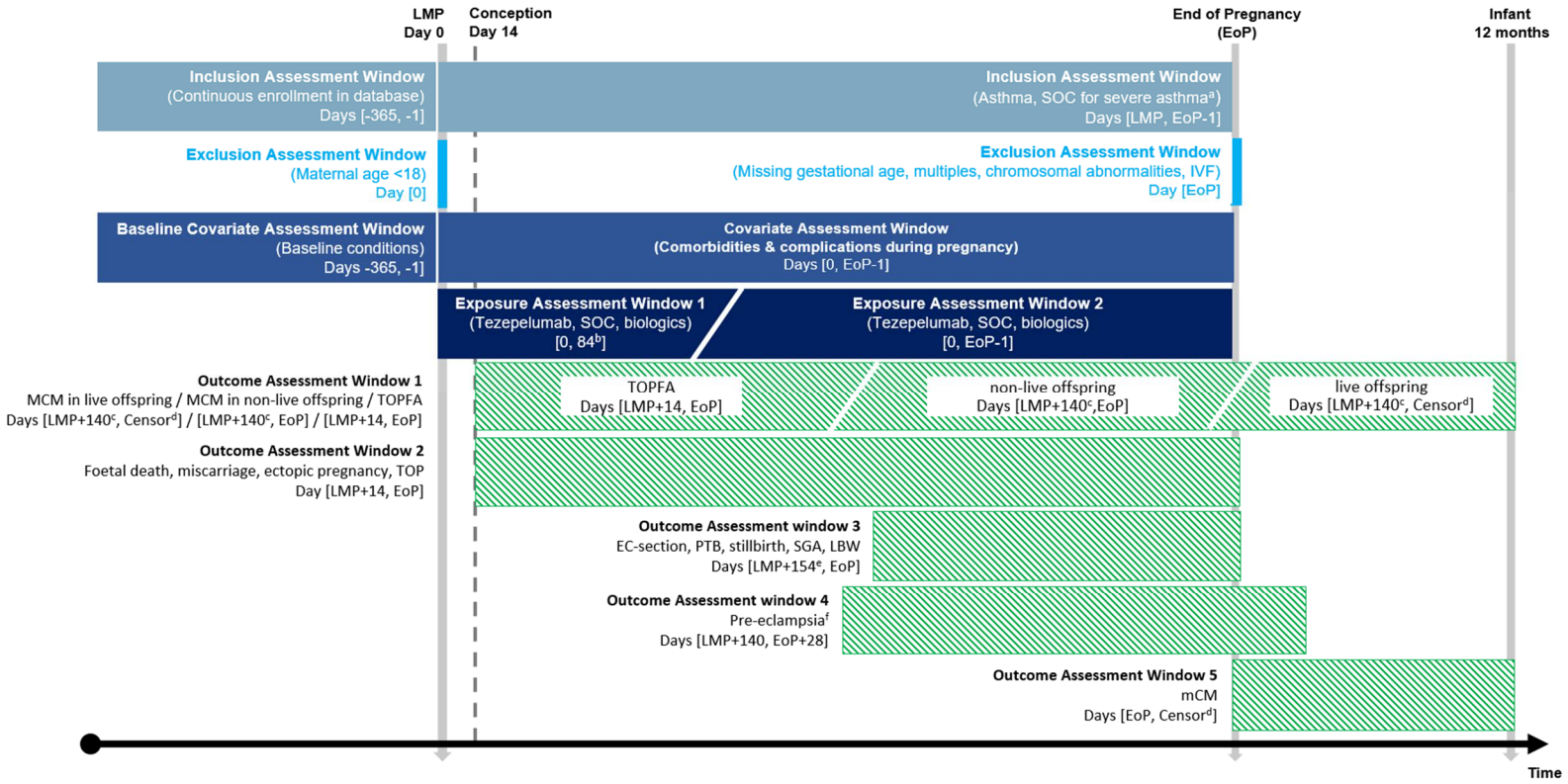
    during pregnancy, by study cohort (study cohorts are detailed in Table 5) overall, and by trimester of exposure for main cohort (all pregnancies)

9. RESEARCH METHODS

9.1 Study design

The study will apply a non-interventional, longitudinal, population-based, cohort design using secondary data derived from multiple data sources in Denmark, France, Sweden, and the USA. The study will describe and compare the following outcomes in pregnancies and offspring from women with severe asthma exposed to tezepelumab and women with severe asthma unexposed to tezepelumab treated with SOC for severe asthma (with or without other biologics) during pregnancy: MCM and mCM, foetal death (a composite of miscarriage, stillbirth, and ectopic pregnancy), individual adverse pregnancy outcomes (ectopic pregnancy, miscarriage, stillbirth, TOP, and pre-eclampsia), and individual adverse birth outcomes (EC-section, PTB, SGA, LBW). The unit of analysis is the pregnancy, i.e., each woman may contribute multiple pregnancies to the study.

Figure 1 Study design diagram



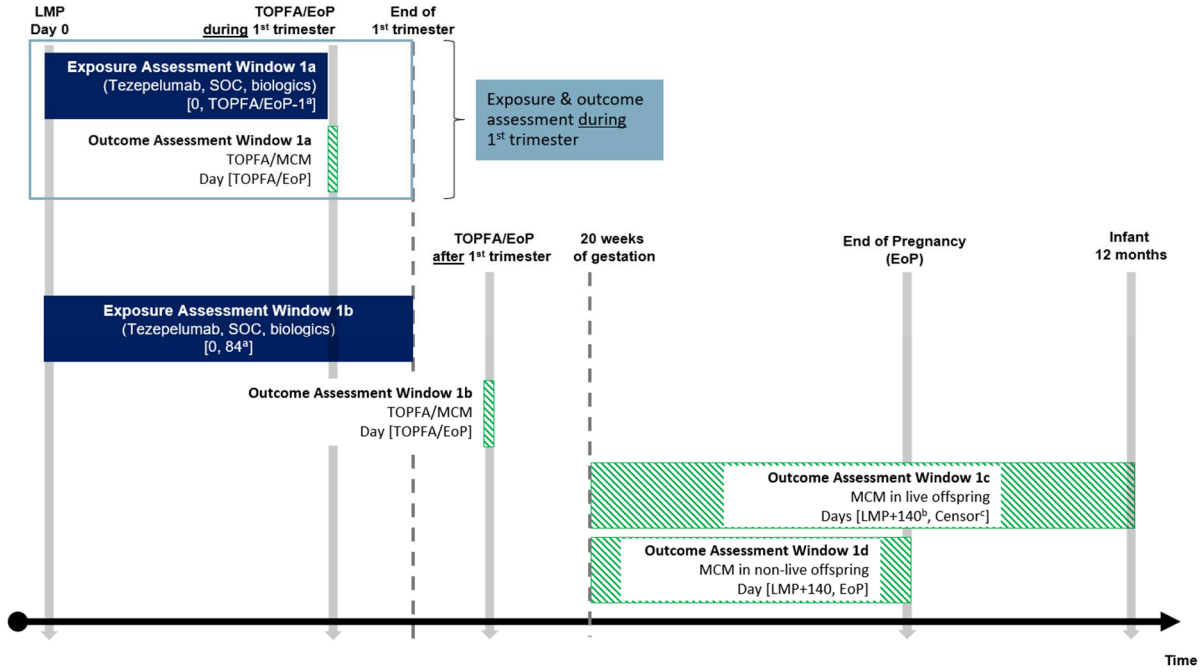
a) Asthma related record; SOC, Standard of Care
b) Exposure assessment during first trimester either defined as LMP (day 0) to day 84 or capped at EoP whichever occur first
c) MCM can be assessed from 20 weeks of gestation for live and non-life offspring, or at any time during pregnancy for TOPFA
d) Infants are followed until their first birthday or censoring whichever occur first
e) Birth outcomes will be assessed from 22 weeks of gestation (154 days)
f) Pre-eclampsia will be assessed from 20 weeks of gestation (140 days) until 4 weeks (28 days) after EoP

Abbreviations: LMP, Last Menstrual Period; EoP, End of Pregnancy; SOC, Standard of Care; IVF, In Vitro Fertilisation; MCM, Major Congenital Malformations; TOPFA, Termination of Pregnancy for Foetal Anomaly; TOP, Termination of Pregnancy; EC-section, Emergency Caesarean section; PTB, Preterm Birth; SGA, Small for Gestational Age; LBW, Low Birth Weight; mCM, minor Congenital Malformations

The exposure of interest is *in-utero* exposure to tezepelumab (see Section 9.3.1) for severe asthma during first trimester, or during pregnancy (depending on outcome of interest). Exposure will be assessed based on prescriptions or administrations between last menstrual period (LMP) and end of first trimester or end of pregnancy (EoP) (depending on the outcome) or occurrence of the outcome of interest (whichever occurs first) if an outcome occurs. For the primary outcome (MCM), exposure assessment window is from LMP to the end of first trimester while for all other outcomes, the exposure window ends at the EoP. A group of pregnant women treated with SOC for severe asthma during the same exposure window will be selected to ensure comparable disease severity in the exposed and unexposed cohorts. Women exposed to tezepelumab during a clearance period of 130 days prior to conception (2 weeks after LMP) and with no tezepelumab exposure during pregnancy (LMP to end of first trimester or EoP) will be excluded from the main analyses. A sensitivity analysis will include these pregnancies in the exposed cohort.

The primary outcome of interest is MCM. MCM will be assessed among TOPFA at any gestational age; among non-live offspring from 20 weeks of gestation to EoP; and among live offspring from 20 weeks of gestation up to the end of the first year of life.

Figure 2 Exposure and outcome diagram for MCM



a) Exposure assessment during first trimester either defined as LMP (0) to day 84 or TOPFA whichever occurs first
b) MCM can be assessed from 20 weeks of gestation (140 days) for live and non-live offspring (not including TOPFA)
c) Infants are followed until their first birthday or censoring whichever occurs first

Exposure window 1a will be capped at TOPFA for terminations before end of first trimester (LMP to day 84). Exposure window 1b will extend to the end of first trimester for TOPFA after end of first trimester, live and non-live offspring.
Abbreviations: LMP, Last Menstrual period; EoP, End of Pregnancy; SOC, Standard of Care; MCM, Major Congenital Malformations; TOPFA, Termination of Pregnancy for Foetal Anomaly; mCM, minor Congenital Malformations

The secondary outcomes of interest are foetal death, mCM, individual adverse pregnancy outcomes, and individual adverse birth outcomes. Foetal death will be assessed from maternal records at the EoP, mCM will be assessed among live births at birth or during the first year of life. Individual adverse pregnancy outcomes (other than pre-eclampsia) and individual adverse birth outcomes will be assessed from either maternal or infant records at birth. Pre-eclampsia will be assessed from 20 weeks of gestation or start of exposure (if initiated after 20 weeks of gestation) until 4 weeks postpartum. Pregnancies with a pre-eclampsia related record prior to treatment initiation will be excluded from the pre-eclampsia analysis. All outcomes will be investigated separately. Specific outcome assessment windows are illustrated in Figure 1.

A summary of the study outcome definitions and assessment windows is outlined in Table 3.

Table 3 Summary of study design

Topic	Outcome	Population	Figure 1		Outcome Assessment Window	
			Exposure Assessment Window	Outcome Assessment Window	Infant Records	Maternal Records
Major Congenital anomalies	MCM	Live births	1	1	from EoP to max 1y of age	during pregnancy from 20 weeks of gestation to EoP
		Non-live births			NA	
		TOPFA				EoP
Foetal death	Composite of miscarriage, ectopic pregnancy, and stillbirth	All pregnancies	2	2	NA	EoP
Minor Congenital anomalies	mCM	Live births	2	5	from EoP to max 1y of age	EoP
Adverse pregnancy outcomes	Ectopic pregnancy	All pregnancies	2	2	NA	EoP
	Miscarriage		2	2		
	Termination of pregnancy		2	2		
	Stillbirth	All pregnancies past 22 weeks of gestation	2	3	NA	EoP
	Pre-eclampsia	All pregnancies past 20 weeks of gestation	2*	4	NA	from 20 weeks of gestation until 4 weeks postpartum
Adverse birth outcomes	Emergency caesarean section	All pregnancies past 22 weeks of gestation	2	3	NA	EoP
	Preterm birth	Live births	2**	3	EoP	EoP
	Small for gestational age		2	3		NA
	Low birth weight		2	3		

Exposure assessment window 1 is considered from LMP to the end of first trimester.
Exposure assessment window 2 is considered from LMP to the end of pregnancy.
*For pre-eclampsia, exposure will be censored at the first record of pre-eclampsia
**For PTB, exposure will be censored at 37 weeks of gestation after which, no-one is at risk of the outcome
Outcome assessment window 1 is considered from LMP to EoP for TOPFA, LMP+140 days to EoP for non-live births, and from LMP+140 days to first year of life for livebirths.
Outcome assessment window 2 is considered from LMP to EoP. Outcome assessment window 3 is considered from LMP+154 days to EoP. Outcome assessment window 4 is considered from LMP+140 days to EoP+28 days. Outcome assessment window 5 is considered from EoP to first year of life for livebirths
Abbreviations: EoP, End of Pregnancy; Max, Maximum; 1 y, 1 year of age; MCM, Major Congenital malformations; mCM, Minor Congenital Malformations; NA, Not applicable; TOPFA, Termination of Pregnancy for Foetal Anomaly

9.2 Setting

A total of four large longitudinal patient-level data sources have been selected for this study, representing four countries: Denmark, France, Sweden, and USA.

The included data sources are:

1. Danish National Health and Socioeconomic Registries (Denmark)
2. French National Health Data System (SNDS) (France)
3. Swedish National Health Registries (Sweden)
4. Carelon (USA)

9.2.1 Study time period

The **start of the study period** is the market launch date of tezepelumab in each country (Table 4). There may be a need for patient data before the market launch date of tezepelumab to fulfil the requirement of at least 12 months look-back period before LMP for the assessment of potential confounders and risk factors (see also Figure 1).

The **end of the study period** is defined as the last possible day of complete follow-up for all included pregnancies. This will likely differ between countries as it depends on the length of data lag in each data source at the time when the last data extraction is performed (Table 4).

Table 4 Relevant dates of the study by country

Country	**Start of study period**[1] Tezepelumab market launch date	**End of study period**[2] Latest inclusion date
Denmark	Q2 2023	30 November 2031
Sweden	Q2 2023	31 November 2031
France	Q3 2022	31 December 2031
USA	Q1 2022	30 September 2032

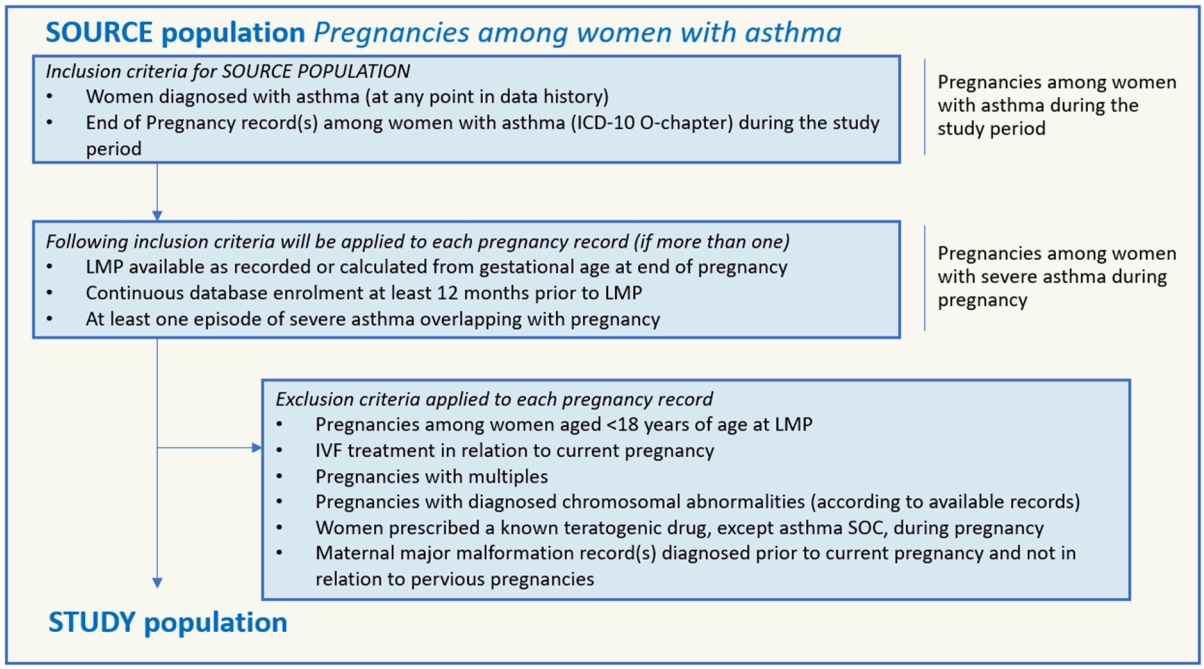
[1] EMA approval 19th September 2022 and US Food and Drug Administration (FDA) approval 17th Dec 2021. Market launch dates are country-specific. Timelines for study period, by database, are subject to change based on tezepelumab data start dates and/or data lag timeline changes during the course of the study
[2] Calculated considering the final study report date and assuming 3 months for data analysis, one year for data extraction and the following data lag times: Denmark – 13 months, Sweden – 13 months, France – 12 months, and USA – 3 months. In addition, for MCM and mCM follow-up will be required until 1 year after EoP. All other outcomes can be assessed at EoP and require no infant follow-up.
[3] Pregnancies are included at EoP event. Follow-up after EoP is only considered for CM outcomes
[4 4] Compassionate use programme began 24 August 2022

9.2.2 Study population

To address the research questions, eligible women and their pregnancies will be identified through a nested selection process (Figure 3). The *source population* comprises of women with asthma and at least one pregnancy record during the study period. Pregnancies are identified using maternal medical records related to pregnancy, including pregnancy loss, antenatal visits, deliveries and other EoP events. Inclusion and exclusion criteria will be

applied to each pregnancy to create the *study population* consisting of pregnancies in women with severe asthma during pregnancy, from which the exposed and unexposed cohorts will be identified.

Figure 3 Overview of selection of the population



Abbreviations: ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th edition; LMP, Last menstrual Period; SOC, Standard of Care; IVF, In Vitro Fertilisation

9.2.2.1 Inclusion criteria

Women will be eligible for inclusion in the source population if they fulfil ALL of the inclusion criteria listed below:

- Women diagnosed with asthma (International Statistical Classification of Diseases and Related Health Problems, 10th edition [ICD10] code J45.x or J46.x)
- Women with at least one EoP record (see code list in Appendix A, Appendix Table 10) during the study period

Inclusion criteria will be applied for *each pregnancy* identified among women identified in above steps. Pregnancies will be eligible for inclusion in the study population if meeting ALL of the *inclusion criteria* listed below:

- LMP available, either as recorded or calculated based on gestational age at pregnancy record (typically at EoP)
- Continuous database enrolment[1] at least 12 months prior to LMP

[1] Continuous enrolment will be defined in the SAP

- At least one event of severe asthma overlapping with pregnancy (based on treatment algorithm for asthma severity as specified in GINA guidelines, see Section 9.2.3)

9.2.2.2 Exclusion criteria

Pregnancies meeting ANY of the *exclusion criteria* listed below will be excluded:

- Pregnancies with in vitro fertilisation (IVF) treatment in relation to current pregnancy
- Pregnancies with multiples
- Pregnancies with diagnosed foetal/infant chromosomal abnormalities (according to available records)
- Pregnancies among women prescribed a known teratogenic drug, except asthma SOC during pregnancy (including but not limited to warfarin, angiotensin converting enzyme inhibitors, antineoplastic agents, isotretinoin, misoprostol, or thalidomide)
- Maternal major malformation record(s) as diagnosed prior to current pregnancy and not in relation to previous pregnancies

Rationale for exclusion criteria:

- Pregnancies following IVF will be excluded to ensure maternal risk factors at baseline are available and relevant to the current pregnancy and not an egg donor. In addition to this, a higher incidence of adverse pregnancy and birth outcomes have been reported for IVF pregnancies compared to natural conception (18,19). Pregnancies following non-IVF assisted reproduction treatments will not be excluded.
- As pregnancy with multiples is associated with an increased risk of many of the adverse pregnancy outcomes of interest (20), and the distribution of exposure between multiple foetuses is impossible to establish, pregnancies with multiples will be excluded.
- Chromosomal abnormalities[2] will be excluded as they are often associated with advanced maternal age, a family history of genetic abnormalities, or a chromosomal abnormality in one of the parents.
- As teratogenic drug exposure is associated with increased adverse pregnancy outcomes, pregnancies exposed to teratogens will be excluded. As we cannot rule out a heritable component for maternal CMs, pregnancies among women with a history of CMs will be excluded.

9.2.2.3 Additional specification of inclusion and exclusion criteria by objective

Objective-specific cohorts and sub-cohorts are outlined in Table 5 below. Cohort 1 (primary cohort) consists of pregnancies ending in TOPFA, live birth, or non-live birth, and sub-cohort 1a consists of live births only. Cohort 2 (main cohort) consists of all pregnancies regardless of outcome of pregnancy. Cohort 2 is further split into two separate sub-cohorts (Cohort 2a and 2b) restricted to pregnancies of at least 20 weeks and 22 weeks gestation, respectively.

[2] Identified with the respective ICD10 codes Q90-Q99, to be further detailed in the SAP.

Table 5 Cohorts and sub-cohorts by objective

Objective	Main Features	Input Cohort/ Population	Additional Specification of Criteria to be Applied to The Cohort/ Population
Objective 1&2	MCM	Cohort 1 (primary cohort): Among live births, TOPFA (at any gestational age), and stillbirths. Exposed/ unexposed during **first trimester**	INCLUSION: • All pregnancies ending in TOPFA, or stillbirth, regardless of mother-baby linkage within the study period, OR • Pregnancies with mother-baby linkage within the study time period
Objective 11	Describe cohort demographics and clinical characteristics.		
Objective 3	Foetal death (composite), overall and by trimester of exposure.	Cohort 2 (main cohort): Among all pregnancies. Exposed/ unexposed during **pregnancy**	INCLUSION: • All pregnancies regardless of outcome (live birth, termination of pregnancy, ectopic pregnancy, miscarriage, and stillbirth) within the study period. No mother-baby linkage required.
Objective 7	Foetal death (composite).		
Objective 5	Individual adverse pregnancy outcomes (ectopic pregnancy, miscarriage, TOP), overall and by trimester of exposure.		
Objective 9	Individual adverse pregnancy outcomes (ectopic pregnancy, miscarriage, TOP).		
Objective 11	Describe cohort demographics and clinical characteristics, overall and by trimester of exposure		
Objective 5	Individual adverse pregnancy outcomes (stillbirth), overall and by trimester of exposure	Sub-cohort 2a: Among all pregnancies with a gestational age ≥ 22 weeks. Exposed/ unexposed during **pregnancy**	INCLUSION: • All pregnancies with a gestational age ≥ 22 weeks regardless of outcome (live birth, termination of pregnancy, and stillbirth) within the study period. No mother-baby linkage required.
Objective 9	Individual adverse pregnancy outcomes (stillbirth)		
Objective 6	Individual adverse birth outcomes (EC-section, PTB), overall and by trimester of exposure		
Objective 10	Individual adverse birth outcomes (EC-section, PTB)		

Objective	Main Features	Input Cohort/ Population	Additional Specification of Criteria to be Applied to The Cohort/ Population
Objective 5	Individual adverse pregnancy outcomes (pre-eclampsia), overall and by trimester of exposure	Sub-cohort 2b: Among all pregnancies with a gestational age ≥ 20 weeks. Exposed/ unexposed during **pregnancy**	INCLUSION: • All pregnancies with a gestational age ≥ 20 weeks regardless of outcome within the study period. No mother-baby linkage required. EXCLUSION: • All pregnancies with a pre-eclampsia record (during current pregnancy) before initiation of exposure of interest.
Objective 9	Individual adverse pregnancy outcomes (pre-eclampsia)		
Objective 4	mCM, overall and by trimester of exposure	Sub-cohort 1a: Among live offspring. Exposed/ unexposed during **pregnancy**	INCLUSION: • Pregnancies ending in live birth • Pregnancies with mother-baby linkage within the study time period
Objective 8	mCM		
Objective 6	Individual adverse birth outcomes (SGA, LBW), overall and by trimester of exposure		
Objective 10	Individual adverse birth outcomes (SGA, LBW)		
Objective 11	Describe cohort demographic and clinical characteristics		

Abbreviations: MCM, Major Congenital Malformations; mCM, Minor Congenital Malformations; LBW, Low Birth Weight; PTB, Preterm Birth; SGA, Small For Gestational Age; TOP, Termination of Pregnancy; TOPFA, Termination Of Pregnancy for Foetal Anomaly

9.2.3 Severe asthma

Severe asthma is defined as asthma that is uncontrolled despite high-intensity treatment including high dose ICS, plus a second non-biologic controller or low dose OCS at least 50% of the past year (21). Figure 4 outlines the identification of patients with severe asthma. Treatments and dose are outlined in Section 9.3.1.2, Table 8, and Table 10. The study population will consist of pregnant women with severe asthma as defined by the GINA guidelines and the ERS/ATS guidelines for severe asthma (21).

Figure 4 Identification of patients with severe asthma among adult asthmatic patients receiving high-intensity treatment

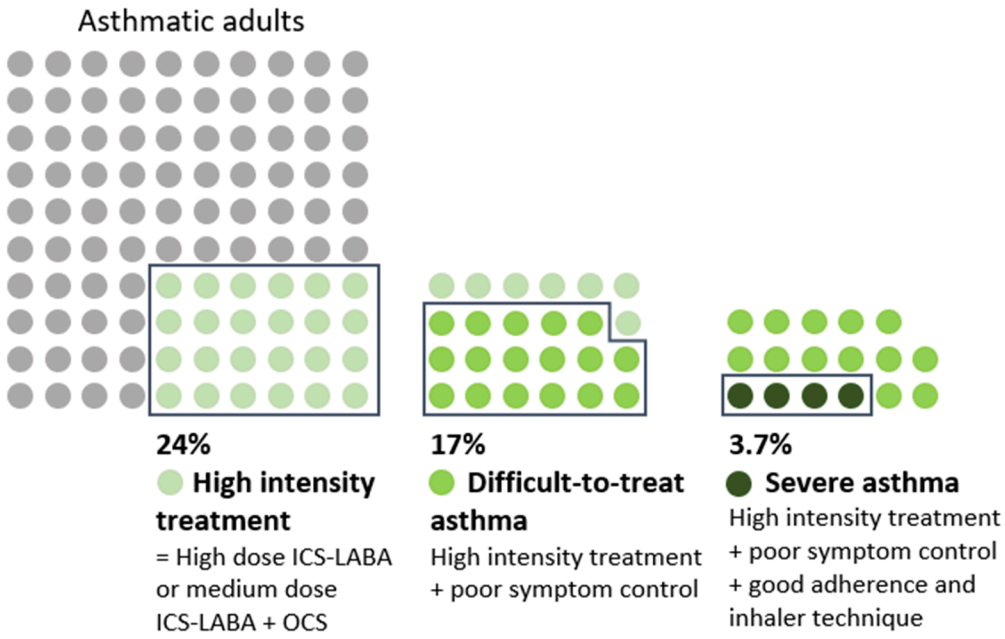


Figure from GINA Main report 2022 (22)

Abbreviations: ICS-LABA, Inhaled Corticosteroid- Long-acting β2-agonist; OCS, Oral Corticosteroid

Asthma control is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. Uncontrolled asthma is defined by the presence of any of four criteria (21), of which two can be assessed in this study: 1) poor symptom control (not available in data), 2) frequent severe exacerbations defined as two or more bursts of high dose OCS prescriptions (≥ 3 days each) in the past year, 3) serious exacerbations defined as at least one hospitalisation for asthma, Intensive Care Unit (ICU) stay or mechanical ventilation in the past year, and 4) airflow limitation (not available in data).

Based on the above definition, in this study, severe asthma will be based on exposure to high-intensity treatment (defined in Section 9.3.1) during the exposure assessment window and level of control defined by number of exacerbations during the past 12 months (proxied either by two or more burst of high dose OCS prescriptions or hospitalisation for asthma), or low dose OCS > 50% of the past 12 months or over-use of Short-acting β2-agonist (SABA) defined as

≥ 3 canisters in the past 12 months. Treatment definitions are further detailed in Section 9.3.1. Women exposed to biologics for severe asthma alone or in combination with other asthma treatments will also be considered to have severe asthma.

9.2.4 Exposed and unexposed cohorts

Each study cohort and sub-cohort will be split into exposed and unexposed cohorts (exposure cohorts). Tezepelumab exposure is defined in Section 9.3.1.1 and will include pregnant women with at least one tezepelumab prescription or administration during the exposure assessment window of interest (objective-specific). Pregnant women exposed to tezepelumab prior to LMP during a clearance period of 130 days will be excluded from the main analyses. In a sensitivity analysis, the exposed cohort will include pregnant women with any tezepelumab exposure during either the clearance period or pregnancy.

The unexposed cohorts will consist of pregnant women exposed to SOC for severe asthma during pregnancy, with no tezepelumab prescription or administration during the exposure assessment window. Women exposed to tezepelumab during the clearance period prior to LMP (130 days prior to conception), will be excluded from the unexposed cohorts.

9.2.5 Study time frames and follow-up

9.2.5.1 Pregnancy dates

Pregnancies will be identified by an EoP event as detailed in Table 6.

Definition of EoP, completeness and validity (if available) for live births, still births, terminations, TOFPA, miscarriages and ectopic pregnancy for each data source is detailed in Appendix C, Appendix Table 3.

Table 6 Pregnancy Dates and Definitions

Time points	Description	Method of identification
Study entry		
EoP	Event defining end of pregnancy (EoP)	Identified by diagnosis of outcome of pregnancy and categorised as • Live birth delivery • Still birth delivery • Miscarriage • Termination • Ectopic pregnancy
Pregnancy time points (relative to Study entry)		
LMP	Index date defined as the start of pregnancy	Calculated or recorded, as in below prioritised order • Ultrasound specified start of pregnancy (estimated gestational age at scan subtracted from date of scan) • Date of last menstrual period (LMP) first day

		• Date of end of pregnancy minus gestational age as recorded • Date of first EMR record minus gestational age (If gestational age at antenatal contact is recorded) • Estimated date of delivery minus 280 days • Country and data source-specific algorithms (see below)
Trim1	1st trimester boundary	Last day of 1st trimester calculated from LMP If EoP occurs before Trim1, the trimester will be capped at the last day of pregnancy. First trimester is defined as the first 12 weeks (0 weeks+0 days [0w+0d] to 11w+6d since LMP) reflecting the duration of the organogenesis (week 2 to 12). Day 84 is the last day of first trimester
Trim2	2nd trimester boundary	Last day of 2nd trimester is 27w+6d since LMP: Day 195 is the last day of second trimester
GA20	20 weeks of gestation	Follow-up starts at 20 weeks of gestation (20w+0d) for outcomes like delivery (live and non-live birth [USA]), pre-eclampsia, MCM
GA22	22 weeks of gestation	Follow-up starts at 22 weeks of gestation (22w+0d) for outcomes like delivery (live and non-live birth [Europe])

Abbreviations: EoP, End of pregnancy; LMP, Last menstrual period (equal to start of pregnancy); EMR, electronic medical record; Trim1, end of first trimester; Trim2, end of second trimester; GA20, 20 weeks of gestation; GA22, 22 weeks of gestation

Index date – Start of pregnancy

The index date will be defined by the start of pregnancy or the first date of the last menstrual period (LMP) either as recorded or calculated based on gestational age at pregnancy-related record, or as estimated by deterministic algorithms for each data source. The selected data sources all have high completeness and validity of gestational age and estimated LMP, as further detailed in Appendix C, Appendix Table 4.

Follow-up time

As pregnancies are identified by EoP events, no pregnancies will be censored during pregnancy. Pre-eclampsia will be assessed from 20 weeks of gestation until the first of the following: four weeks postpartum, death, emigration (where available), loss to follow-up (disenrollment/de-registering), or end of the study period.

For outcomes related to MCM and mCM, live births will be followed until the first of following: offspring reaching the age of 1 year, death, emigration (where available), loss to follow-up (disenrollment/de-registering), or end of the study period. All other outcomes will be assessed at EoP and no follow-up will be required.

To ensure exposure assessment precedes outcome follow-up, the any exposure after the specific outcome of interest will be ignored.

Outcome assessment windows are illustrated in Figure 1 and Figure 2.

Pre-index period

Eligible pregnant women will be required to have at least 12 months of data before LMP, and all covariates will be assessed during this period.

Trimester definitions

Trimester definitions are based on number of days since LMP as defined by the UK National Health Services definition and recognised by the IMI-ConcePTION initiative (23,24). First trimester is defined as days from LMP to day 84 (12 weeks), second trimester from Day 85 to Day 175 (13 weeks), and third trimester from day 176 until EoP. Each trimester is capped at the EoP if the pregnancy ends before start of next trimester.

Trimester subgroups (descriptive objectives) will be based on exposure status (as described in Section 9.3.1) during each trimester. The classification is not mutually exclusive, and pregnancies exposed throughout pregnancy will be assigned as exposed (or unexposed) of each trimester during which they are still pregnant.

9.2.6 Overview of the mother-baby linkage

The mother-baby linkage is mentioned among the inclusion criteria for some of the sub-cohorts, such as those for evaluating CM (major and minor, separately) and birth outcomes (Table 5). As illustrated in Table 7, different time frames and outcomes of interest for mother and offspring are specified.

Table 7 Overview of the mother-baby linkage requirement by outcome

Topic	Outcome	Population	Mother-baby linkage required
Congenital anomalies	MCM composite	Live offspring	yes[1]
		Non-live offspring	no
		TOPFA	no
	mCM composite	Live offspring	yes
Adverse pregnancy outcomes	Foetal death (composite of miscarriage, ectopic pregnancy, and stillbirth) *OR* Specific (ectopic pregnancy, miscarriage, TOP, stillbirth, pre-eclampsia)	All pregnancies[2]	no
Adverse birth outcomes	Specific (SGA, LBW)	Live offspring	yes
	PTB	All pregnancies past 22 weeks of gestation	no
	EC-section	All pregnancies past 22 weeks of gestation	no

[1] Some data sources may not provide mother-baby linkage, but MCM can be identified in maternal records. To be updated to data source-specific approach in SAP.
[2] Requirements for gestational age per outcome is detailed in Table 3
Abbreviations: EC-section, Emergency Caesarean Section, MCM, Major Congenital Malformations; mCM, Minor Congenital Malformations; SGA, Small for Gestational Age; PTB, Preterm Birth; TOP, Termination of Pregnancy; TOPFA, Termination of Pregnancy for Foetal Anomaly.

9.3 Variables

Variables used in this study are subdivided into exposure of interest (Section 9.3.1), outcomes of interest (Section 9.3.2), and participants characteristics and potential confounding variables and risk factors (Section 9.3.3).

In this protocol, ICD10 will be used as the coding system for definition of the outcome variables, other diagnoses, and procedures. International non-proprietary names are used as nomenclature for prescription drugs. World Health Organisation's (WHO) Anatomical Therapeutic Chemical (ATC) classification system will be used for all prescription drugs in this protocol. The ICD10 and ATC codes used in this protocol for variable definitions will be amended to the relevant coding systems as appropriate for the respective data sources (for example, national extensions to ICD10 to identify CM) and will be provided in the statistical analysis plan (SAP).

Appendix A provides an exemplar list of codes for exposure, outcome, and other variables for which either ATC codes and/or ICD10 codes are used. List of codes will be finalised in the SAP.

9.3.1 Exposure

The exposure of interest is tezepelumab, for the treatment of severe asthma. Exposure to tezepelumab and other SOC drugs for severe asthma (see Table 8 to Table 10) will be ascertained from records of outpatient visits, procedures, prescriptions, prescriptions dispensed at community pharmacies, and insurance claims registrations, as available in the different data sources.

Tezepelumab was approved in the US Food and Drug Administration (FDA) on 17 December 2021, and the European Commission issued marketing authorisation in the EU on 19 September 2022. According to the current drug indication, tezepelumab is expected to be prescribed as an add-on maintenance treatment in patients with severe asthma who are inadequately controlled despite high dose ICS and other SOC maintenance drugs for severe asthma. It is possible that the therapeutic indication for tezepelumab and its method of administration may change over the course of the proposed 10-year study. This may result in the use of tezepelumab as monotherapy, or in other forms of administration (currently administered subcutaneous [s/c]). Therefore, to capture current and future tezepelumab exposed patients, no requirement for polytherapy or administration route will be applied in this study. Tezepelumab will be identified using the ATC code R03DX11 (or any future ATC code specific for tezepelumab) or the appropriate country-specific coding system.

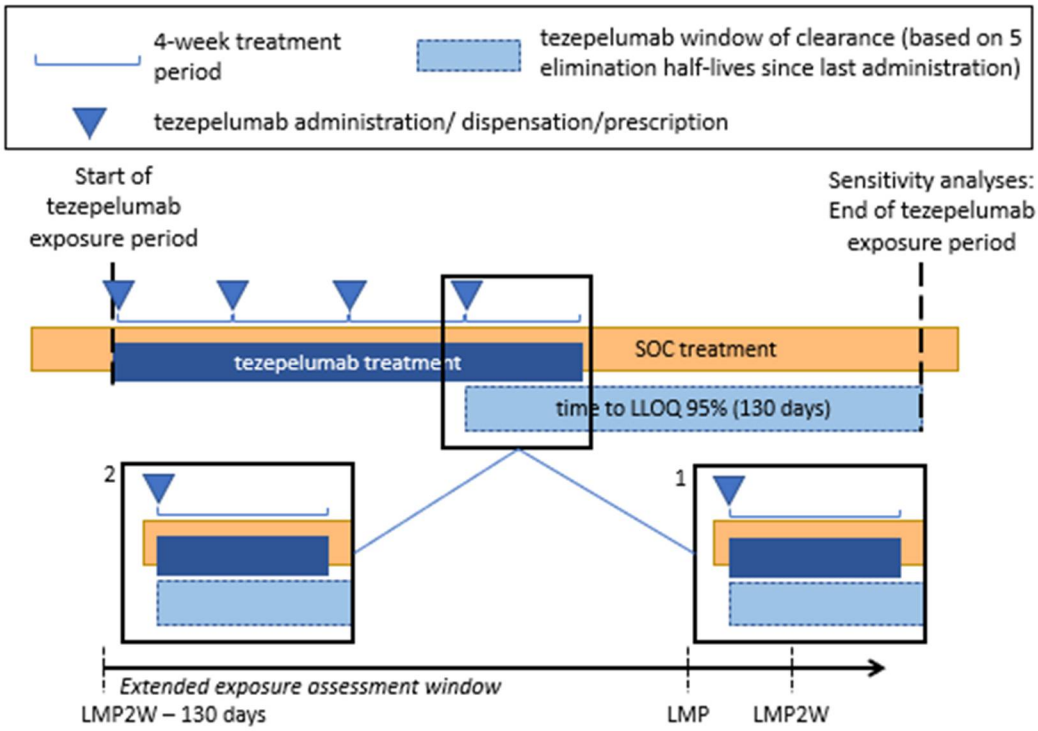
Exposure assessment windows are illustrated in Figure 1.

9.3.1.1 In-utero exposure to tezepelumab

Binary exposure will include pregnancies with one or more prescriptions/administrations of tezepelumab between LMP and end of first trimester or EoP, depending on exposure window (see box 1 in Figure 5).

An extended exposure assessment window will be considered in a sensitivity analysis. This will include pregnancies with a prescription/administration only during a clearance period of 130 days prior to conception/LMP2W (see box 2 in Figure 5). The look-back period in the extended exposure assessment window is based on the expected clearance period of five elimination half-lives (~26 days*5) for tezepelumab.

Figure 5 Tezepelumab exposure after last administration/prescription



[1] Tezepelumab prescription/administration at/after LMP will be considered exposed in the main analyses
[2] Tezepelumab prescription/administration within 130 days prior to LMP2W will be considered exposed in the sensitivity analyses with extended exposure assessment window.
SOC, Standard of Care; LLOQ, Lower Limit of Quantitation; LMP, Last Menstrual Period; LMP2W, Last Menstrual Period plus 2 Weeks

9.3.1.2 SOC for severe asthma during pregnancy

The SOC for severe asthma includes high-intensity baseline and add-on controller (maintenance) (detailed in Table 8) and reliever medication to obtain and/or maintain disease control. The identification of treatment combinations and dosage of SOC for severe asthma is based on the 2022 GINA Global Strategy for Asthma Management and Prevention (22). SOC for severe asthma may change during the study period, and the list of SOC treatments will be finalised during the SAP development (and updated for each report). SOC treatments for severe asthma in adults include (9,22).

Table 8 Baseline treatment(s)

ICS	2nd controller (one of below)
High dose ICS (beclomethasone, budesonide, ciclesonide, fluticasone, mometasone)	Long-acting β2-agonist (LABA) (Including formoterol, salmeterol)
Medium dose ICS (beclomethasone, budesonide, ciclesonide, fluticasone, mometasone)	Long-term OCS (>50% of past year)

Abbreviations: ICS, Inhaled Corticosteroid; OCS, Oral Corticosteroid

ICS dosage is defined in Table 9 below. If prescribed dosage is not available in the data source, an average daily dose will be calculated based on time between prescriptions, dosage strength, and amount (quantity prescribed) in each prescription. If prescribed dosage is unavailable and average daily dose cannot be calculated, combination of treatments will be used as a proxy for high-intensity treatment, i.e., a patient receiving ICS + LABA (2nd controller) as outlined below, is likely receiving medium-high dose ICS.

Table 9 Definition of high daily dose of various inhaled corticosteroids for patients aged 12 years or more (22)

ICS	Preparation	Threshold daily dose in µg	
		MEDIUM	HIGH
Beclomethasone dipropionate	DPI or pMDI, extrafine particle, HFA	>200-400	≥400
	pMDI, standard particle, HFA	>500-1000	≥1000
Budesonide	DPI, or pMDI, standard particle, HFA	>400-800	≥800
Ciclesonide	pMDI, extrafine particle, HFA	>160-320	≥320
Fluticasone furoate	DPI	100	200
Fluticasone propionate	DPI	>250-500	≥500
	pMDI, standard particle, HFA	>250-500	≥500
Mometasone furoate	DPI	Depends on DPI device	
	pMDI, standard particle, HFA	200-400	≥400

Abbreviations: DPI, dry powder inhaler; HFA, hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI, pressurised metered dose inhaler.

In addition to baseline asthma maintenance treatment, add-on therapies are required in high-intensity treatment and include at least one of the add-on treatments listed below:

Table 10 Add-on therapies (3rd controller)

Add-on therapy
LABA (if not used already)
Long-acting muscarinic antagonists (LAMA)
Leukotriene receptor antagonist (LTRA)
Theophylline
Azithromycin (500 mg three times a week)
OCS low dose >50% in past year (≤7.5 mg/day prednisone equivalent)

Despite high-intensity treatment, severe asthma patients may have increased use of OCS and over-use of SABA to relieve symptoms and treat exacerbations. Patients with OCS as part of their maintenance or with two or more exacerbations requiring OCS treatment are eligible for biologic treatment and will be included as severe asthma patients. In such patients, SABA use may also increase, either alone or in combination with OCS. Therefore, patients with either two or more prescriptions for OCS, or over-use of SABA defined as ≥ 3 SABA canisters in the last 12 months, in addition to high-intensity treatment will be considered to have severe asthma.

Biologics for severe asthma are only indicated for patients who remain uncontrolled despite adherence to the high-intensity treatments outlined above. Patients exposed to biologics will be included as severe asthma patients regardless of the use of other asthma drugs.

Biologic therapy[3]:

- anti-immunoglobulin E (anti-IgE),
- anti-interleukin 5/5R (anti-IL 5/5R),
- anti-interleukin 4Rα (anti-IL4R),
- anti-TSLP – *NB! Study drug of interest.*

A full list of drugs and required doses used in the treatment of severe asthma and ATC codes (or the appropriate country-specific coding system) is outlined in Appendix C, Appendix Table 11.

The definition of severe asthma in unexposed pregnancies requires relevant combinations of baseline and add-on treatments as described above to be prescribed between LMP and EoP.

A sensitivity analysis will exclude patients exposed to other biologics from the tezepelumab-unexposed cohort. This will also exclude patients exposed to other biologics during a look-back period prior to conception to ensure a minimum of five half-lives has passed since last

[3] Biologics for severe asthma as monotherapy will be included to allow for changes in drug label, and asthma becoming controlled when treated with biologics.

administration. The duration of look-back will be specific to type of biologics and detailed in the SAP.

9.3.2 Outcome

9.3.2.1 Major congenital malformations

MCMs are defined as defects of prenatal origin that have either cosmetic or functional significance to the child's health, development, or survival (25). MCMs will be classified according to the Description of the Congenital Anomaly Subgroups in the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) (26) and coded using ICD10, or adapted to the relevant coding system for each data source.

The primary outcome of MCM is defined as a composite defined by the presence of a diagnosis code (ICD10) either in maternal or infant records depending on outcome of pregnancy (TOPFA, live or non-live offspring).

A list of MCMs and their respective ICD10 codes are presented in Appendix A, Abbreviations: Anti-IL, Anti-interleukin; LAMA, Long-acting muscarinic antagonist; SABA, Short-acting β2-agonist; OCS, Oral Corticosteroid

Appendix Table 12. Identification of MCM in the data sources is available in Appendix C, Appendix Table 6.

9.3.2.2 Foetal death (Composite of miscarriage, stillbirth, and ectopic pregnancy)

Foetal death is defined as a composite of at least one of the following pregnancy loss outcomes: miscarriage, stillbirth, or ectopic pregnancy. Miscarriage also termed early pregnancy loss or spontaneous abortion, is defined as the unintended loss of an intrauterine pregnancy of less than 22 weeks of gestation (27); Stillbirth is defined as the unintended foetal death occurring at or after 22 weeks of gestation (27); Ectopic pregnancy is defined as the implant of a fertilised egg at a site other than the endometrium of the uterine cavity, usually in one of the fallopian tubes. A list of foetal death outcomes and their respective ICD10 codes are presented in Appendix A, Appendix Table 14.

9.3.2.3 Minor congenital malformations

mCM will be defined as a composite of all minor malformations, classified according to EUROCAT (Description of the Congenital Anomaly Subgroups in EUROCAT Guide 1.5) (26). A list of mCM and their respective ICD10 codes are presented in Appendix A, Appendix Table 13. Identification of mCM in each data source is available in Appendix C, Appendix Table 6.

9.3.2.4 Adverse pregnancy outcomes

Adverse pregnancy outcomes will include ectopic pregnancy, miscarriage, stillbirth (please see definitions in the description of foetal death above), TOP, and pre-eclampsia. TOP is the intentional TOP at any time during gestation for any reason. When possible, reasons for

termination are captured and classified as TOPFA or for other reasons. TOPFA will be defined using any records of malformations in relation to TOP, or if none is available, by identifying malformation records during current pregnancy. To distinguish maternal from foetal malformations, records during pregnancy will be sense-checked and any cases with prior (or future) maternal records outside current pregnancy will be ignored. TOPFA are likely to be recorded as unspecified malformations or high-level organ specific. Pre-eclampsia is defined as the development of new onset hypertension or new onset proteinuria after 20 weeks of gestation, as defined according to IMI-ConcePTION (28). A list of the adverse pregnancy outcomes of interest and their respective ICD10 codes are presented in Appendix A, Appendix Table 14.

9.3.2.5 Individual birth outcomes

The individual birth outcomes include EC-section, PTB, SGA, and LBW. EC-section is defined as an unplanned (non-elective) C-section and will include pre-labour emergencies and c-sections during labour due to unexcepted complications, such as the occurrence of foetal distress (29). EC-section will be distinguished from planned C-section using procedure codes; PTB is defined as live births less than 37 weeks of gestation; SGA is defined as a birth weight lower than the 10^{th} percentile of the distribution of birth weights among live births, by gestational age and sex, using validated national references for foetal weight and birthweight (30). SGA will be based on gestational age and birth weight as recorded, or ICD10 codes if measurements are not available; LBW is defined as weight at birth less than 2500 grams, classified according to the WHO (31), this will be identified using records of birth weight, or ICD10 codes if measurements are not available. A list of the individual birth outcomes of interest and their respective ICD10 codes are presented in Appendix A, Appendix Table 15.

9.3.3 Maternal and infant characteristics

A broad range of characteristics and potential risk factors, related to mother and offspring, will be considered. These include, but are not limited to, demographic and clinical characteristics, comorbidities and concomitant medications. The final choice of characteristics, risk factors and confounders will depend on the availability of data and clinical relevance. The rationale for the choice of variables selected are provided in Appendix E, Appendix Table 19. A summarised overview of potential risk factors for each outcome is detailed in Table 11 below.

Demographic and clinical characteristics: maternal demographic and clinical characteristics will be assessed at LMP of current pregnancy and depending on data availability in different data sources, will include:

- **Demographic characteristics of pregnant women with severe asthma**: maternal age, maternal socioeconomic status, ethnicity.
- **Demographic characteristics of live infants of women with severe asthma**: gender, gestational age, birth weight, apgar score (5 minutes), calendar year of birth.

- **Maternal lifestyle characteristics** (commonly assessed at first antenatal care visit during early first trimester): smoking status, alcohol abuse, substance abuse, maternal weight and height or body mass index (BMI) (kg/m^2) prior to pregnancy.
- **Maternal clinical characteristics**: comorbid conditions (existing diabetes, essential hypertension, anxiety, depression) at the start of pregnancy, during pregnancy (respiratory infections, gestational diabetes, gestational hypertension, anxiety, depression) co-medications during pregnancy (non-steroidal anti-inflammatory drugs [NSAID], betablockers).
- **Health Care Utilisation (HCU)** in the 12 months before LMP will be used as a proxy for burden of maternal comorbidities: number of outpatients and primary care visits, use of emergency department, hospitalisations (number of days, number of hospitalisations), type of health care providers visited.
- **Obstetric history**: parity, previous pregnancies with gestational diabetes, pre-eclampsia, spontaneous abortion, stillbirth, PTB, and SGA birth.

Maternal and infant characteristics are either included as recorded or based on ICD10 codes. A list of maternal characteristics and their respective ICD10 codes are presented in Appendix A, Appendix Table 18. An overview of the availability of the variables in each data source is available in Appendix C, Appendix Table 7 and Appendix Table 8.

Maternal age at conception

Maternal age at conception is considered a major risk factor for the studied outcomes. Multiple epidemiological studies have associated advanced maternal age at conception with increased risk of CM (32), adverse pregnancy (33), birth and infant outcomes (34). Although there is no known association between maternal age and tezepelumab exposure, maternal age is associated with the asthma severity and with the selected outcomes, thus it will be included in the PS models.

9.3.4 Other variables

Gestational age

Is measured from the first day of the LMP and expressed in weeks and days, completed weeks, or in days. Gestational age is usually calculated from the reported LMP (depends on recall of the LMP and assumes that ovulations occurred on average 2 weeks after LMP). For data sources in which the LMP is missing, date of LMP will be estimated based on date of birth and gestational age at birth. In countries where gestational age is calculated from conception, gestational age plus 2 weeks will be subtracted from the date of birth to obtain the date of LMP. Foetal biometric measures from ultrasounds are increasingly being used to confirm or adjust LMP. Current recommendations from the American College of Obstetricians and Gynaecologist, the Society for Maternal-Foetal Medicine, Euro-Peristat Network recommend

use of the best obstetric estimate rather than LMP alone. Hence, in Europe and USA, estimate of gestational age is based on ultrasound dating, and rarely based on LMP alone due to reporting errors (28,35). Thus, gestational age will be assessed using the best obstetric estimate available. Gestational age is rarely available for ectopic pregnancies or miscarriages.

Table 11 Potential confounders/risk factors of MCM and mCM, adverse pregnancy outcomes and adverse birth outcomes in the offspring

	CM	Adverse pregnancy outcomes					Adverse birth outcomes			
	MCM/ mCM	Ectopic pregnancy	Miscarriage	TOP	Stillbirth	Pre-eclampsia	LBW	EC-section[1]	PTB	SGA
Age at conception	×	×	×	×	×	×	×	×	×	×
Socioeconomic status	×	×	×	×	×	×	×	×	×	×
Health care utilisation	×	×	×	×	×	×	×	×	×	×
Comorbid conditions	×	×	×	×	×	×	×	×	×	×
Respiratory comorbidities	×	×	×	×	×	×	×	×	×	×
Co-medications	×	×	×	×	×	×	×	×	×	×
Smoking	×	×	×	×	×	×	×	×	×	×
Alcohol abuse	×	×	×	×	×	×	×	×	×	×
Substance abuse	×	×	×	×	×	×	×	×	×	×
Gestational diabetes									×	×
Pre-pregnancy obesity	×		×		×			×	×	×
History of pre-eclampsia	×				×	×	×			
Pre-pregnancy hypertension	×				×	×		×	×	×
Pre-pregnancy diabetes	×		×		×			×	×	×
Previous spontaneous abortions	×		×	×	×				×	
Previous stillbirth	×				×					
Previous preterm birth									×	
Previous SGA										×
Year of conception	×	×	×	×	×	×	×	×	×	×

[1] A brief overview of the identification of EC-section in the data sources is available in Appendix C, Appendix Table 9.

Abbreviations: CM, Congenital Malformations; MCM, Major CM; mCM minor CM; TOP, Termination of Pregnancy; LBW, Low Birth Weight; EC-section, emergency caesarean section; PTB, Preterm Birth; SGA, Small for Gestational Age

Omitted from this list are potential risk factors and/or potential mediators between SOC for severe asthma treatments and CM that are exclusion criteria in this study (as defined in Section 9.2.2.2): Chromosomal abnormalities and genetic syndromes before delivery and pregnancies with potential *in-utero* exposure to a confirmed teratogenic drug (including but not limited to warfarin, angiotensin converting enzyme inhibitors, antineoplastic agents, isotretinoin, misoprostol, or thalidomide), with look-back period prior to LMP to account for prescriptions/dispensations/administrations that may have led to exposure during pregnancy.

9.4 Data Sources

A preliminary feasibility assessment of 42 potential data bases was completed to inform the selection of the following data sources from four countries: Denmark (National Registries), Sweden (National Registers), France (SNDS), and United States (Carelon). A full feasibility assessment of these data sources was conducted between January and October 2023 to assess in further detail if the data available are sufficient to address the study objectives.

A description of each selected data source was developed based on information collected from data holders and through desktop research, which included:

- Characteristics of the data sources including representativeness, time coverage, size of the source population, inauguration date for each data source, data linkage between different domain-specific data sources, and limitations known by the data holder.
- Access requirements, responsible party, and logistics surrounding analytics including availability of individual-level data or exclusively aggregate-level results (according to the SAP), data access process and timelines, and required partnerships and data holder agreements.
- Availability and coding systems of drugs, medical diagnoses, procedures and laboratory measurements. Availability and expected completeness of the study-specific variables related to: Inclusion/exclusion criteria, Censoring, Exposures, outcomes (pregnancy, birth, and infant), and confounding variables. To include care setting and record types assessment and coding or algorithms planned for each variable.
- Assessment of the expected availability and completeness of the specific proxy variables required to identify the severe asthma patient population.
- Mother-infant linkage.
- Estimated number of pregnancies occurring in women with severe asthma.

Tezepelumab was approved in the US in December 2021, and by the EMA in September 2022. Tezepelumab is administered s/c and is expected to be initially administrated by a health care professional in hospital or outpatient clinic settings. Once patient self-administration training has been completed and no adverse reactions to treatment has been observed (within 4 months),

treatment is expected to be prescriptions for self-administration at home, with one dose/vial per prescription, expected to be filled/administered every four weeks as prescribed.

The final list of data sources was determined based on the results of the feasibility assessment and the ability of the data sources to meet the requirements (ability to capture biologics and SOC treatments for severe asthma, ability to capture study-specific pregnancy, birth, and infant outcomes, mother-baby linkage capability, and data source size) to be included.

A summarised overview of the selection of data sources and main considerations based on the feasibility assessment is available in Appendix C, Appendix Table 2.

9.4.1 Denmark

Denmark holds more than 160 health databases and has the longest-standing civil registration system in the world. Danish National Registers have a 100% coverage of the country, which is approximately 5.9 million individuals (36). In general, the healthcare registries at the Danish Health Data Authority are updated monthly with a lag of 2 months. However, some registries are updated less frequently, and may have a lag of up to 13 months. The estimated timeline for data permits in Denmark is about 8 months. This includes submission of the application (including protocol and code lists) to the health registry authorities (approximately 6 months for review/approval) and gaining access to the data after approval (approximately 2 months). Every individual in Denmark is provided with a unique personal identification number called a Central Person Register (CPR) at birth or upon immigration which allows for follow-up until death or emigration. The CPR number also allows for family linkage of data.

The following Danish registries are considered for the study:

- Danish Civil Registration System

  The Danish Civil Registration System holds information on all persons with a permanent address in Denmark, and the relations between spouses, parents, and offspring. Information on demographics, migration, date of birth and death is electronically registered daily for all Danish residents.

- National Health Insurance Service Register (NHISR)

  This Register records the services supported by public health insurance as well as services provided by general practitioners and specialists in private practice outside of the secondary setting at hospitals. However, individual diagnoses and treatment information are not available.

- Register of Pharmaceutical Sales (RPS)

  Information on prescription drugs dispensed via community pharmacies is available from the RPS. The register contains information on the date of purchase, item number, product name, ATC code, strength per unit, quantity of the WHO defined daily doses (DDD) per package and number of packages filled. Since April 2004, information on medical

indication for prescription and daily prescribed dose by physician has also been available, but completeness and validity are affected by a non-compulsory obligation to record this information.

- Danish Hospital Medication Register (SMR)

  The SMR contains information on drugs administered to patients while admitted to hospital or during outpatient visits: the date and time of administering the drug, the dose administered via number of units and strength per unit, product name, ATC code, and department information. Thus, this register complements the RPS. Data have been captured since May 2018 and is available for research since 2022. Because this is a new register the data may not be 100% complete from the beginning.

- Danish National Patient Register (NPR)

  NPR-Den has since 2007 included information on all patients in Danish hospitals including private hospitals, however, reporting from private hospitals and clinics are not considered complete. The NPR-Den register includes the following information: CPR number, local municipality, admission and discharge information, the date of any incidents over the course of an illness, diagnosis (ICD10), examinations and treatment information – including surgery coded with Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NOMESCO) codes, as well as supplementary information regarding births.

- Register of Laboratory Results for Research (RLRR)

  Information on laboratory tests at the country's large clinical biochemical and clinical immunological, and tests performed in general practice and sent to a hospital laboratory for analysis, are collected in the RLRR. Data from the five regions in Denmark has gradually been included in the register since late 2013 and RLRR is anticipated to have reached 100% coverage by 2020.

- Danish Medical Birth Registry (MBR)

  The MBR contains data on all live and stillbirths in Denmark since 1973. The registry contains high validity data on the actual birth, the results of the birth and whether there were complications during labour. The MBR consists of a main table with index pregnancy (one line for each infant in the same pregnancy) as the key identifier and information on the identity on both parents by CPR number, diagnosis (ICD10) and possible complications, potential risk factors and number of visits. Any congenital abnormalities are retrospectively added to the table if identified within the first year of life. All subsequent health events reported by diagnoses and surgical interventions can be found in the NPR. All deaths of mother or infant within the first 365 days after delivery are registered including the age in days when the infant died.

- Danish Cause of Death Registery (CDR)

The CDR contains information on date and cause of death, place of death, information about any autopsy, and municipality of residence.

9.4.1.1 Study-specific data availability for Denmark

Mother-offspring linkage is available from 1973, and all live births and stillbirths after 22 weeks of gestational age can be linked using a deterministic approach.

In Denmark, tezepelumab received marketing authorisation in September 2022. The team has a pre-reimbursement programme with tezepelumab available for health care professionals to prescribe when a specific request is submitted to the hospital. This has been in action since November 2022. However, the actual tezepelumab launch with reimbursement is planned for April 2023, so the anticipated start of the study period for Denmark is estimated to be Q2 2023. Information on drugs dispensed is through RPS, drugs prescribed in hospital or in other institutional care (RPS), and drugs administered in hospital (SMR), are available. ATC codes and Danish brand names allow the distinction between biologics.

All study outcomes of interest are available, as well as maternal characteristics, other baseline characteristics and covariates.

The DanishClinical Register of asthma estimates that approximately 350,000 people live with asthma in Denmark. However, only about 4% can be captured through the national registries due to diagnoses unable to be registered in primary sector, including those from private specialists. In 2021, 14,283 female encounters between ages 15-49 (childbearing potential) were recorded with an asthma diagnosis, though individual patients may have multiple encounters each.

9.4.2 France

The SNDS is composed of the French National Health Insurance database (Système national d'information interrégimes de l'assurance maladie [SNIIRAM]) available since 2008, and the French hospital discharge database (Programme de médicalisation des systèmes d'information [PMSI]) available since 2006, linked by a unique patient identifier. It covers approximately 99% of the French population, with 67 million persons, from birth (or immigration) to death (or emigration). Updates to data occur annually, so data lag is anticipated to be 12 months. The data application process for France is about 8 – 10 months. This includes the regulatory process for Comite ethique et scientifique pour les recherches, les etudes et les evaluations dans le domaine de la santé (CESREES), Commission Nationale Informatique & Liberties (CNIL), and Conservatoire National des Arts et Metiers (CNAM) review and approval as well as data contracting and access steps.

SNDS includes demographic data, health encounters such as physician or paramedical visits (excluding psychological therapies amongst others), dispensations, medical devices, and lab tests (without results). Through the PMSI, the SNDS also includes medical summaries of all hospitalisations from private or public hospitals, including the date of stay, medical procedures, costly innovative drugs or implantable devices during the hospital stay, the primary diagnosis

(main reason for admission), related diagnosis (specifies the disease context of the primary diagnosis), and diagnoses related to other conditions. All data are encoded according to the ICD10. Information on occupational diseases and sick leaves are also available.

9.4.2.1 Study-specific data availability for France

Mother-offspring linkage is available since 2012, and all live births and stillbirths can be linked using a deterministic approach. Terminations of pregnancy, due to maternal or foetal conditions, are partially recorded.

In France, tezepelumab was made available for compassionate use, a special authorisation provided by Haute Autorité de Santé (HAS) on August 24th, 2022 (Table 4). Data on compassionate use of tezepelumab will be collected in the PMSI, as its dispensation will be mainly from hospital pharmacies. A favourable opinion for the reimbursement of tezepelumab has been issued by HAS in June 2023. Hospital administered drugs are only captured in the SNDS if they are considered to be of high-cost and evaluated to have a significant benefit. Such drugs are included in a high-cost drug list. Once tezepelumab receives marketing authorisation in France, and provided that it is dispensed through retail pharmacies, the drug will be recorded in the *Données de Consommation Interrégimes* (DCIR) (which is part of the SNDS) when reimbursed. Data on biologics are available from 2008 for outpatient (DCIR) and inpatient (PMSI) settings. Drugs prescribed in hospital or in other institutional care can be derived from drug deliveries. In France, all study outcomes of interest are available or partially available, as well as maternal characteristics, other baseline characteristics and covariates.

According to ScanSanté, approximately 2,800 adult patients (≥ 18 years old) were hospitalised for acute severe asthma (ICD10 code J46, in main hospital diagnosis) in 2022. The number of adult patients (≥17 years old) hospitalised for asthma and acute severe asthma (ICD10 codes J45 and J46) was 17,009 in 2021 (13,100 under J45 codes and 3,909 under J46).

9.4.3 Sweden

Sweden National Registers includes 100% of the countries population, which is approximately 10.6 million individuals, as of July 2023 (37). In Sweden, data applications must be reviewed by the Swedish Ethical Review Authority, which can take 2 to 3 months, and next the data application permit request is submitted, and review for that takes approximately 9 months presently. Additionally, a Confidential Disclosure Agreement (CDA) is required, and data holders release these approximately 4 to 6 weeks before data delivery. This agreement regulates who will be able to access the data and when the data should be destructed. The National Registers are governed by National Board of Health and Welfare (NBHW). Time from approval to extraction is approximately 5 months. The sponsor of a study does not have access to the raw data (individual-level data) but can view and comment on the analysed results. Data lag varies by register and is between monthly (Swedish Prescribed Drug Register [SPDR]) to annually (NPR).

- *Total Population Register*

This register is managed by Statistics Sweden and contains information on all persons registered in Sweden. The register was established in 1968 and contains data on life events including birth, death, name change, marital status, family relationships and migrations, residence, citizenship, and country of birth. The information in the register is updated daily. All citizens in Sweden are assigned a PIN which is used in all of the national registries for identification and can be used to link information across registries.

- *Swedish Prescribed Drug Register*

The SPDR was established in July 2005 and is maintained by the NBHW. It contains all medicines that are collected against prescriptions at pharmacies, but also information on collected preferential consumables. Furthermore, it includes information on the patient (sex, age, place of registration) and product information (including ATC code, drug name, strength, pack size). Monthly data are available with a lag time of 1 to 2 months. Annual data (data up until December of previous year) is available in April the following year. Completeness of the data is considered to be high. Possibility to conduct chart review is not known.

- *National Patient Register*

The National Patient Register (NPR-Swe) was established in 1964, with complete coverage starting from 1987, and is maintained by the NBHW. The registry comprises data on healthcare encounters in inpatient (hospital) and outpatient specialist care given in public hospitals. The coverage for inpatient care is complete since 1987 (ICD10 from 1998) and specialised outpatient care from 2001 onwards. Outpatient care data is included from a proportion of private hospitals, but the data is partly missing, while for public hospitals it is close to 100%. The NPR-Swe contains information on, e.g., details of hospitalisation, all disease areas, hospital, and hospital department, visit date, diagnosis, diagnosis date, comorbidities at diagnosis, (ICD-9 or -10 codes), procedures, and patient demographics.

Once a month, each of the 21 county councils in Sweden and private caregivers deliver information to the register. Quarterly updates are available, with some missingness to be expected. Full updates are available once a year with data up to end of December of previous year. The data are available for research from NBHW with ~6 to 9 months lag time for the annually updated data and 3 months lag time for the quarterly data.

The register includes all inpatient care since 1964 (and comprehensive since 1984), Data on patients treated by physicians in specialised outpatient care since 2001, and information on emergency waiting times and emergency operations since 2016. From October 2016 onwards, abortions are registered in the NPR, however coverage is expected to be low. Spontaneous abortions occurring at home and not requiring medical help or abortions carried out by a non-physician are not registered in the NPR. Chart reviews are possible after Ethic Committee and data permit approvals, potential patient consent collection, and contract between IQVIA and the hospital where the care was given.

- *Swedish Cause of Death Register*

The Swedish Cause of Death Register is a high-quality virtually complete register of all deaths in Sweden since 1952. The main strengths of the Swedish Cause of Death Register are the high completeness and long history, with data electronically available since 1952. The quality of the whole register has not been checked since 1995. The data are updated yearly and includes 4 to 6 months lag for date of death. Cause of death data for previous year is available for research in April next year.

- *Swedish Register of CM*

All births in Sweden (approximately 100,000 annually) are covered, with TOPFA included since 1999. Information is obtained from paediatrics, obstetrics, and laboratory records including annual reports from cytogenic laboratories which contain all prenatal and infant abnormal karyotypes. Data on CMs is mainly reported prior to one month of age, however may be reported for up to one year post birth. In Sweden, TOPFA can be granted after 18 weeks and up to 23 weeks of gestation following ethical committee approval from the NBHW. All stillbirths (22+ weeks of gestation) are registered at the Swedish Registry of CM.

- *Swedish Medical Birth Register*

The Swedish Medical Birth Register is maintained by the NBHW and contains data from 1973 on practically all deliveries (live and stillbirth), with a gestational age of at least 22 weeks, in Sweden. It is compulsory for every maternal clinic to report to the register. Information is obtained from medical records from the prenatal, delivery and neonatal care. No data on elective terminations or spontaneous abortions are available and information on stillbirths is only available from the gestational Week 22 onwards (Week 28 before July 2008). Albeit compulsory reporting, the records for a small percentage of all infants – 1 to5 percent per year – are missing completely. Even though the basic structure of the register has remained unchanged during the years, there have been modifications to content and methods of data collection. The register is updated once a year with ~12 months lag and data for the previous calendar year is usually available in December. Together, the lag and delay mean that data from the first of January will be available in December the following year. Applications for data access are sent to the NBHW and processed by a pre-defined data permit process, preceded by ethical review by the Swedish Ethical Review Authority. The registry includes information on;

- Diagnoses of mother and child recorded using ICD10 codes;
- Reproductive care, covering the duration of pregnancy and the infant period;
- Maternal diagnoses and exposures during pregnancy, including drug use since 1995, the delivery and the neonatal care;
- Mothers' personal identification numbers.

9.4.3.1 Study-specific data availability for Sweden

The number of patients in Sweden with J45 and J46 asthma diagnosis codes recorded in 2022 was 74,509, with 5,010 being female between the ages of 18-44. Tezepelumab is reimbursable in Sweden, and uptake has been confirmed as beginning in March 2023, with counts confirmed available in the data set. Mother-infant linkage is 100% and captured in MBR. Sweden captures

data in secondary outpatient settings such as pulmonology and obstetric/gynaecology as well as most hospital data. Sweden does not capture hospital administered drugs however, nor primary care data presently. Sweden is presently working to add primary care data to the National registers in the near future. Sweden National registers are expected to capture the study-specific outcomes, censoring, temporal anchors, and covariates. Most exposures are expected to be captured with the exception of hospital administered drugs.

9.4.4 The United States of America

Carelon is a large administrative healthcare database maintained by Carelon Research (previously Health Core) for use in health outcomes and pharmacoepidemiologic research. Carelon contains a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from one of the largest commercially insured populations in the USA. Currently, approximately 21 million individuals are actively enrolled in Carelon. Member enrolment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and healthcare utilisation may be tracked for health plan members in the database dating back to January 2006, and with diagnoses recorded in ICD10 since October 2015. Data is updated every 3 months, providing a short data lag time for this data source. There is not a data application nor Ethics Committee review process for Carelon data access so no additional delays for data access are expected. Regulatory submission to the local Institutional Review Board (IRB) will not be required for this study, unless outcome validation is requested, in which case during the time of outcome validation request, IRB submission will be required to gain that additional data. As of 2020, there were 1.2 million mother-infant linkages in Carelon that are available for research. Carelon Research systems will be used to link the claims data in Carelon to complementary data sources including, but not limited to, inpatient and outpatient medical records, national vital statistics records (e.g., National Death Index for date and cause of death), and disease registries. This data holder also has substantial experience conducting reproductive drug safety studies. Carelon is a part of the Sentinel Network utilised by the FDA and as such validates the data as stipulated by the FDA.

9.4.4.1 Study-specific data availability for the USA

Mother-offspring linkage dates back to 2006, and approximately 73% of live births can be linked. This linkage is achieved using a deterministic approach. Data on TOPFA are available in the data source for a subset of patients (to the extent that a claim was filed for the procedure) with a diagnosis code for the anomaly. Data on terminations due to reasons other than foetal anomaly are not available. Among the female asthma patients 17th December 2021 through 30th September 2022, 18,073 had at least one pregnancy code, and about 11 were dispensed tezepelumab, according to current Carelon data.

In the USA, tezepelumab received FDA approval in December 2021 and entered the market in January 2022. In Carelon, information on drugs dispensed through retail pharmacies is available. Data on drugs administered via a procedure in outpatient and inpatient settings are available via

procedure codes. Additionally, data on drugs administered may be captured via abstraction from requested medical records (available for a subset of patients) or asked via a patient survey. However, drugs taken by oral route may not be available.

The annual number of pregnancies in women with severe asthma was estimated to be 531 for the USA (see Section 9.5.1, Table 13). Carelon includes 439,985 female patients who received an asthma diagnosis from 17th Dec 2021 through 30th Sep 2022. Of that population, 151 had at least one tezepelumab dispensing during the time period; Among the female asthma patients 18,073 had at least one pregnancy code in the study period (< 11 was dispensed tezepelumab).

In Carelon, all study outcomes of interest are available, as well as maternal characteristics, other baseline characteristics and covariates.

Table 12 Summary of data availability by data source

Country	Start of Data Availability	National Coverage	Mother-infant Linkage	Asthma Population (J45.x & J46.x)[1,4]	Data Lag (Months)	Availability of Exposure		Availability of Outcomes		
						Tezepelumab[2]	SOC	CM[3,4]	Adverse Pregnancy Outcomes[4,5]	Adverse Birth Outcomes[4,6]
Denmark (National Registers)	1970 - 2018[7]	100%	100%	Available	6-14	Available[8,15]	Available	Available	Available	Available
France (SNDS)	2008 (DCIR) 2006 (PMSI)	99%	96%	Available[14]	12	Available[8,9]	Partial[8,9]	Available	Partial[13]	Available
Sweden (National Registers)	1952 - 2016	100%	100%	Available[15]	1-12	Available	Partial	Available	Available	Available
USA (Carelon)	2006	7%[10]	73%	Available	3	Available	Available	Available	Available	Available

Abbreviations: CM: Congenital malformations; DCIR: Données de Consommation Interrégimes; PMSI, Programme de Médicalisation du Système d'Information; SNDS: French National Health Data System; SOC: Standard of Care; USA: United States of America.

[1] ICD10 codes for asthma diagnoses include J45 and J46, as well as any subcategories, which are notated as xx (Appendix A, Appendix Table 16)

[2] Exposure to tezepelumab is based on the availability/information of biologics

[3] Refers to major and minor congenital malformations.

[4] Availability was not considered "available" if listed as "partial" or "not available" in at least one of the outcomes.

[5] Refers to ectopic pregnancy, spontaneous abortion, termination of pregnancy and stillbirth.

[6] Refers to preterm birth, small for gestational age, low birth weight, pre-eclampsia and unplanned caesarean section

[7] Varies between registers

[8] Availability of data is subject to the data lag which would begin after the date of EMA approval 19Sep22, so that data may not be available until after the data lag assumption time period

[9] Only high-cost hospital administered drugs are captured in SNDS. Therefore, exposure to drugs in hospital setting can only be captured provided it is among the list of high-cost drug.

[10] Approximately 20% of USA population (75 million) have ever been recorded by Carelon, and approximately 7% of USA population (21 million) are actively enrolled

[11] Pharmacy drug dispense is available however drugs prescribed and administered during hospital admission are not available. Additionally, time and date of drug administration is not available and must be estimated based on pharmacy dispense dates

[12] Linkage is not available directly in SHI, however information on infant live births and still births, including associated abnormalities is available in the maternal records during pregnancy, at birth, and for about 1-3 weeks post birth until infant receives their own respective insurance ID code.

[13] Able to capture termination of pregnancy, but unable to determine if it is for foetal anomaly

[14] Only hospital encounters diagnoses can be captured, asthma diagnoses from outpatient clinic visits will be mostly available as they are expected to be under the Long-Term Disease code. Hospital administered drugs are not expected to be captured

[15] Hospital and secondary outpatient care diagnoses available. Primary care data is not presently available however in Sweden they are currently working to add primary care data to the National Registers in the near future.

9.5 Study size

In this study, both sample size and power calculations were carried out separately for the primary outcome (MCM) at the meta-analysis level. The assumptions and methods used for the sample size and power calculations are introduced in Sections 9.5.1 and 9.5.2.

In the sample size analysis, the **minimum required sample size to achieve 80% power to rule out a target RR of 2.5**, (i.e., have it outside the 95% CI) at the meta-analysis level was calculated (see Section 9.5.3).

Two approaches were used in the **power calculations**. Both are performed at the meta-analysis level and use **the expected number of exposed pregnancies** by the end of study period:

- Approach 1: **Minimum detectable RR** that could be ruled out with 80% power (see Section 9.5.4;
- Approach 2: **Expected power** to rule out a target RR of 2.5 (see Section 9.5.5).

A smaller RR here indicates a more conservative approach to safety.

The expected sample allocation across the countries were used in both power calculations.

9.5.1 Assumptions and methods for the sample size and power calculations

Assumptions used for the sample size and power calculations

- **A prevalence of 8% for MCM outcome.** Estimates for MCM (as a composite) in patients with severe asthma range from 4.3%-11.8%: 4.3%-4.5% in those classified as severe based on GINA treatment (38); 6.2% in those with exacerbations during pregnancy (39); and 11.8% in mothers hospitalised for asthma in the first trimester of pregnancy (40). The incidence of MCM is approximately 3% in the general population (41).
- **Uptake of tezepelumab among pregnant women with severe asthma of 0.8 to 11.5%,** depending on study country and year since the market authorisation in the respective country**.** Year-specific uptake percentages during the study period were calculated assuming 0.8% uptake for the year of market authorisation, doubling the rate in subsequent year, and an increase in uptake equal to the increase in projected sales provided by the Marketing Authorization Holder (MAH) for subsequent years. This is a conservative approach that does not account for patients switching from other biologics. The uptake is expected to meet that of other biologics. For example, if projected year-to-year increase in sales is 50%, then the same increase is applied to calculate the uptake value for the current year from the uptake in previous year, e.g.,

$$2\%\ (previous\ year) + \ 50\%(increase) \times \ 2\%\ (previous\ year) = \ 3\%(current\ year).$$

- **A non-inferiority margin of RR of 2.5 (target effect size)**. The RR of 2.5 was based on previously reported increase in risk of MCM for exposure to a major teratogenic drug (42,43).
- **Exposed to unexposed pregnancy ratios of 1:2 and 1:3.** Since tezepelumab has launched only recently (Q1 2022 in USA), it is expected that the number of patients exposed to tezepelumab will be lower than the number of patients unexposed to tezepelumab (exposed to asthma SOC). Matching each patient in the exposed cohort to more than one patient in unexposed cohort will increase statistical power, and thus, allocation ratios of 1:2 and 1:3 were used for the sample size and power calculations.

Assumptions on data sources and number of pregnancies in severe asthma patients

For the analysis of MCMs, live and non-live offspring, and TOPFA will be considered. However, because research evidence suggest that the proportion of stillbirths and TOPFA are only around 1% (44), power and sample size calculations for MCMs will be based on the number of live births in data sources. This assumption will have a negligible effect on these calculations.

To assess the anticipated study size in the data sources, an estimate for the annual number of live births in women with severe asthma was computed using the following parameters and assumptions:

a) Latest available data on annual live births in the respective country of the data source (obtained from official statistical offices) (45,46);

b) Data source coverage: proportion of the country's total population covered by the data source (information obtained from the data sources during feasibility assessment);

c) Proportion of live births from women with asthma among all live births. This information was available for the USA (47,48), Denmark (49) and France (50). The proportion for Denmark was applied for Sweden, considering the similarity of reported asthma prevalence in both countries (51,52)].

Based on the parameters and assumptions above, the number of live births in women with asthma captured in the data source was calculated as the number of annual live births in the country (parameter a) multiplied by the data source coverage (parameter b) multiplied by the proportion of live births that occur in women with asthma (parameter c).

The final estimates for the annual number of live births in women with asthma were 1,463 (Denmark), 4,796 (Sweden), 31,867 (France), and 9,764 (USA).

Note that for simplicity, we refer to countries in this section instead of the respective data sources from each country as presented in Table 11. However, the extent to which results can be extrapolated to the whole country will be considered when discussing the results.

As stated in Section 7.1, 3 to 10% of people with asthma diagnosis have severe asthma. In study size calculations, an assumption of 3% was used as a conservative estimate, and the expected number of live births in women with severe asthma was obtained by multiplying the number of estimated live births in women with asthma (step 2) by 3%. This resulted in an estimate for the annual number of live births in women with severe asthma to be 44 (Denmark), 144 (Sweden), 956 (France), and 293 (USA) (Table 13).

Table 13 Estimated annual number of live births in women with severe asthma eligible for the primary outcome analysis by the data sources

Data source	Annual number of live births in women with severe asthma	Annual number of live births in women with severe asthma eligible for MCM analysis[1]
Denmark	44	44
Sweden	144	144
France	956	918[2]
USA	293	214[3]
Total	1,437	1,320

Abbreviations: USA: United States of America; MCM: Major Congenital Malformation.
[1] due to imperfect linkage in USA (OPTUM) and France (SNDS)
[2] 918 = 956*0.96, where 0.96 represent proportion of live births that can be linked to mothers
[3] 214 = 293*0.73, where 0.73 represent proportion of live births that can be linked to mothers

All live births are expected to have a mother-infant linkage in Denmark and Sweden and almost all in France (96%). In Carelon (USA), only 73% of the pregnancies resulting in a live birth can be linked to the offspring, however the study-specific linkage will be assessed during the interim reports. Thus, the MCM analysis can only be conducted in Carelon using the pregnancies resulting in live birth that can be linked to the mother or resulting in a recorded pregnancy loss or TOPFA which reduces the number of live births available for analysis by 27% in this data source. The estimated annual number of live births in women with severe asthma that are eligible for MCM analysis were 44 (Denmark), 144 (Sweden) 918 (France), and 214 (USA) (Table 13).

Estimated annual number of live births (Table 13) are then multiplied by year-specific uptake rates (0.8-11.5%) to get the expected number of tezepelumab exposed live births for each year until the end of study period by country. The resulting yearly numbers are summed to obtain the expected total number of tezepelumab exposed live births eligible for MCM outcome analysis by the end of the study time period (see Table 4) in each country – 16 (Denmark), 50 (Sweden), 254 (France), and 121 (USA). These represent the expected number of live births used for minimum detectable risk ratios (RR) and expected power calculations as described in Sections 9.5.4 and 9.5.5.

To explore the data sources that are likely to contribute to the meta-analysis, the probability of observing at least one MCM outcome event among exposed in the data source during the

study period was estimated. The data source was included in the analysis during each simulation if at least one exposed and unexposed outcome event was observed.. Under the assumed uptake scenario, the probabilities of observing at least one MCM event in the exposed group during the study time period range from 74% (Denmark) to >99% (France, USA) (Table 14). These results were deemed sufficient to consider all data sources for inclusion in the meta-analysis level study size and power calculations. As the exact uptake of tezepelumab among pregnant women with severe asthma is unknown at this time, these assumptions will be evaluated in the first interim report, and the study milestones will be adjusted as necessary to ensure a sufficient sample is obtained to address the research objectives.

Table 14 Expected number of live births in women with severe asthma exposed to tezepelumab and expected number of MCM outcomes expected in the data sources by final study reporting year, under the assumed uptake scenario.

Data source	Among women with severe asthma exposed to tezepelumab and eligible for analysis:		
	Expected number of live births[1]	Estimated number (95% CIs) of MCM events from live births[2]	Probability of observing at least one MCM event from live births[3]
Denmark	16	1 (0 – 6)	**74%**
Sweden	50	4 (1 – 10)	**98%**
France	254	20 (12 – 31)	**>99%**
USA	121	10 (5 – 18)	**>99%**

Abbreviations: USA: United States of America; MCM: Major Congenital Malformation.
[1] Calculated as (annual number of severe asthma live births)*(Year 1 uptake + Year 2 uptake + … + Final year uptake)
[2] Confidence interval (CI) calculated using Poisson exact method.
[3] Based on theoretical cumulative distribution function of the binomial distribution.

9.5.2 Methods for study size calculations

The required sample size and power calculations were based on the assumptions described above and were carried out for primary outcome (MCM) at the meta-analysis level.

The sample size and power calculations were performed using simulations under the assumption that the true RR is 1.0 across all data sources. Although unexpected, should heterogeneity arise, (i.e, the true RR differs across data sources) a random-effects meta-analysis approach would be required thereby necessitating a larger sample size to achieve the same study size indicators.

The following steps constitute a single simulation and are the same for all study size calculations:

1. For a given overall sample size (in terms live births), a proportion of the overall population was assigned to each of the data sources included in the meta-analysis (proportions are presented in Table 15). The assigned proportion corresponds to

expected distribution of sample across data sources by the final study reporting year (see Table 14).

2. The number of primary outcome events in each exposure group were randomly drawn for each data source from a binomial distribution. In the binomial distribution, the number of trials was set equal to the estimated data source level sample size and the probability of success, assumed consistent across all countries, was set equal to the prevalence of the outcome in each exposure group, assuming that the true RR is 1 (no effect of exposure).
3. The estimated data source level log (RRs), their standard errors, and their 95% confidence intervals (CIs) were computed using a log-link Poisson regression (in place of log-binomial regression which tended to not converge) from the simulated number of events.
4. The data source level log (RRs) and their standard errors were entered into a fixed-effect[4] meta-analysis model where pooled 95% CIs were computed. The inverse-variance method was used for the meta-analysis. The meta-analysis was run using the *meta* package in R (53).

For **minimum required sample size**, the steps 2-4 were repeated 5,000 times for all sample sizes in a grid with precision of two live births. For each sample size, the proportion (which represents the power) of the 5,000 simulated 95% CI upper bounds that were smaller than the target RR of 2.5 was computed. The sample size for which this proportion was the closest to 80% was selected.

For **minimum detectable RR**, the steps 2-4 were repeated 5,000 times for the sample size equal to expected number of exposed live births in total across the data sources at the end of study period. For all RRs in a grid with precision of 0.02, the proportion (which represents the power) of the 5,000 simulated 95% CI upper bounds that were smaller than the corresponding RR was computed. The RR for which this proportion was the closest to 80% was selected.

For **expected power**, the steps 2-4 were repeated 5,000 times for the sample size equal to expected number of exposed live births in total across the data sources at the end of study period. The proportion (which represents the power) of the 5,000 simulated 95% CI upper bounds that were smaller than the target RR of 2.5 was computed.

9.5.3 Minimum required sample size

The required total sample size was estimated as the minimal sample size necessary to achieve 80% power to rule out a target threshold of RR 2.5 for the primary outcome (MCM). The minimum sample size per data source was calculated based on the expected percentage that the data source would contribute to the total sample size in the meta-analysis by the final study reporting year.

[4] Under the assumption of no study drug effect, RR must be equal to 1 in all countries, see Section 9.7.1.4.

Based on the meta-analysis approach described in Section 9.7.1.4, for the MCM outcome, a total number of 570 live births (190 tezepelumab and 380 comparator) using a matching ratio of 1:2, or 676 live births (169 tezepelumab and 507 comparator) using a matching ratio of 1:3 would be required to achieve at least 80% power to rule out an RR of 2.5 or greater.

Table 15 Data source level sample size percentages and required sample sizes for the analysis of the MCM outcome.

Data source	Percentage of the total sample size in the data sources for MCM analysis[1]	Required sample size per tezepelumab exposure group for meta-analysis of MCM	
		1:2 matching ratio	1:3 matching ratio
Denmark	4%	8	7
Sweden	11%	21	19
France	58%	108	96
USA	27%	53	47
In Total	100%	190	169

Abbreviations: USA: United States of America; MCM: Major Congenital Malformation.
[1] Based on the expected number of live births in women with severe asthma eligible for the analysis and exposed to tezepelumab by final study reporting year, as shown in Table 14.

9.5.4 Minimum detectable risk ratio

While the above calculation shows the sample size required to rule out a RR of 2.5 or greater, this study will extract data on all eligible patients which should lead to a larger sample size than indicated in the previous section. Therefore, the minimum detectable RR for 80% power was computed at the meta-analysis level based on the expected number of 441 exposed live births in total across the data sources at the end of study period (Table 14). The minimum detectable RR for MCMs is 1.79 for the 1:2 matching ratio and even lower at 1.74 using the 1:3 matching ratio (Table 16). These lower minimum detectable RRs will provide a more conservative value when examining the safety of the drug.

Table 16 Minimum detectable RR in the meta-analysis of MCM outcome for live births in women with severe asthma exposed to tezepelumab

Data sources included in the meta-analysis of MCM	Minimum detectable RR for the meta-analysis of MCM	
	1:2 matching ratio	1:3 matching ratio
According to uptake scenario 0.8-11.5%		
4 (all)	1.79	1.74

Abbreviations: MCM: Major Congenital Malformation.

9.5.5 Expected power

The expected power was computed at the meta-analysis level based on the expected number of 441 exposed live births in total across the data sources at the end of study period

(Table 14). The expected power to rule out an RR of 2.5 was >99% in both matching scenarios (Table 17).

Table 17 Expected power in the meta-analysis of MCM outcome for live births in women with severe asthma exposed to tezepelumab

Data sources included in the meta-analysis of MCM	Expected power for the meta-analysis of MCM	
	1:2 matching ratio	1:3 matching ratio
According to uptake scenario 0.8-11.5%		
4 (all)	>99%	>99%

Abbreviations: MCM: Major Congenital Malformation.

9.6 Data management

IQVIA (who will perform this PASS on behalf of AstraZeneca) will take responsibility for application for the study permits, obtaining necessary approvals (ethical or otherwise), and access to the study data. Generally, the data will be stored and analysed in accordance with local policy. All data used in this study will be in the form of electronic records, and the data holders collect and manage data according to their own standards.

The identification of the study population will be conducted by the individual data source holders according to the specifications given in Section 9.2. After the identification of the study population from different data sources, study data from each data source will be extracted. Data extraction will be conducted by the individual data source holders.

After data is extracted, the data holders will make data accessible to IQVIA, according to data permits in each specific country. The details of the data permits will be confirmed only once the data permits are granted. If the data permits allow, individual-level data will be accessed by IQVIA. However, individual-level data from some of the data holders (e.g., Carelon [USA]) cannot be accessed by IQVIA but will be managed and analysed by the data provider (e.g., HealthCore). All individual-level data accessible to IQVIA will have original personal identifiers replaced with a study identification number (SID). Thus, IQVIA will not have access to data that allow individuals to be directly identified. Data harmonisation between data sources will be ensured by the implementation of a common data model for all analyses.

IQVIA will adhere to all local and regional laws on data protection and privacy. IQVIA will also adhere to IQVIA standard operating procedures. Data management for this study will be conducted using standard IQVIA processes. IQVIA will maintain appropriate data storage, including periodic backup of files and archiving procedures and will comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all programmes.

The general principles for data management and statistical analyses will be described in detail in the SAP. Therein all data checks to be performed on completeness, plausibility and consistency of collected data will be described in detail with identification of data

discrepancies. IQVIA will perform all data management and statistical analyses using statistical software (Statistical Analysis System [SAS] version 9.4 or later, STATA or R [version 4.1.1 or later]). The data providers conducting the data management and statistical analysis for the study will store the datasets and analytic programmes according to the data provider's procedures.

Full audit trail starting from raw data obtained from register holders and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses will be kept for inspection for 5 years after publication of results. The study may be inspected by the AstraZeneca's independent representative(s), scientific committee, or by the competent authorities.

9.7 Data analysis

All data analysis will be performed separately for each data source in the study population as defined in Section 9.2.2. The study population selection process will be reported using a STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) diagram that shows cohort and sub-population exclusions step by step, as defined in Sections 9.2.2.1 to 9.2.2.3.

All study results will be presented separately for each data source in the study reports, as appropriate when data become available. The full study results for all data sources, including all descriptive, comparative, and sensitivity analyses, as well as the meta-analysis results will be provided in the final report. Details of the study reports are described in Section 12.

A full description of the analytical approach will be developed and described in the SAP. Also details on data derivations, category definitions, analyses, and presentation of the study results will be provided in the SAP. The SAP will be finalised prior to the conduct of the study analyses.

In this study, methods commonly used in non-interventional studies for handling missing data, such as imputation, complete case analysis or indicators for missing values, will be considered (54). The SAP will describe the full details on handling missing data that will include the methods for identifying where missing data methods should be applied, the techniques for identifying the type of missing information and the appropriate imputation methods to be used, if any.

Some data sources apply small cell masking rules as a data protection restriction. These rules define the lower limit for the number of units that can be reported in a table cell. The lower limit varies between data sources. For example, Denmark has a limit of 5, US (Carelon) has a limit of ten and France has a limit of 11. The small cell masking rules of the data sources will be considered when presenting the study results for descriptive and comparative analysis. If the small cell masking rules apply, the descriptive analysis results for the relevant study outcomes might be provided as ranges, corresponding to lower and upper boundary values

implied by actual masking. The comparative analysis results for the relevant study outcome will be provided, if no inadvertent unmasking of small numbers can be ensured.

9.7.1 Methods

9.7.1.1 Accounting for potential confounding

Confounding will be accounted for separately in each data source using a multiple step adjustment methodology. In a first step, propensity scores (PS) will be computed for each separate study cohort. In a second step, exact matching between exposed and unexposed pregnancies will be carried out for a set of three criteria (see *Adjustment algorithm* section below). In a final step, PS adjustment will be applied to the exposed and unexposed pregnancies selected in Step 2. The following section further describes PS methodology and the adjustment methodology.

PS methodology

Methods based on PS are frequently used in non-interventional studies to control for confounding when estimating treatment effects (55). PS methods allow for control of measured confounding in treatment effects when the measured confounders related with the treatment are correctly modelled in the PS (56). Although very frequently PS is estimated employing a logistic regression model, in general, PS can be estimated using any appropriate statistical or machine learning method. In this study, a method to estimate the PS other than logistic regression (e.g. gradient boosting machines) might be used (57), if it improves the estimates or provides more robustness with respect to model misspecification. The potential confounders listed in Table 11 will be used in the PS modelling as appropriate.

In non-interventional studies, the widely used PS methods in adjusting for confounders include PS matching and PS weighting. In PS matching, each patient within the study treatment is matched either to one (i.e. 1:1 matching) or more (i.e. 1:n matching) patients who have the same or a similar PS value (58). In PS matching, the patients in the study treatment cohort who do not have a close enough match in the comparator treatment cohort need to be excluded from the analysis (58).

In this study, PS matching will be used. Each patient in the tezepelumab exposed cohort may be matched to more than one patient (e.g., 1:2 or 1:3 matching) to increase statistical power. An additional benefit of using PS matching is that it does not imply any restrictions on the use of methods in the meta-analysis. Thus, PS matching allows one to use methods such as the Mantel-Haenszel that is generally considered preferable to the generic inverse-variance method in case of fixed-effect meta-analysis of rare events (59). If PS matching significantly reduces the sample size, PS weighting in combination with exact matching will be further investigated. More details on the PS methods that will be used for this study will be provided in the SAP.

The number of confounders included in the PS model will depend on available sample size, to avoid unreliable estimates. Additionally, comparative analysis using PS matching will be performed only if the PS model fit is considered appropriate and if the covariate balance in the adjusted cohorts is sufficient. The SAP will provide a list of scenarios as to when the PS matching algorithm will no longer be suitable/beneficial due to limitations that may arise in PS estimation and matching and what alternatives will be considered, including resorting to exact matching and possible adjustment of unbalanced variables, if feasible. Should there remain some imbalance between exposure cohorts, details will be added in the limitations section. To check the overlap and similarity of the PS distributions between the exposure cohorts (exposed to tezepelumab and unexposed to tezepelumab, as defined in Section 9.2.4), the distribution of the PS in the study sub-cohorts by exposure will be examined (61). To evaluate the balance of covariates between the exposure cohorts, the characteristics of the study sub-cohorts will be tabulated by exposure before and after application of PS matching. Covariate balance will be assessed by examining the distribution of variables in the study sub-cohorts using summary statistics, and by estimating standardised mean differences (SMD) for each variable between the exposure cohorts. No statistical tests are planned for this comparison, but variables with standardised differences above 0.1 will be further evaluated and may lead to a re-evaluation of the PS estimates. Further details will be provided in the SAP.

PS matching algorithm

PS matching will be performed separately within each data source and for each study cohort that is derived from the study populations as defined in Section 9.2.2.3.

First, the PS will be computed using all eligible exposed and unexposed pregnancies in the study cohort.

After PS computation, individuals will be stratified using the following list of variables (exact matching part of the algorithm):

- Age of the mother at LMP
- Calendar year of pregnancy
- Treatment for severe asthma in the same trimester

The list of exact matching variables can be revised or modified if difficulties to find matches significantly reduce the sample size or if any other variables are considered more important at the time of analysis.

In the second part, additional potential confounders (Table 11) will be accounted for using PS methodology as described above. PS matching will be performed within each of the strata identified above. Further details about the implementation of the algorithm and possible alternatives will be provided in the SAP.

9.7.1.2 Descriptive analyses

In descriptive analyses, the total number of patients at risk and the number of events for each study outcome in the study sub-cohorts (exposed to tezepelumab and unexposed to tezepelumab as defined in Section 9.2.2.3) will be tabulated before and after application of confounder adjustment as described above. Analyses by trimester of exposure will be conducted for secondary objectives 3-6 in addition to the overall analysis. The measures of study outcomes will be estimated before and after application of PS matching to obtain crude and adjusted estimates, respectively. The measures of study outcomes, with associated 95% CIs, will be estimated for the study sub-cohorts exposed to tezepelumab and unexposed to tezepelumab (as defined in Section 9.2.2.3). In this study, prevalence by exposure status to tezepelumab during pregnancy will be assessed for the following study outcomes: MCM (objective 1 & 2), foetal death (objective 3 & 7), mCM (objective 4 & 8), adverse pregnancy outcomes (objective 5 & 9), and adverse birth outcomes (objective 6 & 10).

In addition, descriptive analysis will be conducted for study objective 11 to describe the demographic and clinical characteristics of pregnancies and infants (defined in Section 9.3.3) in the study sub-cohorts exposed to tezepelumab and unexposed to tezepelumab as defined in Section 9.2.2.3. For the main cohort, additional analysis by trimester of exposure will be conducted. For the descriptive analysis of continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1^{st}) and upper (3^{rd}) quartiles, as well as 5^{th} and 95^{th} percentiles will be presented. For categorical variables, the numbers and percentages of observations for each of the categories and numbers and percentages of missing values will be presented in descriptive analysis.

9.7.1.3 Comparative analyses

For the comparison of the exposure cohorts exposed to tezepelumab and unexposed to tezepelumab within the study cohorts (as defined in Section 9.2.2.3), the association metrics of RRs will be estimated. The RRs will be estimated if there is at least one outcome event observed per exposure group. Both crude and adjusted RRs will be estimated for each relevant study outcome. Crude and adjusted RRs will be estimated before and after PS modelling (exact and PS matching), respectively. The statistical model to be used for the estimation of the crude and adjusted RRs will be the log-binomial regression or the robust, modified Poisson regression as seen appropriate for the study data (62,63). If covariate balance is not achieved through PS matching, additional adjustment by using these covariates in the outcome regression model will be considered. Additionally, any other potential confounders (or risk factors) that are not included in the PS model but are hypothesised to be associated with the study outcomes may be used as covariates in the statistical models. Further details on the statistical models will be provided in the SAP.

9.7.1.4 Meta-analysis

Data source level analyses' results will also be combined in a meta-analysis. Meta-analysis will be performed only for the primary study objective. The meta-analysis will be performed

using effect size estimates from all study countries for which RR were estimated, so long as RR estimates were available from a minimum of three countries.

Prior to conducting the meta-analysis, heterogeneity across the study countries will be assessed using:

- Cochran's Q test (significance level: 0.1). Q is calculated as the weighted sum of squared differences between individual studies and the pooled value across studies.

- The I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity) (59). I^2 is calculated as follows:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

where Q is Cochran's statistic and 'df' is its degrees of freedom. The I^2 is a statistic that estimates the percentage of variance in effects attributable to study heterogeneity rather than sampling error.

- The τ^2 statistic

Results of the meta-analysis will be derived using fixed-effect or random-effects model. The choice of the primary meta-analysis approach will be based on the investigation of the effect heterogeneity between countries (which will be evaluated starting from the second interim report). Irrespective of the chosen primary meta-analytic approach, full results from both random-effects and fixed-effect models, as suggested in (59), will be presented to assess the robustness of results with respect to analytical approach. Data source-specific results and the overall combined estimate will be presented in forest plots including effect size and 95% CI for each study country included in the analysis. Further details will be presented in the SAP.

9.7.2 Primary objectives

The analysis for the primary study objectives will be conducted separately for each data source. In addition, meta-analysis will be performed including the individual data sources that have enough outcome events to conduct the comparative analysis as described in Section 9.7.1. The description of the analysis to be conducted, using methods outlined in Section 9.7.1, for each primary study objective is provided in the following sections.

Objective 1

The analysis to estimate the risk of MCM in live and non-live offspring, and TOPFA among women with severe asthma who were exposed or unexposed to tezepelumab during first trimester of pregnancy (study objective 1) will be performed using the objective-specific cohort as defined in Section 9.2.2.3. The crude and adjusted prevalence (with corresponding 95% CI) of the MCM in live births, stillbirths, and TOPFA among women with severe asthma who were exposed or unexposed to tezepelumab during first trimester of pregnancy will be

estimated separately. The crude prevalence (i.e., risk) will be calculated as the total number of live and non-live offspring, or TOPFA with MCM divided by the total number of live and non-live offspring, or TOPFA. In the calculation of the adjusted prevalence (i.e., risk), the adjusted cohort will be used.

Objective 2

To estimate the relative risk of MCM in live and non-live offspring, and TOPFA among women with severe asthma exposed to tezepelumab during first trimester of pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during first trimester of pregnancy (study objective 2), the crude and adjusted RRs (with corresponding 95% CIs) will be estimated using the objective-specific cohort as defined in Section 9.2.2.3. The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1.3. The adjusted RR and its 95% CIs will be estimated by using a regression model and using PS matching as described in Section 9.7.1.1. In addition, meta-analysis on the data source-specific crude and adjusted RRs of MCM will be conducted as described in Section 9.7.1.4.

9.7.3 Secondary objectives

Using methods outlined in Section 9.7.1, the analysis for the secondary study objectives will be conducted separately for each data source. The description of the analysis to be conducted for each secondary study objective is provided in the following sections.

Objective 3

The analysis to estimate the risk of foetal death (composite of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy (study objective 3) will be performed using the objective-specific cohort as defined in Section 9.2.2.3 overall and by trimester of exposure. The crude and adjusted prevalence (with corresponding 95% CI) of the foetal death in pregnancies among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy will be estimated separately. The crude prevalence (i.e., risk) will be calculated as the total number of pregnancies with foetal death divided by the total number of pregnancies. In the calculation of the adjusted prevalence (i.e., risk), the adjusted cohort will be used.

Objective 4

The analysis to estimate the risk of mCM in live births among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy (study objective 4) will be performed using the objective-specific cohort as defined in Section 9.2.2.3 overall and by trimester of exposure. The crude and adjusted prevalence (with corresponding 95% CI) of the mCM in live births among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy will be estimated separately. The crude prevalence (i.e., risk)

will be calculated as the total number of live births with mCM divided by the total number of live births. In the calculation of the adjusted prevalence (i.e., risk), the adjusted cohort will be used.

Objective 5

The analysis to estimate the risk of individual adverse pregnancy outcomes (as defined in Section 9.3.2) in pregnancies among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy (study objective 5) will be performed using the objective-specific cohort as defined in Section 9.2.2.3 overall and by trimester of exposure. The crude and adjusted prevalence (with corresponding 95% CI) of the individual adverse pregnancy outcomes will be calculated for cases where the mother was exposed to tezepelumab during pregnancy and for cases where the mother was unexposed to tezepelumab during pregnancy. The crude prevalence (i.e., risk) will be calculated as the total number of each individual adverse pregnancy outcome divided by the total number of pregnancies. The adjusted prevalence (i.e., risk) will be calculated using the adjusted cohort.

Objective 6

The analysis to estimate the risk of individual birth outcomes (as defined in Section 9.3.2) in pregnancies among women with severe asthma who were exposed or unexposed to tezepelumab during pregnancy (study objective 6) will be performed using objective-specific cohort as defined in Section 9.2.2.3 overall and by trimester of exposure. The crude and adjusted prevalence (with corresponding 95% CI) of the individual birth outcomes will be calculated for cases where the mother was exposed to tezepelumab during pregnancy and for cases where the mother was unexposed to tezepelumab during pregnancy. The crude prevalence (i.e., risk) will be calculated as the total number of each individual birth outcome divided by the total number of pregnancies. The adjusted prevalence (i.e., risk) will be calculated using the adjusted cohort.

Objective 7

To estimate the relative risk of foetal death (composite outcome of miscarriage, stillbirth, and ectopic pregnancy) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy (study objective 7), the crude and adjusted RRs (with corresponding 95% CIs) will be estimated using the objective-specific cohort as defined in Section 9.2.2.3. The crude RR and its 95% CI will be estimated using a regression model as specified in Section 9.7.1.3. The adjusted RR and its 95% CIs will be estimated by using a regression model and using PS adjustment as described in Section 9.7.1.1.

Objective 8

To estimate the relative risk of mCM (as defined in Section 9.3.2) in live offspring of women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy (study objective 8), the crude and adjusted RR (with corresponding 95% CI) will be estimated using the objective-specific cohort as defined in Section 9.2.2.3. The crude and adjusted RRs and their corresponding 95% CIs will be estimated using regression and PS matching.

Objective 9

To estimate the relative risk of individual adverse pregnancy outcomes (as defined in Section 9.3.2) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy (study objective 9), the crude and adjusted RRs (with corresponding 95% CI) will be estimated using the objective-specific cohort as defined in Section 9.2.2.3. The crude and adjusted RRs and their corresponding 95% CIs will be estimated using regression and PS matching.

Objective 10

To estimate the relative risk of individual birth outcomes (as defined in Section 9.3.2) in pregnancies among women with severe asthma exposed to tezepelumab during pregnancy compared to women with severe asthma exposed to SOC for severe asthma and unexposed to tezepelumab during pregnancy (study objective 10), the crude and adjusted RRs (with corresponding 95% CI) will be estimated using the objective-specific cohort as defined in Section 9.3.2. The crude and adjusted RRs and their corresponding 95% CIs will be estimated using regression and PS matching.

Objective 11

To describe the demographic and clinical characteristics of pregnant women with severe uncontrolled asthma who were exposed or unexposed to tezepelumab during any trimester of pregnancy and their live births (study objective 11), the descriptive analysis of the demographic and clinical characteristics (as defined in Section 9.3.3) by exposure cohort will be provided as described Section 9.7.1.2. The demographic and clinical characteristics of the pregnant women and their live births will be presented separately for each study cohort and sub-cohorts as defined in Table 5 (Section 9.2.2.3). For the main cohort (all pregnancies), analysis by trimester of exposure will also be presented. No statistical testing comparing the distribution of demographic and clinical characteristics distribution between the study cohorts or sub-cohorts is planned.

9.7.4 Sensitivity analyses

Exclusion of pregnancies with in-utero exposure to other biologic agents

To estimate the relative risk of MCM in live and non-live offspring, and risk of selected foetal death outcomes (composite of ectopic pregnancy, miscarriage, and stillbirth) among women with severe asthma exposed to tezepelumab (excluding other biologics) anytime during the exposure window compared to women with severe asthma unexposed to tezepelumab but exposed to SOC (no biologics) for severe asthma.

Expanded exposure window

To ensure all pregnancies with potential exposure to tezepelumab are included in the exposed cohort, an alternative exposure definition include pregnancies among women with severe asthma exposed to tezepelumab during a 130-day clearance period before LMP, i.e., pregnancies with at least one prescription/administration of tezepelumabd during this period. Clearance of 130 days is calculated back from conception two weeks after LMP.

Timing of treatment for severe asthma during pregnancy

To maximise comparability between pregnant women exposed to tezepelumab and pregnant women unexposed to tezepelumab but exposed to SOC for severe asthma during pregnancy, trimester of exposure will be included as an additional exact matching variable.

9.8 Quality Control

The study will be conducted according to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) Guidelines and IQVIA standard operating procedures. At the study level, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System.

According to the policies and procedures above, a Quality Control (QC) plan for the study will be developed and executed, which will include QC on the protocol in general, study methodology, SAP, programming, data management and analysis, and study report including study results and conclusions.

Furthermore:

- The study QC plan will establish ownership for the execution of the individual QC steps. The principle of the independence of QC applies.
- IQVIA project management will ensure that individuals responsible for the execution of specific QC steps will have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the QC plan will be documented, and include the required corrective actions, if any.

- The execution of any required corrective action will be documented.
- Datasets and analytic programmes will be stored according to IQVIA and data holder procedures, with access restricted to authorised study personnel at the respective entities.
- Upon data extraction, a data quality assessment will establish the availability and level of missingness for key variables.

Also, the study Project Manager will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure RWI_WI_PM0035 "Real-World Project-Specific Training and Staff Transition".

The executed QC plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.

9.9 Limitations of the research methods

This study will assess safety outcomes in pregnant women with severe asthma comparing exposure to tezepelumab to SOC for severe asthma, including other biologics. Potential limitations of the study are discussed below.

Identification of severe asthma and potential under-ascertainment in unexposed pregnancies

Asthma severity is defined in this study according to the GINA treatment classification. Severity of asthma, including relevant symptoms and lung function is not consistently recorded in the study databases and an algorithm based on treatment is employed instead. Asthma severity will be measured through an algorithm including requirements to controller and reliever treatments used in high-intensity treatment, combined with additional information on exacerbations proxied by hospitalisations or OCS usage, as well as any over-use of SABA treatment. As severity of asthma is usually indicated by episodes of uncontrolled asthma or asthma exacerbation, a comprehensive window of inclusion assessment starting one year prior to LMP and ending the day before the EoP was set to allow an equivalent chance of detection of disease among the groups exposed or unexposed to tezepelumab, minimising, thus, the possibility of detection bias.

Patients treated with biologics for severe asthma will be included regardless of other asthma treatment, hospitalisations, OCS or SABA use.

In the absence of biologic treatment (which is only indicated for severe asthma), unexposed pregnancies were required to be exposed to high-intensity treatment during pregnancy and have at least one of the proxies for uncontrolled asthma during the past 12 months (hospitalisation, two or more OCS prescriptions, or over-use of SABA). To ensure patients with treatment discontinuation and subsequent exacerbations will not be considered, uncontrolled asthma is only identified retrospectively from SOC for severe asthma.

Misclassification of exposure

In addition to pregnancies with tezepelumab exposure between LMP and end of first trimester or EoP (depending on outcome of interest), a sensitivity analysis also includes pregnancies where tezepelumab treatment occurred only in the assigned pre-LMP period. It could be that this represents little exposure for that particular pregnancy, leading to a potential attenuation of the risk estimates. However, the main analysis, that excludes such pregnancies, is designed to minimise any such potential exposure misclassification bias.

The identification of critical windows of exposure in-utero will provide insights to possible mechanisms of the outcomes of interest. Therefore, in this study an approach to examine the effect of exposure in-utero to tezepelumab in specific pregnancy trimesters is proposed. It is recognised that this approach could result in small sample sizes impairing the ability to identify statistically significant associations.

Considering the s/c administration as the current route of administration of tezepelumab, definition of exposure may be challenging. Outpatient visits with a recording of the relevant ATC and/or procedure codes, in addition to the prescribing/dispensing records may be needed to determine the exposure status of study subjects. This could potentially lead to misclassification of the exposure (i.e., use of tezepelumab may be under-detected, and SOC for severe asthma prescriptions may overestimate actual exposure). Such a potential bias would yield attenuated measures of association, since the exposure status of the cohorts would not be fully established, and the cohorts of exposed and non-exposed pregnancies will therefore be more similar. Based on the feasibility assessment, prescriptions and administration will be captured in different settings (outpatient clinics, in hospital setting, outpatient pharmacies) in each data source. Of note, drugs dispensed in inpatient settings are not available in Sweden and France. However, tezepelumab is expected to be captured in outpatient settings and pharmacy dispensations. Additionally, tezepelumab is not recommended during exacerbations, which may suggest limited use during hospitalisations.

Misclassification of outcomes

Insufficient accuracy and specificity of codes used to identify study outcomes could lead to outcome misclassifications. For instance, for pregnancy terminations the reason for termination is not always recorded, preventing an accurate classification of one of the study outcomes (MCM as reason for TOP [TOPFA]). The likelihood that TOPFA would be recorded differently in the data sources across exposed and unexposed pregnancies is low. For this reason, only TOPs with a recorded reason for termination are included in the analysis of MCM. Also, early pregnancy loss that does not require hospitalisation is equally likely to be underreported, however this is likely to be similar for both exposed and unexposed pregnancies. Such misclassification would lead to an overall underestimation of the outcome rates.

Gestational age will be calculated from LMP as reported in maternal records or calculated from gestational age at EoP event or estimated by ultrasound scan as part of the antenatal care. Miscalculation of LMP may lead to misclassification of outcomes (miscarriage vs stillbirth,

PTB, and SGA) or of the period of exposure. The LMP is also subject to accuracy of recall by the woman, regularity of her cycles, and variations in the interval between bleeding and anovulation. When based on gestational age, the degree of misclassification depends on the method and accuracy of the gestational age assessment. However, the misclassification is expected to be within the range of days for most patients and is expected to be similar in exposed and unexposed pregnancies.

Confounding by indication

Confounding by indication cannot be ruled out. As usual for observational studies based on secondary use of healthcare data, the detailed reason for treatment prescription remains unknown and it could be that exposed and unexposed pregnancies differ by disease severity and other patient characteristics that could confound the results. For example, treatment for severe asthma such as OCS can have the potential for poor pregnancy outcomes, i.e., congenital anomalies and increased risks of PTB, LBW, or pre-eclampsia (64). It is believed that the key approaches to include comparable unexposed pregnancies:

- Common inclusion criteria for severe asthma for the total study population
- Matching by age of the mother at LMP, severe asthma treatment by trimester and calendar year of pregnancy
- PS matching/adjustments for further potential confounders

While these approaches will minimise potential confounding, residual confounding may remain. In addition, the inability to capture suitable matches in data sources with limited sample sizes might limit the extent to which confounding is accounted for.

Data on some potential confounders may not be available or poorly documented, such as poor treatment compliance (of SOC for severe asthma treatments), behavioural and lifestyle characteristics (i.e., alcohol, smoking and substance abuse), socioeconomic disparities, and genetic factors. Likewise, in addition to maternal disease, paternal disease history can be an important predictor of the risk of adverse pregnancy outcomes because of shared environmental and paternal genetic risk factors. However, paternal risk factors are likely to be of a smaller magnitude than maternal severe asthma during pregnancy. For this study, no paternal data will be available as linkage to paternal data is not possible for most data sources.

Evolving time trends

The study time period is expected to be about 10 years. Patient baseline profile and SOC for severe asthma may evolve over time, and exposure to tezepelumab or to SOC treatment can occur differentially over time. For instance, tezepelumab is a drug with market launch date between 2022 and 2024, and thus, a lower proportion of patients treated with this biologic is expected to be observed in early years of the study, and a higher proportion of patients on SOC for severe asthma is expected. As biologics may become more common for treatment of

severe asthma over the years, this trend may change. To mitigate time trend bias, calendar years will be accounted in descriptive and comparative analyses.

Existing database studies and differences between data sources

Differences in databases due to specific nature and reason for data capture (claims data, administration etc) as well as differences in healthcare systems and healthcare practices will be considered. For some data sources, there are reporting restrictions on small number of events. For example, in Danish data sources, observations with less than five cases cannot be reported, and may require cross masking of other results to prevent calculation of small number observations. This is because of the potential of patient identification. This may be a potential limitation for analyses that require stratifications, such as the risk of CM by different pregnancy trimesters. In these instances, minimum and maximum values cannot be reported.

Data in the study databases are collected only for administrative purposes, so some medical information not directly related to reimbursement may be incomplete or not available at all. The accuracy of the available information may vary between data sources. This can affect the measurement of exposure to tezepelumab, the outcomes of interest and/or the covariates. To ensure that the accuracy of the retrieved information is acceptable, all data will be reviewed for possible inconsistencies or implausible information. Also, missing information may vary between data sources, and whenever applicable, missing information will be reported.

Information on all the study outcomes and individual covariates may not be available in all databases, in particular lifestyle variables and the up to 1-year assessment of growth of the infant.

Specificities of each database have been described in the data source section and will be further described in the local feasibility assessment, and limitations will be addressed in the study report.

General advantages of secondary data base studies

Secondary use of data collected and maintained in electronic databases offers several scientific and operational advantages for conducting a pregnancy study, including specifically:

- The possibility of removing information and selection bias that may affect primary data collection in a self-selected population of pregnant women and their infants.
- The opportunity to study all the exposed and non-exposed pregnancies (i.e., no individual informed consent for this study is required) in women with severe asthma.
- The potential to optimise statistical efficiency with a 1:n (e.g., 1:3) match of exposed and non-exposed pregnancies.

Additionally, national databases such as those from Nordic countries are known to be representative of the population of the country, typically containing lifetime data of patients

and have demonstrably been used for research to obtain insights into the real-world use of pharmaceutical products.

General disadvantages of pregnancy studies in secondary data base studies

As pregnancies are identified by a recorded outcome of pregnancy (delivery, miscarriage, termination, or diagnosis of ectopic pregnancy), the study population will be subject to immortal time bias. Pregnancies with no recorded outcome, either due to loss to follow-up or not requiring medical attention, will be missed from the study population. This is a general issue and unlikely to affect exposed and unexposed differently.

9.10 Other aspects

None

10. PROTECTION OF HUMAN SUBJECTS

This non-interventional study involves the use of pseudonymised electronic healthcare records and does not affect the treatment of the patients. The study is conducted in accordance with the ENCePP Code of Conduct (65), the Guidelines for GPP (66), the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations. AstraZeneca, the Contract Research Organisation (CRO), other participating entities and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety.

The CRO will receive pseudonymised data including dummy SIDs only. AstraZeneca will not have access to the patient-level data at any time of the study.

Due to data protection restrictions in the study countries (e.g., Denmark), the cells in tables with few observations need to be masked. Thus, cells in tables must include a minimum of five observations and summary statistics can only be calculated if a minimum of 5 observations are used. In addition, minimum and maximum values may not be reported due to the protection of subjects' privacy in specific study countries (e.g., Denmark).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This PASS is designed to investigate the risk of MCM (major and minor separately), as well as adverse pregnancy, birth, and infant outcomes (up to 1 year of age) in the offspring of women with severe asthma exposed *in-utero* to tezepelumab and SOC for severe asthma. According to Good Pharmacovigilance Practices (GVP) Module VI.C.1.2.1.2. "Non-interventional post-authorisation studies with a design based on secondary use of data", suspected adverse reactions reporting, in the form of Individual Case Safety Reports, is not required (67). Safety data addressing the objectives of the study will be summarised in the final study report.

11.1 Independent Ethics Committee/Institutional Review Board

The study protocol will be submitted to the responsible IRB/Independent Ethics Committee for its review/approval whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to Ethics Review Boards (ERB) and regulatory authorities as required by local laws and regulations.

When the approval has been granted, the formal procedure of applying for access to and retrieval of patient-level health information can be performed to each governing health authority in the respective countries. A prerequisite for approval from an ERB is that the research project is thoroughly described in a study protocol with a clear scientific objective and purpose.

The overall ethical review and data access time is expected to vary between 3 and 18 months, depending on the data source/country.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Progress Report

A progress report is planned for May 2025 which is 12 months after PRAC endorsement of protocol which is currently assumed to be Q2 2024. It will contain a status update of database applications and any relevant amendments pertaining to database applications. Database access may take between 7 to 18 months; therefore, the progress report may not include study population specific patient numbers from each data source. If feasible, data source-specific counts for the uptake of tezepelumab among women of childbearing potential and/or during pregnancy will be included. Study population counts will not be included if the identification of severe asthma requires full data extract.

12.2 Interim Analyses and Reporting

Two interim reports will be submitted 46 (March 2028) and 82 (March 2031) months after PRAC endorsement of the protocol. The first interim report will monitor the uptake of tezepelumab in the planned study populations, update sample size assumptions, and describe the study outcomes among individuals exposed to tezepelumab in the study populations,,, using all available data at the time of reporting. The first interim report will only contain descriptive analyses relevant to primary and secondary objectives. The second interim report will similarly provide monitoring of the tezepelumab uptake and describe the study outcomes among individuals exposed and unexposed to tezepelumab in the study populations to form a comparator cohort, as relevant to the descriptive primary and secondary objectives from all available data at the time of reporting. Neither of the interim reports will include comparative analyses, sensitivity analyses, or meta-analyses.

12.3 Final Analyses and Reporting

The final study report is planned for March 2034 and will include all descriptive, comparative, sensitivity, and meta-analytic analyses for all data sources. The ability to achieve this milestone will be reviewed in the interim reports, when assumptions of tezepelumab uptake among pregnant women will be assessed.

The interim/progress report(s) and the final study report will be written in accordance with the GVP guidelines module VIII (68), and the RECORD-PE Checklist (69).

In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), and Regulation No 1027/2012, information about this PASS will be entered into the publicly available EU PAS Register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

12.4 Publications

Based on the study report, the principal investigator, and co-investigators (together referred to as "investigators"; members of the responsible parties and possible other contributors approved by the responsible parties) will prepare (a) scientific manuscript(s) for academic publication. The responsible parties decide the publication forums.

The investigators will inform AstraZeneca in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by AstraZeneca.

The principal investigator and AstraZeneca are committed to ensuring that authorship for all publications comply with the criteria defined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors, updated April 2010. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content. These conditions apply equally to external investigators and to employees of AstraZeneca.

Within 3 months following the final study report, an abstract of the study findings will be made available to the public through the EU PAS Register (The EU electronic Register of Post-Authorisation Studies). According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial, or personal interests. AstraZeneca is entitled to view the final results and interpretations prior to submission for publication in the EU PAS Register, and to comment on these without unjustifiably delaying the publication. AstraZeneca will maintain the right to delay publication in order to protect intellectual property rights. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period due to pending response from the peer-review process.

In line with GVP Module VIII, AstraZeneca will communicate with EMA and the competent authorities of the Member States in tezepelumab is authorised and share the final manuscript of any article within two weeks after first acceptance for publication. This will allow competent authorities to review the results and interpretations in advance of publication.

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Appendix A List of stand-alone documents

None

Appendix Table 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	<< >>	*<<DD Month YYYY>>*	<< >>
2	<< >>	*<<DD Month YYYY>>*	<< >>
3	<< >>	*<<DD Month YYYY>>*	<< >>

Appendix B ENCePP Checklist for Study protocols

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:
A Non-Interventional Multi-Database Post-Authorisation Study to Assess Pregnancy-Related Safety Data from Women with severe asthma Exposed to Tezepelumab

EU PAS Register® number: Study not registered **Study reference number (if applicable): D5180R00010**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[5]	☒	☐	☐	6 & 9.2.1
1.1.2 End of data collection[6]	☒	☐	☐	6 & 9.2.1
1.1.3 Progress report(s)	☒	☐	☐	6 & 12.1
1.1.4 Interim report(s)	☒	☐	☐	6 & 12.2
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6 & 12.3

[5] 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.

[6] Date from which the analytical dataset is completely available.

Comments:

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)	☒	☐	☐	7.4-7.6
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.5
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

2.1.4 Mainly descriptive study

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8 & 9.7
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))	☒	☐	☐	9.7.1.3
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)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.3
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.4

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

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)	☒	☐	☐	9.3.1 & 9.7.5
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1.1 & 9.3.1.2
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1.2

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?	☒	☐	☐	8 & 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
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, subgroup analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:	☒	☐	☐	9.4
	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

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				9.4
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	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	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.1.2
10.4	Are stratified analyses included?	☒	☐	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1.1
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4

Comments:

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

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?	☒	☐	☐	9.9
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).	☒	☐	☐	9.9
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)	☒	☐	☐	9.2.1 & 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	11.1
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?	☒	☐	☐	12.4

Comments:

Name of the main author of the protocol: PPD (epi) & PPD (stats)

Date: dd/Month/year 31/10/2023

Signature: PPD

Appendix C Additional information on selected data sources and availability of key variables

Appendix Table 2 Selection of data sources based on feasibility assessment and data availability.

Country	Data source	Selected	Key findings from feasibility assessment	Rationale for decision
Denmark	**National Registers**	**Yes**	• Substantial female asthma patient populations of childbearing age. • Uptake of tezepelumab currently unavailable due to market entry dates. • Uptake of biologic comparator available. • Mother-offspring linkage fully available (exact deterministic linkage). • Temporal anchors fully available. • Partial completeness of at least two outcome variables expected (termination of pregnancy, spontaneous abortion).	Included following feasibility assessment due to ability to capture tezepelumab and other biologics, expected sample size, and overall availability of key variables (i.e., outcomes, covariates, temporal anchors)
Finland	**National Registers**	No	• Female asthma population unknown. • Uptake of tezepelumab currently unavailable due to market entry dates. • Uptake of biologic comparator available. • Mother-offspring linkage fully available (direct linkage). • Temporal anchors fully available. • Partial completeness of at least one outcome variables expected (pre-eclampsia).	Excluded after feasibility assessment due to expected low sample size.
France	**French National Health Data System (SNDS)**	**Yes**	• Substantial female asthma patient population (captured with long-term disease status, i.e., persistent severe asthma). • Uptake of tezepelumab currently unavailable due to market entry dates. • Uptake of biologic comparator available. • Mother-offspring linkage available for approximately 96% of pregnancies (deterministic linkage). • Temporal anchors fully available.	Included following feasibility assessment due to ability to capture tezepelumab and other biologics, expected sample size, and overall availability of key variables (i.e., outcomes, covariates, temporal anchors)
Germany	Statutory Health Insurance (SHI)	No	• Substantial female asthma patient population of childbearing age. • Uptake of tezepelumab currently unavailable due to market entry dates. • Uptake of biologic comparator available. • Mother-offspring linkage is not available in SHI. • Two temporal anchors not available (last menstrual period, infant follow-up for 12-months). • Partial completeness of at least one outcome variable expected (birth weight).	Excluded after feasibility assessment due to unavailability of key variables (infant outcomes of interest, covariates, temporal anchors)
Spain	Information System for the Development of Primary Care	No	• Substantial female asthma patient population of childbearing age. • Uptake of tezepelumab currently unavailable due to market entry dates. • Uptake of biologic comparator unavailable. • Mother-offspring linkage available for 70% of live births (deterministic linkage). • High risk pregnancies are followed at secondary care, and data on hospital outpatient appointments during pregnancy are not available. • Two temporal anchors partly available (gestational age, last menstrual period).	Excluded after feasibility assessment due to expected low sample size and inability to capture outpatient information on high risk pregnancies. Additionally, some key variables (outcomes of interest, covariates, temporal anchors) are unavailable.

	Research (SIDIAP)		• Partial completeness of at least two outcome variables expected (TOPFA, EC-section).	
Sweden	**National Registers**	**Yes**	• Substantial female asthma patient population of childbearing age. • Uptake of tezepelumab has been confirmed as beginning in March 2023 and available in this dataset. • Mother-offspring linkage fully available (exact deterministic linkage). • Temporal anchors fully available. • Partial completeness of at least one outcome variable expected (spontaneous abortion).	Included following feasibility assessment due to ability to capture tezepelumab and other biologics, expected sample size, and overall availability of key variables (i.e., outcomes, covariates, temporal anchors)
USA	**Carelon**	**Yes**	• Substantial female asthma patient population of childbearing age. • Uptake of tezepelumab and other biologics available. • Mother-offspring linkage available for approximately 73% of pregnancies (deterministic linkage). • One temporal anchor partly available (infant follow-up for 12-months).	Included following feasibility assessment due to ability to capture tezepelumab and other biologics, expected sample size, and availability of key variables (i.e., outcomes, covariates, temporal anchors)
	OPTUM Dynamic assessment of pregnancies and infants (DAPI)	No	• Substantial female asthma patient population of childbearing age. • Uptake of tezepelumab and other biologics available. • Mother-offspring linkage available for approximately 85% of pregnancies (deterministic linkage). • One temporal anchor partly available (infant follow-up for 12-months). • Partial completeness of at least one outcome variable expected (TOPFA).	Suitable but excluded after feasibility assessment due to MAH's preference to use Carelon due to geographical representation, logistical constraints, and slightly lower tezepelumab and asthma population counts to date.

Abbreviations: EC-section, Emergency caesarean section; DAPI, Dynamic Assessment of Pregnancies & Infants; SNDS, Système National des Données de Santé; SIDIAP, Information System for the Development of Primary Care Research; SHI, Statutory Health Insurance; MAH, Marketing Authorization Holder; TOPFA, Termination of pregnancy for foetal anomaly; USA, United States of America.

Appendix Table 3 End of Pregnancy (EoP) definitions in the data sources

	Denmark National Registers	France SNDS	Sweden National Registers	USA Carelon[1]
Live births				
EoP Definition	Date of delivery as defined by diagnosis or procedure code.	Date of delivery as defined by diagnosis or procedure code.	Date of delivery as defined by diagnosis or procedure code.	Algorithm with diagnostic and procedure codes applied to pregnancy episodes (70).
Source	MBR	PMSI	MBR	Carelon Research
Completeness and validity (if available)	Deliveries in Denmark (including live and still births from ≥22 completed gestational weeks are fully captured with high validity) (71).	Completeness of 99-100%. High degree of agreement on live births with official data (72). High validity (73).	Deliveries in Sweden (including livebirths and stillbirths from ≥22 completed gestational weeks) are fully captured (>99%) with high validity (74).	High completeness expected.
Still births				
EoP Definition	Date of delivery and MBR marker for stillbirth.	Date of delivery as defined by diagnosis or procedure code.	Date of delivery and MBR marker for stillbirth.	Algorithm with diagnostic and procedure codes.
Source	MBR	PMSI	MBR	Carelon Research
Completeness and validity (if available)	Full completeness after ≥22 completed gestational weeks.	Full completeness after ≥22 completed gestational weeks.	Full completeness after ≥22 completed gestational weeks.	High completeness after ≥20 completed gestational weeks. PPV=82.5% (75)
Terminations				
EoP Definition	Date of diagnosis or procedure code.	Additional diagnosis in relation to termination. Window to be determined in SAP.	Date of diagnosis or procedure code.	Algorithm with diagnostic and procedure codes.
Source	NPR	PMSI and DCIR	NPR	Carelon Research
Completeness and validity (if available)	100% completeness, high validity.	99-100% completeness with high validity. Prevalence consistent with official data (72). Terminations not managed in hospital settings are not captured.	100% completeness, high validity.	Low completeness (76). Validity Unknown.
TOFPA				
EoP Definition	Additional diagnosis codes in relation to termination. Window to be determined in SAP.	Additional diagnosis codes in relation to termination. Window to be determined in SAP.	Additional diagnosis in relation to termination. Window to be determined in SAP.	Algorithm with diagnostic and procedure codes.

Source	NPR	PMSI and DCIR	National Patient registry	Carelon Research
Completeness and validity	Unknown.	Unknown.	Unknown.	Low completeness (76). Validity Unknown.
Miscarriages[2]				
EoP Definition	Date of diagnosis or procedure code.	Date of diagnosis or procedure code.	Date of diagnosis or procedure code.	Algorithm with diagnostic and procedure codes.
Source	NPR	PMSI	NPR	Carelon Research
Completeness and validity (if available)	100% completeness with high validity of miscarriages treated in hospital (in or outpatient). Miscarriages not requiring medical attention or handled in primary care not captured.	99-100% completeness with high validity of miscarriages treated in hospital. Miscarriages not requiring medical attention or handled in primary care not captured. Prevalence is consistent with official data (72).	100% completeness with high validity of miscarriages treated in hospital (in or outpatient). Miscarriages not requiring medical attention or handled in primary care not captured.	Unknown.
Ectopic pregnancy				
EoP Definition	Date of diagnosis code.	Date of diagnosis or procedure code.	Date of diagnosis code.	Algorithm with diagnostic and procedure codes.
Source	NPR	PMSI	NPR	Carelon Research
Completeness and validity (if available)	100% completeness with high validity. Ectopic pregnancies successfully captured in the Danish NPR (77)	99-100% completeness with high validity. Prevalence consistent with French official data (72).	100% completeness, high validity.	High completeness. PPV of 75% (75)

Abbreviations: DCIR, Données de Consommation Interrégimes, EoP, End of Pregnancy; MBR, Medical Birth Register; PMSI, Programme de Médicalisation du Système d'Information; MCM, major congenital malformations; PPV, Positive Predictive Value; TOPFA, Termination of Pregnancy due to Foetal Anomalies; SAP, Statistical Analysis Plan; SNDS, Système National des Données de Santé; USA, United States of America.

[1]Pregnancy episodes, gestation periods, and pregnancy outcomes can be identified in the Carelon database through a series of algorithms using diagnosis and procedure codes. Algorithms used in similar claims databases are currently being validated and results are consistent with national estimates (78).

[2] Miscarriages for which medical attention was required. Miscarriages not requiring medical attention are poorly captured in all data sources.

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Appendix Table 4 Data Source-Specific Start of Pregnancy Dates

Countries	*Database*	*Start of pregnancy*
Denmark	*National Registries*	**Gestational age directly recorded in the database.** Gestational age is recorded at EoP and to some extent at antenatal contacts during pregnancy. LMP is available in the MBR ~99% completeness (79). Gestational age of non-live births is identified in the NPR at antenatal contacts during pregnancy or at an EoP event (80).
Sweden	*National Registries*	**Gestational age determined based on algorithm.** Gestational age is recorded in the MBR and is calculated by combining information from date of birth and estimated date of birth by ultrasound, LMP, or a postnatal assessment of gestational age in weeks and days (74). Gestational age of non-live births is identified in the NPR at antenatal contacts during pregnancy or at an EoP event. Completeness unknown. Gestational age is also available for TOPFA from the National Register of Congenital Anomalies
France	*SNDS*	**Gestational age directly recorded in the database.** Gestational age has been recorded exhaustively since 2010 in the PMSI for all births with high completeness and validity (72,73,81). For inpatient abortions and other pregnancy outcomes, the number of days after the LMP has been recorded exhaustively since 2012 (72).
USA	*Carelon*	**Gestational age determined based on algorithm.** Gestational age will be identified using diagnosis codes used for gestational age identified based on the closest encounter to the pregnancy outcome, adapted from previously validated algorithms (75,82). The potential use of a stepwise algorithm consisting of both deterministic and probabilistic algorithms will be considered. Start of pregnancy or first day of LPM can be estimated based on Z3A code and median LMP or previously published algorithms (83–86)).

Abbreviations: EoP, End of Pregnancy; ICD10, International Classification of Diseases 10th Edition; LPM, Last menstrual period; MBR, Medical Birth Register; PMSI, Programme de Médicalisation du Système d'Information; SNDS, Système National des Données de Santé; USA, United States of America.

Appendix Table 5 Data Source-Specific mother-baby linkage for live offspring

Countries	***Database***	***Mother-baby linkage***
Denmark	*National Registers*	Exact deterministic linkage with 100% coverage, as recorded in the MBR, based on one observation per infant including both infant and maternal unique personal identification (79). The unique identifier allows deterministic linkage to other National Registers. (87)
France	*SNDS*	Deterministic linkage with approximately 96% coverage in 2015. Linkage between maternal and neonatal data has been possible in the PMSI database by a common identifier shared by the mother and her child and present in both the delivery stay and the birth stay (72).
Sweden	*National Registers*	Exact deterministic linkage, with 100% coverage. As recorded in the MBR, based on person-unique number for mothers and live born infants. The unique identifiers allows deterministic linkage to other National Swedish registers (74,88)
USA	*Carelon*	Deterministic linkage of pregnancies with a liveborn infant was successful for 73%. The linkage algorithm uses the infant's date of birth and estimated delivery date.

Abbreviations: PMSI, Programme de Médicalisation du Système d'Information; SNDS, Système National des Données de Santé; USA, United States of America.

Appendix Table 6 Identification of MCM and mCM in the data sources

Countries	Database	Identification of MCM (and mCM)
Denmark	*National Registers*	Danish adaptation of EUROCATs classification based on the Danish extension of ICD10 (ICD10-DK). Primary and secondary diagnoses from both the MBR and infant records from the NPR and the Cause of Death register will be utilised, while tentative diagnosis and referrals will be ignored. This approach has previously been demonstrated to align with the Danish prevalence of MCM and mCM reported to EUROCAT, all of which are adjudicated by a paediatrician with expertise in congenital malformations (89).
France	*SNDS*	EUROCATs classification will be adapted to the French extension of ICD10. MCM and mCM will be identified from PMSI based on discharge diagnoses and medical procedure codes.
Sweden	*National Registers*	EUROCATs classification will be adapted to the Swedish extension of ICD10 (ICD10-SE) codes for malformations (90). Primary and secondary diagnoses from both the MBR and infant records from the NPR will be utilised. Data from the National Register of Congenital Anomalies may also be used. In statistics from the National Board of Health and Welfare, selected malformations are not reported (91)
USA	*Carelon*	EUROCATs classification will be adapted to the US extension of ICD10 (ICD10-CM). In similar claims database, a PPV=44.0% was estimated for MCM (based on 125 cases of which 55 case were confirmed by adjudicator) (70)

Abbreviations: ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th edition; MCM, major congenital malformations; mCM, minor Congenital Malformations; PMSI, Programme de Médicalisation du Système d'Information; USA, United States of America.

Appendix Table 7 Availability of variables to characterise live offspring at birth in each data source

	Denmark	France	Sweden	USA
	National Registers	**SNDS**	**National Registers**	**Carelon**
Birth weight	Birth weight (in grams) is available in the MBR and is virtually complete and of very high validity (79).	Birth weight (in grams) available in the SNDS. Information on validity unknown but variable described in prior research (92).	Birth weight (in grams) is available from MBR. The variable is virtually complete and very good validity (74).	Low birth weight available through diagnoses codes. Additionally, measured birth weight available only following procurement and adjudication. High completeness according to the data owner and validity unknown.
Small for gestational age	Small for gestational age will be defined by birth weight below the 10th percentile at a given gestational age (weeks and days). Both weight and gestational age are available in MBR and NPR. Is virtually complete (98%) and of very high validity (79).	Gestational age available in the SNDS. Information on completeness of birth weight is unknown, but both birth weight and SGA have been described in prior research (92,93).	Gestational age (weeks and days) and birth weight is available from MBR. Information on validity not available (74).	Small for gestational age available through diagnoses codes. Algorithms in similar claims databases performed poorly (70)
Apgar score	Apgar score virtually complete and of very high validity (79). Completeness 97%.	Unavailable.	Apgar score available. Information on validity described elsewhere (74).	Apgar score may be extracted from medical records. Completeness and validity unknown.

Abbreviations: Apgar, Appearance, Pulse, Grimace, Activity, and Respiration; SNDS, Système National des Données de Santé; USA, United States of America.

Appendix Table 8 Availability of variables on maternal characteristics in each data source

	Denmark National Registers	France SNDS	Sweden National Registers	USA Carelon
Maternal demographic characteristics				
Age at LMP	Yes (100%)	Yes	Yes	Yes
Socioeconomic status	No	Yes[1]	Yes	No
Ethnicity	Partial[2]	No	Partial[2]	Yes
Maternal lifestyle characteristics				
Pre-pregnancy BMI	Yes (96%)	No	Yes	Partial[3]
Smoking (during pregnancy)	Yes (96%)	No	Yes	Partial[3]
Alcohol and substance abuse (during pregnancy)	Yes	No	Yes	Partial[3]
Maternal clinical characteristics				
Comorbid conditions at start of pregnancy	Yes[4]	Yes[4]	Yes[4]	Yes[4]
Comorbid conditions during pregnancy	Yes[4]	Yes[4]	Yes[4]	Yes[4]
Co-medications	Yes[4]	Yes[4]	Yes[4]	Yes[4]
Obstetric history				
Pre-pregnancy diabetes	Yes	Yes	Yes	Yes
Gestational diabetes	Yes	Yes	Yes	Yes
Pre-eclampsia	Partial[5]	Yes	Yes	Yes
Previous spontaneous abortions	Yes	Partial[6]	Yes	No[6]
Previous stillbirths	Yes	Yes	Yes	Partial[6]
Previous elective terminations of pregnancies	Yes	Yes	Partial[6]	Partial[6]
Previous preterm births	Yes	Yes	Yes	Partial[6]
Previous small for gestational age births	Yes	Yes	Yes	Partial[6]
Health Care Utilisation (HCU)				
Number of healthcare visits 12 months before LMP	Yes	Yes	Yes	Yes

Abbreviations: BMI, body mass index; LMP, Last menstrual period; SNDS, Système National des Données de Santé; USA, United States of America
[1] Deprivation index of the city of residence
[2] Migrant status and country of origin available from linkage with other data sources
[3] Lifestyle characteristics in Carelon are partially available: BMI limited to diagnoses codes, completeness unknown for smoking and alcohol use, drug use is not available.
[4] Code list for diagnosis, drug dispensations and procedures codes to be provided in the SAP.
[5] Diagnostic criteria for pre-eclampsia were under review in 2017 and existing validation (PPV=70%, data not yet published) is unlikely to be relevant for the study period
[6] Pending confirmation with data source

Appendix Table 9 Identification of EC-section in the data sources

Countries	Database	EC-section
Denmark	*National Registers*	As recorded in MBR. Based on procedure codes from the NPR.
France	*SNDS*	Planned and emergency c-sections will be distinguished with medical procedure codes CCAM.
Sweden	*National Registers*	As recorded in MBR. Based on procedure codes from the NPR.
USA	*Carelon*	Identified using diagnoses and procedures codes.

Abbreviations: CCAM, Classification Commune des Actes Médicaux; MBR, Medical Birth Register; NPR, National Patient Register.

Appendix D Exemplar Code lists

Code lists included in this appendix are still under development and will be finalised in the SAP.

Appendix Table 10 End of pregnancy record, EXAMPLARY code list

Pregnancy outcome	ICD10 code	Description
Ectopic pregnancy	O00	Ectopic pregnancy
Miscarriage	O03	Spontaneous abortion
Termination of Pregnancy	O04	Medical abortion
	O05	Other abortion
	O06	Unspecified abortion
Stillbirth	P95	Foetal death of unspecified cause
	Z37.1	Single stillbirth
	O36.2	Maternal care for hydrops foetalis
	O36.4	Maternal care for intrauterine death
Birth, TBD if live or still birth	O80	Single spontaneous delivery
	O81	Single delivery by forceps and vacuum extractor
	O82	Single delivery by caesarean section
	O83	Other assisted delivery
	O84	Multiple delivery
	Z37	*Outcome of delivery*
Live birth	Z37.0	Single live birth
	Z38	*Liveborn infants according to place of birth*

Abbreviations: TBC, to be confirmed

Appendix Table 11 Drug classes and active substances used in SOC for severe asthma

Drug	ATC code Index 2023	Combination drugs
ICS		
beclometasone	A07EA07, R01AD01, R03BA01	ICS
budesonide	R01AD05, R03BA02	ICS
ciclesonide	R01AD13, R03BA08	ICS
fluticasone	R01AD08, R03BA05	ICS
fluticasone furoate	R01AD12, R03BA09	ICS
mometasone	R01AD09, R03BA07, R01AD59	ICS
ICS-LABA		
salmeterol and fluticasone	R03AK06	ICS-LABA
formoterol and budesonide	R03AK07	ICS-LABA
formoterol and beclometasone	R03AK08	ICS-LABA
formoterol and mometasone	R03AK09	ICS-LABA
vilanterol and fluticasone furoate	R03AK10	ICS-LABA
formoterol and fluticasone	R03AK11	ICS-LABA
salmeterol and budesonide	R03AK12	ICS-LABA
salbutamol and beclometasone	R03AK13	ICS-LABA
indacaterol and mometasone	R03AK14	ICS-LABA
ICS-LABA-LAMA		
vilanterol, umeclidinium bromide and fluticasone furoate	R03AL08	ICS-LABA-LAMA
formoterol, glycopyrronium bromide and beclometasone	R03AL09	ICS-LABA-LAMA
formoterol, glycopyrronium bromide and budesonide	R03AL11	ICS-LABA-LAMA
indacaterol, glycopyrronium bromide and mometasone	R03AL12	ICS-LABA-LAMA
Leukotriene receptor antagonists		
montelukast	R03DC03	LTRA
montelukast, combinations	R03DC53	LTRA
pranlukast	R03DC02	LTRA
zafirlukast	R03DC01	LTRA
zileuton	-	zileuton
Chromones		
reproterol and sodium cromoglicate	R03AK05	SABA- mast cell stabiliser
salbutamol and sodium cromoglicate	R03AK04	LABA- mast cell stabiliser
nedocromil	R01AC07, R03BC03	mast cell stabiliser
LAMA		
formoterol and tiotropium bromide	R03AL10	LABA-LAMA
olodaterol and tiotropium bromide	R03AL06	LABA-LAMA

tiotropium bromide	R03BB04	LAMA
tiotropium bromide, combinations	R03BB54	LAMA
Biologic		
omalizumab	R03DX05	Anti-IgE
reslizumab	R03DX08	Anti-IL5/ anti-IL5R
mepolizumab	R03DX09	Anti-IL5/ anti-IL5R
benralizumab	R03DX10	Anti-IL5/ anti-IL5R
dupilumab	D11AH05	Anti-IL4R
tezepelumab	R03DX11	
Systemic corticosteroids	H02AB	
Dexamethasone	H02AB02	OCS
Prednisone	H02AB07	OCS
SABA		
salbutamol	R03AC02, R03CC02	SABA
terbutaline	R03AC03, R03CC03	SABA
terbutaline, combinations	R03CC53	SABA
ipratropium bromide	R01AX03, R03BB01	SABA
oxitropium bromide	R03BB02	
salbutamol and sodium cromoglicate	R03AK04	SABA- mast cell stabiliser
salbutamol and beclometasone	R03AK13	ICS-SABA
fenoterol and ipratropium bromide	R03AL01	LABA-SABA
salbutamol and ipratropium bromide	R03AL02	SABA

Abbreviations: Anti-IL, Anti-interleukin; LAMA, Long-acting muscarinic antagonist; SABA, Short-acting β2-agonist; OCS, Oral Corticosteroid

Appendix Table 12 Major congenital malformations, EXEMPLARY code list

	ICD10-BPA	Description	mCM exclusions
MCM	Q-chapter	Congenital malformations	Exclude all minor anomalies as specified in EUROCAT Guide 1.5, section 3.2
	D215	Sacral teratoma	
	D821	Di George syndrome	
	D1810	Cystic hygroma	

ICD10-BPA: ICD10 with the British Paediatric Association one-digit extension
This table will reflect the ICD10 codes listed in the EUROCAT guide 1.5 and will be finalised during the SAP development. Country-specific extensions to WHO ICD10 will be detailed.

Appendix Table 13 Minor Congenital Malformations, EXEMPLARY code list

	ICD10-BPA	Description
mCM	Q07.80	Jaw-winking syndrome, Marcus Gunn's syndrome
	Q04.61	Single congenital cerebral cyst
	Q67.1	Compression facies
	Q67.40	Depressions in skull, lacunar skull, temporal flattening

The full list of mCM is a combination of ICD10-BPA codes and free text descriptions. The complete list of codes will be data source-specific and will be completed in parallel with the SAP development.

Appendix Table 14 Adverse pregnancy outcomes, EXEMPLARY code list

Adverse outcomes	Description	ICD10
Ectopic pregnancy	Ectopic pregnancy	O00
Miscarriage	Spontaneous abortion	O03
Termination of pregnancy	Medical abortion	O04
	Other abortion	O05
	Unspecified abortion	O06
Stillbirth	Foetal death of unspecified cause	P95
	Single stillbirth	Z37.1
	Maternal care for hydrops foetalis	O36.2
	Maternal care for intrauterine death	O36.4
Emergency caesarean section	Delivery by emergency caesarean section	O82.1
Pre-eclampsia	Pre-eclampsia	O14
	Pre-eclampsia superimposed on chronic hypertension	O11

Abbreviations: ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th edition.

Appendix Table 15 Adverse birth outcomes, EXEMPLARY code list

Adverse outcomes	Description	ICD10
Preterm birth	Preterm spontaneous labour with preterm delivery	O60.1
	Preterm delivery without spontaneous labour	O60.3
	Extreme immaturity	P07.2
	Other preterm infants	P07.3
Small for gestational age	Small for gestational age	P05.1

Abbreviations: ICD10, International Statistical Classification of Diseases and Related Health Problems, 10th edition.

Appendix Table 16 Asthma, EXEMPLARY code list

Chapter J - Diseases of the respiratory system (J00-J99)	
ICD10 code	ICD10 Definition
J45.x	Asthma
J46.x	Status asthmaticus

Appendix Table 17 In vitro fertilisation, EXEMPLARY code list

ICD code for in vitro fertilisation	
Z31.2	In vitro fertilisation

Appendix Table 18 Maternal and infant characteristics, EXEMPLARY code list

Condition	Description	ICD10
Infant characteristics		
Apgar score	Severe birth asphyxia (Score 0-3)	P21.0
	Mild and moderate birth asphyxia (score 4-7)	P21.1
	Birth asphyxia, unspecified	P21.9
Maternal characteristics		
Alcohol abuse	Alcohol abuse counselling and surveillance	Z71.4
Drug abuse	Drug abuse counselling and surveillance	Z71.5
Diabetes	Diabetes mellitus	E10-E14
	Pre-existing diabetes mellitus	O24.0-O24.3
Hypertension	Essential hypertension	I10
Anxiety	Other anxiety disorders	F41
Depression	Depressive episode	F32
	Recurrent depressive disorder	F33
	Persistent mood disorders	F34
During pregnancy		
Respiratory infections	Influenza, viral pneumonia, bacterial pneumonia	J09-J18
Gestational diabetes mellitus	Diabetes mellitus arising in pregnancy	O24.4
Gestational hypertension	Gestational [pregnancy-induced] hypertension	O13
Obstetric history		
Gestational diabetes	As above	
Pre-eclampsia	Pre-eclampsia	O11 + O14
Miscarriage	Described in Table 22	
Stillbirth	Described in Table 22	
PTB	Described in Table 23	
SGA birth	Described in Table 23	

Appendix E Literature references for Variables

Appendix Table 19 Rationale (literature references) for the choices of variables

Variable	Title	Journal	Increased risk
Congenital malformations			
Any, including MCM	The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis	https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.12224	No
	Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study	doi:10.1136/thx.2008.098244	No
	Asthma exacerbations during the first trimester of pregnancy and congenital malformations: revisiting the association in a large representative cohort	doi:10.1136/thoraxjnl-2014-206634	Yes, in severe cases
	Effect of Maternal Asthma on the Risk of Specific Congenital Malformations: A Population-Based Cohort Study	https://onlinelibrary.wiley.com/doi/epdf/10.1002/bdra.20651	Yes
Adverse pregnancy outcomes			
Ectopic pregnancy	-	-	-
Miscarriage	Recurrent pregnancy loss and asthma: A nationwide study	https://erj.ersjournals.com/content/58/suppl_65/PA621#:~:text=Background%3A%20Women%20with%20asthma%20have,so%20far%2C%20not%20been%20investigated. **DOI:** 10.1183/13993003.congress-2021.PA621	Yes, risk increased with recurrent loss
	Relationship between maternal asthma, its severity and control and abortion	https://academic.oup.com/humrep/article/28/4/908/653363	Yes, for miscarriage and in uncontrolled asthma
Stillbirth	Maternal asthma is associated with increased risk of perinatal mortality	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5959067/	Yes
	Perinatal Outcomes Associated with Maternal Asthma and Its Severity and Control During Pregnancy	https://www.sciencedirect.com/science/article/abs/pii/S2213219820300568	No
Termination of pregnancy	Relationship between maternal asthma, its severity and control and abortion	https://academic.oup.com/humrep/article/28/4/908/653363	No
	Perinatal Outcomes Associated with Maternal Asthma and Its Severity and Control During Pregnancy	https://www.sciencedirect.com/science/article/abs/pii/S2213219820300568	No
Pre-eclampsia	Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes	Thorax. 2006 Feb;61(2):169-76. doi: 10.1136/thx.2005.049718	No

Variable	Title	Journal	Increased risk
	Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study	https://www.jaci-inpractice.org/article/S2213-2198(17)30561-5/fulltext	Yes
Adverse birth outcomes			
Emergency caesarean section	Adverse Pregnancy Outcomes in Asthmatic Women: A Population-Based Family Design Study	https://www.jaci-inpractice.org/article/S2213-2198(17)30561-5/fulltext	Yes
	Asthma and Pregnancy	https://link.springer.com/article/10.1007/s12016-011-8277-8#Sec10	Yes for caesarean, not emergency
Preterm birth	Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes	Thorax. 2006 Feb;61(2):169-76. doi: 10.1136/thx.2005.049718	No
	Asthma control during pregnancy and the risk of preterm delivery or impaired foetal growth	https://www.annallergy.org/article/S1081-1206(10)60201-3/fulltext	Yes, if asthma is not controlled
	Perinatal Outcomes Associated with Maternal Asthma and Its Severity and Control During Pregnancy	https://linkinghub.elsevier.com/retrieve/pii/S2213-2198(20)30056-8	Yes, in uncontrolled cases
	Maternal asthma is associated with increased risk of perinatal mortality	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5959067/	No, if adjusted to treatment (treated)
Small for gestational age	Perinatal Outcomes Associated with Maternal Asthma and Its Severity and Control During Pregnancy	https://linkinghub.elsevier.com/retrieve/pii/S2213-2198(20)30056-8	Yes, in severe asthma cases
	Maternal asthma is associated with increased risk of perinatal mortality	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5959067/	Yes, in treated asthma
Low birth weight	Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes	Thorax. 2006 Feb;61(2):169-76. doi: 10.1136/thx.2005.049718	Yes
	Maternal asthma is associated with increased risk of perinatal mortality	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5959067/	Yes
Exposure			
Tezepelumab	-	-	-
SOC	Managing asthma in pregnancy	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818212/	No
	Asthma and Pregnancy	https://link.springer.com/article/10.1007/s12016-011-8277-8#Sec10	No
Maternal variables			
Age at conception	Risk Factors for Birth Defects	Obstet Gynecol Surv. 2017 Feb;72(2):123–35. doi: 10.1097/OGX.0000000000000405	Yes
	Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis.	Lancet. 2011 Apr 16;377(9774):1331–40 doi: 10.1016/S0140-6736(10)62233-7.	Yes

Variable	Title	Journal	Increased risk
	Epidemiology and causes of preterm birth	Lancet. 2008 Jan 5;371(9606):75–84	Yes
Socioeconomic status (at index date)	Epidemiology and causes of preterm birth	Lancet. 2008 Jan 5;371(9606):75–84	Yes, for low socioeconomical status
	Socioeconomic status can affect pregnancy outcomes and complications, even with a universal healthcare system	https://equityhealthj.biomedcentral.com/articles/10.1186/s12939-017-0715-7#Bib1	Yes, for low socioeconomical status
	Socioeconomic Disparities in Adverse Birth Outcomes: A Systematic Review	https://doi.org/10.1016/j.amepre.2010.05.012	Yes, for low socioeconomical status
Health care utilisation (at index date)	Asthma and Pregnancy	https://link.springer.com/article/10.1007/s12016-011-8277-8#Sec10	Increased, if asthma is not controlled
	Managing asthma in pregnancy	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818212/	Yes, during pregnancy
Asthma-related comorbid conditions (at index date)	Respiratory viral infections in pregnant women with asthma are associated with wheezing in the first 12 months of life	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7168064/	Respiratory infections increase risk of wheezing illness in infants of mothers with asthma
	Asthma and Pregnancy	https://link.springer.com/article/10.1007/s12016-011-8277-8#Sec10	Yes
Asthma severity algorithm (at index date)	Pocket Guide for Asthma Management and Prevention [Internet]. Global Initiative for Asthma - GINA. [cited 2023 Jan 11]	Available from: https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/	-
	Managing asthma in pregnancy	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4818212/	-
Co-medications (non-asthma SOC) (at index date)	Prenatal exposure to teratogenic medications in the era of Risk Evaluation and Mitigation Strategies.	Am J Obstet Gynecol. 2022 Jan 12:S0002-9378(22)00008-4. doi: 10.1016/j.ajog.2022.01.004.	Yes, non-live births were observer higher if exposure was during first trimester
	Drugs associated with teratogenic mechanisms. Part II: a literature review of the evidence on human risks.	Hum Reprod. 2014 Jan;29(1):168-83. doi: 10.1093/humrep/det370.	-

Variable	Title	Journal	Increased risk
Smoking (prior to pregnancy)	Systematic Review and Meta-Analyses of Perinatal Death and Maternal Exposure to Tobacco Smoke During Pregnancy.	Am J Epidemiol. 2016 Jul 15;184(2):87-97. doi: 10.1093/aje/kwv301.	Yes
	Smoking cessation in the first trimester reduces most obstetric risks, but not the risks of major congenital anomalies and admission to neonatal care: a population-based cohort study of 1,164,953 singleton pregnancies in Finland.	J Epidemiol Community Health. 2014 Feb;68(2):159-64. doi: 10.1136/jech-2013-202991.	Yes
Alcohol abuse (prior to pregnancy)	Foetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review.	Am J Perinatol. 2015 Apr;32(5):405-16. doi: 10.1055/s-0034-1393932.	Yes
	Risk Factors for Birth Defects.	Obstet Gynecol Surv. 2017 Feb;72(2):123-135. doi: 10.1097/OGX.0000000000000405.	Yes
Substance abuse (prior to pregnancy)	Foetal anomalies and long-term effects associated with substance abuse in pregnancy: a literature review.	Am J Perinatol. 2015 Apr;32(5):405-16. doi: 10.1055/s-0034-1393932.	Yes
	Relationship between Self-Reported Maternal Substance Abuse and Adverse Outcomes in the Premature Newborn.	Am J Perinatol. 2016 Jan;33(2):165-71. doi: 10.1055/s-0035-1563549.	Yes
	Risk Factors for Birth Defects.	Obstet Gynecol Surv. 2017 Feb;72(2):123-135. doi: 10.1097/OGX.0000000000000405.	Yes
Gestational diabetes (during pregnancy)	Association of Maternal Pre-pregnancy Diabetes and Gestational Diabetes Mellitus With Congenital Anomalies of the Newborn.	Diabetes Care. 2020 Dec;43(12):2983-2990. doi: 10.2337/dc20-0261.	Yes
	Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis.	BMJ. 2022 May 25;377:e067946. doi: 10.1136/bmj-2021-067946.	Yes
	Characteristics and pregnancy outcomes across gestational diabetes mellitus subtypes based on insulin resistance.	Diabetologia. 2019 Nov;62(11):2118-2128. doi: 10.1007/s00125-019-4961-7.	Yes
Pre-pregnancy obesity (at index date)	Preconceptional and maternal obesity: epidemiology and health consequences.	Lancet Diabetes Endocrinol. 2016 Dec;4(12):1025-1036. doi: 10.1016/S2213-8587(16)30217-0.	Yes
	Is there an increased risk of caesarean section in obese women after induction of labour? A retrospective cohort study.	PLoS One. 2022 Feb 25;17(2):e0263685. doi: 10.1371/journal.pone.0263685.	Yes
	Impact of maternal pre-pregnancy body mass index on maternal, foetal and neonatal adverse outcomes in the worldwide populations: A systematic review and meta-analysis.	Obes Res Clin Pract. 2021 Nov-Dec;15(6):536-545. doi: 10.1016/j.orcp.2021.10.005.	Yes
History of pre-eclampsia (at index date)	Adverse maternal and perinatal outcomes in women with previous pre-eclampsia: a prospective study.	Am J Obstet Gynecol. 2011 Jun;204(6):512.e1-9. doi: 10.1016/j.ajog.2011.02.014.	Yes
	Is pre-eclampsia associated with foetal malformation? A review and report of original research.	J Matern Foetal Neonatal Med. 2015;28(18):2135-40. doi: 10.3109/14767058.2014.980808.	Yes

Variable	Title	Journal	Increased risk
Pre-pregnancy hypertension (at index date)	Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis.	BMJ. 2014 Apr 15;348:g2301. doi: 10.1136/bmj.g2301.	Yes
	A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis.	Clin J Am Soc Nephrol. 2010 Nov;5(11):2060-8. doi: 10.2215/CJN.00240110.	Yes
Pre-pregnancy diabetes (at index date)	Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997-2011.	Am J Obstet Gynecol. 2020 Feb;222(2):176.e1-176.e11. doi: 10.1016/j.ajog.2019.08.028.	Yes
	Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: A population-based cohort study in China.	PLoS Med. 2019 Oct 1;16(10):e1002926. doi: 10.1371/journal.pmed.1002926.	Yes
	Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study.	Lancet Diabetes Endocrinol. 2021 Mar;9(3):153-164. doi: 10.1016/S2213-8587(20)30406-X.	Yes
Previous spontaneous abortions (at index date)	Adverse pregnancy outcomes among women with prior spontaneous or induced abortions.	Am J Perinatol. 2014 Oct;31(9):765-72. doi: 10.1055/s-0033-1358771.	Yes
	Association of Maternal History of Spontaneous Abortion and Stillbirth With Risk of Congenital Heart Disease in Offspring of Women With vs Without Type 2 Diabetes.	JAMA Netw Open. 2021;4(11):e2133805. doi:10.1001/jamanetworkopen.2021.33805.	Yes
	Association between a Maternal History of Miscarriages and Birth Defects.	Birth Defects Res. 2017 Mar 1;109(4):254-261. doi: 10.1002/bdra.23563.	Yes
Previous stillbirth (at index date)	Association of Maternal History of Spontaneous Abortion and Stillbirth With Risk of Congenital Heart Disease in Offspring of Women With vs Without Type 2 Diabetes.	JAMA Netw Open. 2021;4(11):e2133805. doi:10.1001/jamanetworkopen.2021.33805.	Yes
	Previous miscarriage and stillbirth as risk factors for other unfavourable outcomes in the next pregnancy.	Br J Obstet Gynaecol. 1992 Oct;99(10):808-12. doi: 10.1111/j.1471-0528.1992.tb14411.x.	Yes
Previous preterm birth (at index date)	Recurrence of Preterm Birth and Early Term Birth.	Obstet Gynecol. 2016 Aug;128(2):364-372. doi: 10.1097/AOG.0000000000001506.	Yes
Previous small for gestational age (at index date)	Recurrence of small for gestational age pregnancy: analysis of first and subsequent singleton pregnancies in The Netherlands.	Am J Obstet Gynecol. 2013 May;208(5):374.e1-6. doi: 10.1016/j.ajog.2013.01.045.	Yes

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