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An Observational Multi-Country Post-Authorisation Safety Study to Evaluate the Risk of Serious Adverse Cardiovascular Events in Adolescent and Adult Patients with Severe Asthma taking Tezepelumab

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PASS INFORMATION

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Joint PASS	No
Research question and objectives	The aim of this longitudinal population-based cohort study is to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking tezepelumab compared to a matched population receiving other treatment for severe asthma. **Primary objectives** 1. To estimate the risk of a composite of major adverse cardiovascular events (MACE), defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with standard of care [SOC] for severe asthma) 2. To compare the risk of MACE in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)

	Secondary objectives 3. To estimate the risk of a composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma) 4. To compare the risk of the composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma) 5. To estimate the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma) 6. To compare the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)
Countries of study	Denmark, France, Germany, and the USA
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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AUC	Area under the curve
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CDM	Common data model
CDR	Cause of Death Registry
CESREES	*Comite ethique et scientifique pour les recherches, les etudes et les evaluations dans le domaine de la sante*
CI	Confidence interval
CM	Clinical modifications
CNAM	*Conservatoire National des Arts et Metiers*
CNIL	*Commission Nationale Informatique & Liberties*
COPD	Chronic obstructive pulmonary disease
CPH	Cox proportional hazard
CPR	Central Person Register
DCIR	*Données de consommation interrégimes* (National health insurance reimbursement database)
DMP	Data management plan
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethics Review Boards
EU	European Union
FDA	Food and Drug Administration
GDPR	General data protection regulation
GINA	Global Initiative for Asthma
GM	German modification
GVP	Good pharmacovigilance practices
HCRU	Health care resource utilisation
HR	Hazard ratio
ICD	International Classification of Diseases
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IL	Interleukin
IRB	Institutional Review Board

Abbreviation or special term	Explanation
KM	Kaplan-Meier
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTD	Long-term disease
LTRA	Leukotriene receptor antagonist
MACE	Major adverse cardiovascular event
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NPR	National Patient Register
NPR-Den	National Patient Register-Denmark
OCS	Oral corticosteroids
PAS	Post-authorisation study
PASS	Post-authorisation safety study
PMSI	*Programme de médicalisation des systèmes d'information* (Hospital discharge summaries database system)
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity scores
QBA	Quantitative bias assessment
QC	Quality control
RCT	Randomised control trial
RMP	Risk management plan
RPS	Register of Pharmaceutical Sales
RUKS	*Register for udvalgte kroniske sygdomme* (Register of Selected Chronic Diseases and Severe Mental Disorders)
SABA	Short-acting beta$_2$-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SHI	Statutory Health Insurance
SMR	Hospital Medication Register
SNDS	*Système National des Données de Santé* (National Health Data System)
SNIIRAM	*Système national d'information interrégimes de l'Assurance maladie* (French National Health Insurance database)
SOC	Standard of Care
TSLP	Thymic stromal lymphopoietin
USA	United States of America

Abbreviation or special term	Explanation
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

An Observational Multi-Country Post-Authorisation Safety Study to Evaluate the Risk of Serious Adverse Cardiovascular Events in Adolescent and Adult Patients with Severe Asthma taking Tezepelumab

Protocol version 2.0, 30 January 2024, [redacted] *(IQVIA) and* [redacted] *(IQVIA)*

Rationale and background

Severe asthma is characterised by poor control of symptoms 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. The preferred baseline treatment for severe asthma patients includes high-intensity treatment with medium to high dose maintenance inhaled corticosteroids (ICS) plus formoterol (a long-acting β_2-agonist [LABA]). Several add-on therapies including long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), low dose azithromycin, low dose oral corticosteroids (OCS), and LABA may be considered. For patients experiencing symptoms or exacerbations despite high -intensity treatment, the preferred therapy is a high dose ICS concomitant with other controller options and add-on therapies with LAMA or biologics. Tezepelumab (brand name: TEZSPIRE®), a human monoclonal antibody specific for the epithelial cell–derived cytokine thymic stromal lymphopoietin (TSLP), was recently launched as a first-in-class biologic add-on treatment for patients with severe asthma. Results from DESTINATION, a long-term extension, phase 3 trial, showed a numeric imbalance in the occurrence of cardiac disorder system organ class serious adverse events (SAEs) in participants receiving tezepelumab compared to placebo. The observed imbalance resulted in the inclusion of serious cardiovascular events as an important potential risk to be addressed in the European Union (EU) risk management plan (RMP). AstraZeneca proposed to evaluate the risk of serious cardiovascular events with long-term tezepelumab treatment to meet regulatory requirements under a category 3 Post-Authorisation Safety Study (PASS).

Research question and objectives

The aim of this longitudinal population-based cohort study is to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking tezepelumab compared to a matched population receiving other treatment for severe asthma.

Primary objectives

1. To estimate the risk of a composite of major adverse cardiovascular events (MACE), defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death in adolescent and adult patients with severe asthma who initiated tezepelumab and in

matched patients unexposed to tezepelumab (treated with standard of care [SOC] for severe asthma)

2. To compare the risk of MACE in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)

Secondary objectives

3. To estimate the risk of a composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma)
4. To compare the risk of the composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)
5. To estimate the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma)
6. To compare the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)

Study design

This study is a non-interventional, longitudinal, population-based cohort study, using secondary data derived from multiple data sources. The study will consist of descriptive and a prevalent new-user design for comparative analyses of serious cardiovascular events outcomes in adolescent and adult patients with severe asthma exposed and unexposed to tezepelumab.

Population

The study will be conducted using data sources from Denmark, France, Germany, and the United States of America (USA). The start of the study period will correspond to tezepelumab market launch date in each country of interest (i.e. between Q1 2022 – Q3 2023). An approximately five-year study period is planned in each country, with an anticipated last date of study period on 28 February 2029.

The *source population* will consist of patients with a diagnosis of asthma receiving tezepelumab or high-intensity SOC treatment for severe asthma at any point during the study inclusion period. From this source population, the *exposed study population* (i.e. patients who initiate tezepelumab treatment) and the *unexposed study population* (i.e. comparable patients who are unexposed to tezepelumab) will be identified. Inclusion of unexposed patients will be based on the presence of a trigger exposure designed to mirror the start of tezepelumab in exposed patients (i.e. augmentation or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation).

Exclusion criteria for both exposed and unexposed groups include <12 months of data availability prior to index date, age <12 years at index date, and history of congenital heart disease or heart transplant. Additionally, outcome-specific exclusion criterion applied for each objective will include the presence of non-fatal myocardial infarction or stroke and the specific outcome of interest in the 180 days prior to index date. For comparative analysis (objectives 2, 4 and 6), an additional exclusion criterion will be considered, i.e. exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic. Lastly, matching criteria (including, among other variables, the type and duration of SOC exposure in the 12 months before index date and propensity score [PS] matching) will be applied to ensure exposed and unexposed patients' comparability.

Variables

Exposure

The exposure of primary interest is tezepelumab. Severe asthma treatments in the comparison group include medium and high dose ICS, LABA, low dose OCS, LAMA, LTRA, theophylline, and azithromycin.

Outcomes

The primary outcome of interest is the composite outcome MACE, consisting of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The secondary outcomes of interest are a composite of four serious adverse cardiovascular events, including arrhythmias, coronary artery disease, heart failure and myocardial disorders, and the individual components of the primary and secondary composite outcomes.

Covariates

Covariates of interest include patients' sociodemographic, clinical characteristics (including asthma characteristics, respiratory diseases other than asthma, cardiovascular disease, history of malignancies and other comorbidities), health care resource utilisation (HCRU) and prior concomitant use of drugs.

Data sources

The planned data sources include the Danish National Registers (Denmark), the French National Health Data System (France), Statutory Health Insurance (SHI) (Germany), and Carelon (USA).

Study size

Both sample size and power calculations were carried out for the primary outcome MACE at the meta-analysis level. The following assumptions were made in the sample size and power calculations: baseline rate of 0.45 events per 100 person-years, mean follow-up duration of 2.3 years, uptake of tezepelumab among patients with severe asthma according to projected number of patients treated with tezepelumab, non-inferiority margin of hazard ratio (HR) of 1.8, exposed to unexposed patient ratios of 1:1, 1:2, and 1:3. Various levels of between-study heterogeneity in HRs were considered and a fixed-effect or random-effects meta-analysis models applied as appropriate to combine the results from data sources.

Depending on matching ratio used, 3,100 to 4,530 (assuming no between-country heterogeneity) up to 11,890 to 16,640 (assuming considerable between-study heterogeneity) tezepelumab exposed severe asthma patients across the data sources would be required to achieve 80% power to rule out an HR of 1.8 or greater for the MACE outcome.

Additionally, the minimum detectable HR that could be ruled out with 80% power, and the expected power to rule out a target HR of 1.8 were computed given the expected number of 95,574 patients exposed to tezepelumab in the data sources under the assumed uptake scenarios per country during the study period. The minimum detectable HR was at least 1.14 to 1.58 for MACE, depending on the assumed between-study heterogeneity; the expected power to rule out an HR of 1.8 was ≥99% assuming no between-country heterogeneity and 93% assuming considerable between-country heterogeneity.

Data analysis

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

Selection of comparable unexposed patients will be based on the presence of a trigger exposure that mirrors tezepelumab initiation and matching on clinical and treatment characteristics that are similar to the exposed patients in the 12-month baseline period.

The matching criteria aim to identify unexposed patients with comparable baseline SOC treatments and similar baseline risk of cardiovascular events to tezepelumab initiators. Exposed and unexposed patients will be matched on: 1) date of the trigger exposure in unexposed patients ± 1 month of the exposed tezepelumab initiation, 2) type of SOC, 3) duration of SOC, 4) age, 5) sex, and 6) PS including additional potential confounders (e.g. comorbidities).

Time-based exposure sets will be used to find comparable matches for patients initiating tezepelumab. The time-conditional PS model will be fitted on a dataset that combines all time-

based exposure sets using Cox proportional hazards (CPH) regression or conditional logistic regression model. The fitted model will be used to compute time-conditional PS values for all study units in each exposure set. Matching will be done chronologically based on the calendar time starting from the first tezepelumab initiator. Up to three matches will be selected amongst the unexposed triggers within the time-based exposure set with PS scores closest to the score of the tezepelumab initiator. Matched comparators will be removed from all subsequent time-based exposure sets (i.e. matching without replacement).

The effectiveness of the matching on confounding adjustment will be assessed by examining the distribution of variables and estimating standardised differences for each variable between the exposed and unexposed cohort before and after matching.

In the descriptive analysis of study outcomes, the total number of study units, the descriptive statistics of the follow-up time and the number of outcome events for each study outcome in the exposed and unexposed matched cohorts will be presented. Kaplan-Meier (KM) analysis will be used to estimate the risk of primary and secondary outcome events in the exposed and unexposed cohorts after matching.

For the comparative analysis, CPH regression models will be used to estimate the HRs for each primary and secondary outcome event within the matched population for each of the relevant study outcomes. HRs and the corresponding 95% confidence intervals (CIs) will be reported.

Data source level analyses' results will also be combined in a meta-analysis. Meta-analysis will be performed for the primary and secondary study objectives using the 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 but results from both approaches will be presented.

Milestones

A progress report is planned for April 2025 which is 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of the protocol which is currently assumed to be Q2 2024. The two interim reports will be submitted 24 (April 2026) and 48 (April 2028) months after PRAC endorsement of the protocol. The final study report is planned for May 2030.

5. AMENDMENTS AND UPDATES

None (original protocol).

6. MILESTONES

The study milestones are outlined in Table 1 below.

The progress report will provide a status update of data sources' application approvals and, if applicable, relevant amendments pertaining to database application forms. Data access may take between 7 to 18 months; therefore, the progress report may not include counts of tezepelumab users from all planned data sources.

Two interim reports will be generated throughout the project duration to monitor and characterise tezepelumab use among patients with severe asthma. As such, the first interim report will provide descriptive statistics to characterise the source population, namely by quantifying the use of tezepelumab and potential eligible trigger exposures to define the unexposed population and providing the number of individual outcomes relevant to primary and secondary objectives, using all available data at the time of reporting.

The second interim report will, in addition, inform subsequent analyses (including timing) for signal evaluation in the final study report. It will provide updated descriptive statistics including tezepelumab use characterisation (namely on proposed matching criteria) to improve the definition of a comparable unexposed population to form a comparator cohort. Neither of the two interim reports will include the incidence of cardiovascular outcomes, comparative analyses, explorative analyses, sensitivity analyses, or meta-analyses.

The final study report is planned for May 2030.

Table 1 Study milestones

Milestone	Planned date[a]
PRAC approval	11 April 2024
Registration in the EU PAS register	31 May 2024
Progress Report	30 April 2025
Start of data collection[b]	1 May 2025
Interim report 1	30 April 2026
Interim report 2	30 April 2028
End of data collection[c]	31 May 2029
Final report of study results	31 May 2030

[a] Schedule is dependent on the date of protocol approval by PRAC. Any deviations from this tentative date may lead to an amendment of all subsequent dates.
[b] Date at which data extraction starts for the first data source.
[c] Date at which the analytical dataset is completely available.
Abbreviations: EU PAS, European Union electronic Register of Post-Authorisation Studies; PRAC, Pharmacovigilance Risk Assessment Committee.

7. RATIONALE AND BACKGROUND

Burden of severe asthma

Asthma is a common chronic disorder caused by a combination of inflammation and bronchial hyper-responsiveness leading to airflow obstruction characteristic clinical symptoms, include an intermittent cough, wheezing, chest tightness, and shortness of breath (1).

According to the Global Initiative for Asthma (GINA), asthma remains a major public health challenge due to premature death, reduced quality of life, and economic costs (1). Asthma affects individuals of all age groups, including children and adolescents (2). A Global Burden of Disease study estimated 262 million cases of asthma worldwide in 2019, corresponding to an age-standardised prevalence of 3,416 cases per 100,000 population (3). In North America, the age-standardised prevalence of asthma is 9,848 cases per 100,000 population, and an estimated 461,000 deaths have been attributed to asthma, with an age-standardised mortality of 5.8 cases per 100,000 population (3).

Asthma intensity varies over time, and treatment is based on the control of symptoms and frequency of exacerbation, in addition to the management of contributing comorbidities and triggers. Some asthma patients require high-intensity treatment, and a subset of them experience symptoms or exacerbations despite treatment. Severe asthma is characterised by poor control of symptoms 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 (4).

Variation in the prevalence estimates of severe asthma has been found across studies. The 2023 GINA report indicates that around 4% of asthma patients experience severe asthma, based on data from the Netherlands (1, 5). Similarly in Sweden, around 4% of adult asthma patients had severe disease (6). Surveys in Denmark described a higher proportion of approximately 8% of asthma patients with severe disease (7). The proportion of severe asthma patients appears to be lower in childhood (8). For example, a birth cohort in Sweden showed a prevalence of 2.1% of severe asthma amongst children with asthma (9).

Current treatment paradigm

Recent evidence has highlighted the complex and heterogeneous mechanisms of asthma, considering molecular pathways and clinical presentation of the disease (10). The current asthma treatment paradigm focuses on the clinical management of disease symptoms, clinical presentation, and the immune components of asthma (11).

The 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 (4). For severe asthma patients, a high-intensity therapy with medium to high dose maintenance inhaled corticosteroids (ICS) plus formoterol (a

long -acting β_2-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), and 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 biologics (4, 12).

Tezepelumab

Tezepelumab (brand name: TEZSPIRE®) was recently launched as a first-in-class biologic add-on treatment for patients with severe asthma (13, 14). Tezepelumab is a human monoclonal antibody specific for the epithelial cell–derived cytokine thymic stromal lymphopoietin (TSLP). This cytokine is involved in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, as well as inducing downstream inflammatory processes and bronchial hyper-responsiveness (15). TSLP has also been shown to be a mediator between immune cells and structural cells (e.g. fibroblasts and airway smooth muscle) in the airway (16). In asthma, both allergic and non-allergic triggers induce TSLP production. Tezepelumab binds with high affinity to TSLP and subsequently prevents the interaction of TSLP with its heterodimeric TSLP receptor. By blocking the interaction of TSLP with its receptor complex, tezepelumab reduces the initiation and persistence of airway inflammation in asthma and interferes with multiple downstream inflammatory pathways, as evidenced by the reduction in multiple biomarkers (e.g. blood eosinophils, Immunoglobulin E, fractional exhaled nitric oxide, Interleukin-5, and Interleukin-13) from baseline in patients with severe asthma treated with tezepelumab (15).

The efficacy and safety of tezepelumab in adults and adolescents with severe uncontrolled asthma on medium to high dose ICS and at least one additional asthma controller medication with or without OCS has been demonstrated in the NAVIGATOR phase 3 randomised control trial (RCT) (NCT03347279) (17). The efficacy of tezepelumab in reducing OCS use in adults with OCS dependent asthma has been evaluated in the SOURCE trial (NCT03406078) (18). An extension study (DESTINATION, NCT03706079) included patients from both RCTs and demonstrated the long-term safety, tolerability, and sustained efficacy of tezepelumab in adults and adolescents with severe uncontrolled asthma. Treatment was associated with reductions in asthma exacerbations, improved lung function, asthma control, and health--related quality of life (19).

Because of its action at the top of the inflammation cascade, tezepelumab is considered an alternative treatment for a broader population of patients with severe asthma, fulfilling a high unmet need in asthma control (20). The United States Food and Drug Administration (FDA)

approved in December 2021 the use of tezepelumab as add-on maintenance treatment of adult and paediatric patients aged 12 years and older with severe asthma (14). Marketing authorisation in European Union (EU) has been granted by the European Medicines Agency (EMA) in September 2022 as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose ICS plus another medicinal product for maintenance treatment (13).

Asthma and cardiovascular disease

Recent evidence from observational research suggests an increased risk of cardiovascular disease among asthma patients. A meta-analysis of prospective and retrospective cohort studies showed that patients with asthma had a 32% higher risk of cardiovascular disease compared to people without asthma. Asthma patients also presented a 25% increased risk of cardiovascular mortality compared to people without asthma (21).

While the biological mechanisms involved in the association between asthma and cardiovascular events remain unclear, several mechanisms have been proposed. Asthma and cardiovascular disease share many risk factors, including inflammation (21). Persistent asthma has been associated with carotid plaque burden, a strong predictor of atherosclerotic cardiovascular events, and higher levels of inflammatory biomarkers (22). Prior research has also shown a significantly lower risk of cardiovascular events in patients with chronic coronary disease receiving anti-inflammatory drugs, suggesting inflammation to be a risk factor for cardiovascular events and mortality (23). Poor lung function and eosinophilia, which are common in patients with asthma, have also been identified as risk factors of cardiovascular mortality (21).

Cardiovascular safety of asthma medications

Apart from common pathophysiological mechanisms and risk factors, as well as mutual reinforcement between asthma and cardiovascular disease, asthma therapies may also carry an increased risk of cardiovascular events independent of the disease, especially if it takes a form of high-intensity treatment. Some of asthma standard of care (SOC) medications, such as inhaled β_2-agonists, have been associated with an increased risk of cardiovascular events (24).

ICS are a fundamental element of severe asthma treatment used in combination with other medications and are considered safe in respect to cardiovascular risk if used as recommended (25). In contrast, OCS, usually prescribed for quick resolution of acute exacerbations, have potential systemic side effects and are associated with a significantly increased risk of adverse cardiac and cardiovascular events (26). Short-acting and long-acting bronchodilators, being standard medications, are generally considered safe in terms of cardiovascular risk in asthma patients (27). However, there is evidence that short-acting beta$_2$-agonists (SABA) might cause tachycardia or cardiac arrhythmias in asthmatic patients with concomitant cardiovascular conditions (28) and elderly patients (29). Also, patients with asthma-chronic obstructive

pulmonary disease (COPD) overlap who initiated SABA were more likely to suffer from major adverse cardiovascular events (MACE) compared to matched comparators treated with ICS (30).

Biologics targeting interleukin (IL)-5 (omalizumab, mepolizumab. reslizumab, benralizumab) and both IL-4 and IL-13 (dupilumab) are a rapidly developing class of treatment reserved for severe asthma not controlled with standard medications. Clinical trials have reported on overall favourable safety profile of biologics, however specific risks, including cardiovascular outcomes, have not been well discussed (31-33). There are few studies directly addressing cardiovascular safety during treatment with biologics, namely resluzimab and dupilumab, suggested that there is no significant increase in adverse events when compared to placebo (34, 35). In addition, a prospective cohort study showed a non-significant difference in the incident rate of cardiovascular and cerebrovascular serious adverse events (SAEs) between omalizumab and non-omalizumab treated patients, after adjustment for measured differences in asthma severity (rate ratio of 1.32 [95% confidence interval: 0.83-2.12]) (36). Despite the results, the authors emphasised that potential increased risk for adverse events due to the treatment cannot be ruled out. Robust observational data on cardiovascular safety of biologic therapies are limited, however new evidence is expected to emerge given ongoing development of the area.

Knowledge gap and study rationale

The results from the DESTINATION trial show an imbalance between patients receiving tezepelumab or placebo in terms of individual Medical Dictionary for Regulatory Activities (MedDRA)-coded categories of SAEs. A lower incidence of respiratory, thoracic, and mediastinal disorder system organ class SAEs, and a higher incidence of cardiac disorder system organ class SAEs were observed in participants receiving tezepelumab compared to those receiving placebo. The reason for this imbalance in cardiac SAEs is not understood since there is no known mechanism by which TSLP blockade is associated with cardiac pathophysiology (19). The observed imbalance resulted in the inclusion of serious cardiovascular events as an important potential risk to be addressed in the EU risk management plan (RMP). AstraZeneca included a proposal within the EU RMP to further evaluate the risk of serious cardiovascular events with long-term tezepelumab treatment to meet regulatory requirements under a category 3 Post-Authorisation Safety Study (PASS).

The study design and objectives are described in this protocol, which aims to assess the incidence of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who are exposed to tezepelumab compared with severe asthma patients not exposed to tezepelumab.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this longitudinal population-based cohort study is to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking tezepelumab compared to a matched population receiving other treatment for severe asthma.

8.1 Primary objectives

1. To estimate the risk of a composite of MACE defined as non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma)
2. To compare the risk of MACE in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)

8.2 Secondary objectives

3. To estimate the risk of a composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma)
4. To compare the risk of the composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders) in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)
5. To estimate the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma)
6. To compare the risk of the individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with non-biologic SOC for severe asthma)

9. RESEARCH METHODS

9.1 Study design

The study is a non-interventional, longitudinal, population-based cohort study, using secondary data derived from multiple data sources in Denmark, France, Germany, and the United States of America (USA).

The study will consist of descriptive analyses of patient characteristics and treatment patterns and employ a prevalent new-user design for comparative analyses of serious cardiovascular events outcomes in adolescent and adult patients with severe asthma exposed and unexposed to tezepelumab. The primary outcome of interest is a composite outcome of MACE, consisting of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The secondary outcomes of interest are a composite outcome, including arrhythmias, coronary artery disease, heart failure and myocardial disorders, and the individual components of the primary and secondary composite outcomes.

The exposure of primary interest is tezepelumab (see Section 9.3.1.1) for severe asthma. Exposure will be assessed based on prescriptions or administrations depending on the data source. A comparable cohort of unexposed patients treated with high-intensity SOC treatment will be identified based on the presence of a trigger exposure (i.e. augmentation or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation) to mirror tezepelumab start in the exposed cohort. Due to the limited knowledge of the cardiovascular profile of biologics, SOC for comparative analyses will only include non-biologic high-intensity treatment.

The comparability of the cohorts will be ensured by matching tezepelumab and comparator patients on the type and duration of SOC exposure in the last 12 months, as well as date of trigger exposure, sex, age and, in addition, by time-conditional propensity score (PS) matching (Section 9.2.5). The type of SOC will be data driven, defined from the observed treatments' frequency, and supported by clinical input and available knowledge to assure comparability on asthma severity and cardiovascular safety. Details are provided in Section 9.3.1.3.

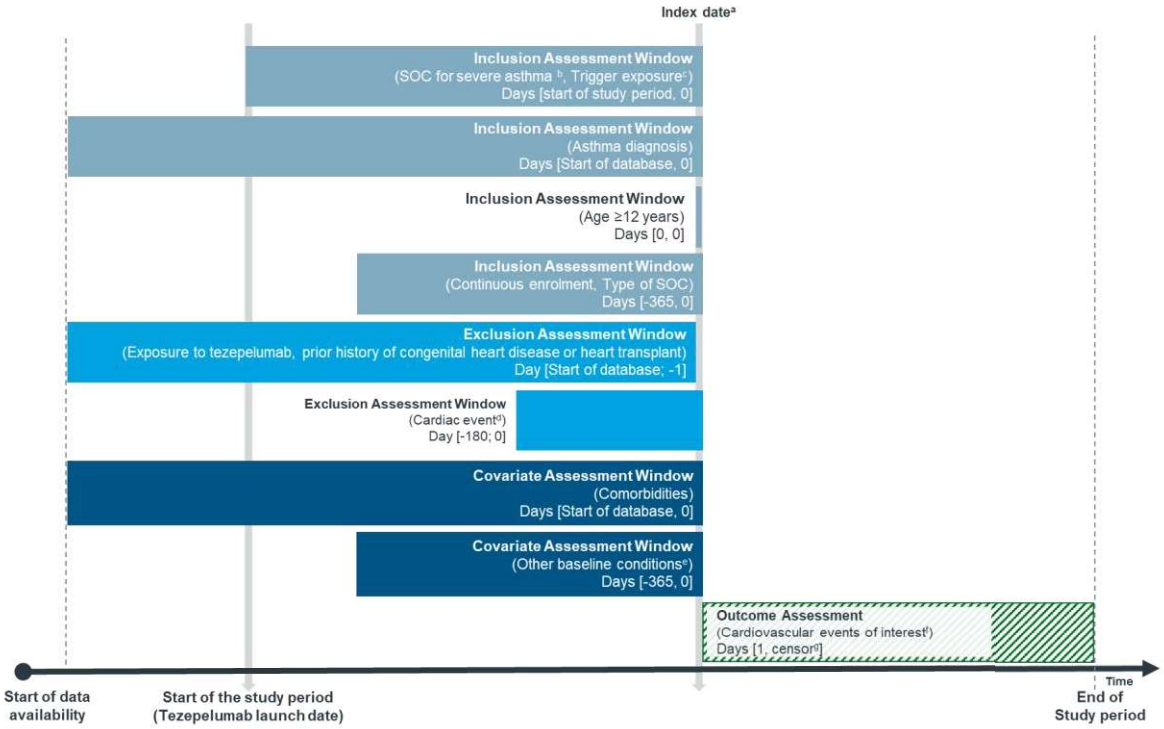
The comparative analyses of study outcomes between patients exposed to tezepelumab and unexposed patients will account for potential confounders, including demographic characteristics, asthma disease severity and other clinical risk factors. Asthma severity will be determined by treatment history and health care resource utilisation (HCRU). Details on the selection of the unexposed comparator cohorts are provided in Section 9.2.5.3.

Summary of the study design, study outcome definitions and assessment windows are outlined in Appendix C.

9.1.1 Study design diagram

A summary of the study design is presented in Figure 1.

Figure 1 Study design diagram



[a] Date of the first tezepelumab prescription (exposed) or date of a trigger exposure within ± 1 month around tezepelumab initiation date (unexposed). Treatment episodes are defined by prescription/administration dates and days covered by therapy. Gaps shorter than 60 days will be bridged and added to the last prescription/administration in an exposure episode.

[b] SOC for severe asthma in this study comprises high-intensity treatments (note that for comparative analyses, only non-biologic high-intensity treatments will be considered).

[c] Augmentation or change in non-biologic treatment that is not de-escalation (for exposed patients this refers to tezepelumab initiation).

[d] Non-fatal myocardial infarction, non-fatal stroke, or other outcome-specific serious cardiovascular events in the prior 180 days.

[e] Including lifestyle, healthcare resource utilisation and other concomitant drugs use, as appropriate

[f] Composite of the MACE of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death; composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders); individual serious adverse cardiovascular events included in either MACE or the composite of serious adverse cardiovascular events.

[g] Earliest of outcome of interest (specific for each objective), treatment discontinuation + days covered by therapy, death, disenrollment, end of the study period

Abbreviations: MACE, Major adverse cardiovascular events; SOC, Standard of care.

9.2 Setting

A total of five large longitudinal patient-level data sources are planned for this study, representing five countries: Denmark, France, Germany, and USA.

The considered data sources are:

- Danish national health and socioeconomic registries (Denmark)
- French National Health Data System (*Système National des Données de Santé* [SNDS]) (France)
- Statutory Health Insurance (SHI) Claims (Germany)
- Carelon (USA)

9.2.1 Study period (calendar time)

The **start of the study period** will correspond to tezepelumab market launch date in the countries of interest. Country specific study start dates are provided in Table 2. A minimum baseline period of 12 months is applied to enable the evaluation of inclusion/exclusion criteria as well as disease and treatment characterisation and other covariates (Figure 1).

The **end of the study period** is defined as the last day of follow-up when all patients still in the study are censored and will depend on length of data lag in each country at the time when the final data are extracted (Table 2). The rationale for this choice is to make use of all data recorded in individual data sources during the period prior to the planned delivery of the final report. In general, an approximately five-year study period is planned in each country with an anticipated last date of study period on 28 February 2029.

Inclusion period will begin at the start of the study period and end one year before the end of the study period, to allow for sufficient follow-up time for outcome identification.

Table 2 Relevant dates of the study by country

Country	Tezepelumab market launch[a]	Start of the baseline period (Earliest date)	Start of study period (Earliest inclusion date)	End of inclusion period (Latest inclusion date)	End of study period[b] (Latest follow-up date)
Denmark	May 2023	01 May 2022	01 May 2023	30 April 2027	30 April 2028
France	May 2023[c]	01 June 2022	01 June 2023	31 May 2027	31 May 2028
Germany	November 2022	01 January 2022	01 January 2023	31 December 2026	31 December 2027
USA	January 2022	01 January 2021	01 January 2022	29 February 2028	28 February 2029

[a] EMA approval 19 September 2022 and US FDA approval 17 December 2021. Market launch dates are country specific.
[b] Calculated by subtracting one year to the final study report date (31 May 2030) and the following data lag times: Denmark – 13 months, France – 12 months, Germany – 16 months (after the end of the calendar year), and USA – 3 months.
[c] Compassionate use programme was in place between 24 August 2022 and February 2023; availability in the outpatient setting began 15 May 2023.
Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; US, United States; USA, United States of America.

9.2.2 Index date

Index date in exposed patients will be defined as the date of first prescription, dispensation, or any other record of tezepelumab use within the study inclusion period depending on the data availability within data sources. Index date in an unexposed patient will be defined by the date of a trigger exposure (i.e. augmentation or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation) within the study period that occurs closely to tezepelumab initiation in a matched exposed patient. Once the trigger exposure is selected as part of the exposed-unexposed pair, the patient is not considered any longer as a potential comparator for another exposed patient (matching without replacement).

Details on trigger exposure definition and matching procedure are described in Sections 9.3.1.4 and 9.7.1.1 respectively.

9.2.3 Follow-up and censoring

Patient follow-up will start on the index date and continue until the outcome of interest or any of the censoring criteria. Specifically, end of follow-up is defined as (whichever occurs first):

- Disenrollment from the data source
- Death
- End of study period
- Date of the first occurrence of the adverse event defined for each objective (Section 9.3.2). This means that follow-up will be outcome-specific. For composite outcomes, follow-up will end at the occurrence of the first event that is included in the composite outcome.
- End of the assigned treatment for asthma, which is defined differently for exposed and unexposed patients (Section 9.3.1):
    - Exposed patients: end of tezepelumab treatment episode or date of start of any other biologic[1]
    - Unexposed patients: end of the treatment episode of SOC for severe asthma (i.e. end of any of the treatments that classify patients as being on high-intensity treatment) or date of tezepelumab initiation or date of start of any other biologic

[1] Biologics may include anti-immunoglobulin E (anti-IgE), anti-interleukin 5/5R (anti-IL5/5R), and anti-interleukin 4rα (anti-IL4R) but availability may vary during the study period (e.g. discontinuation or approval of new drugs).

9.2.4 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 and/or low dose OCS at least 50% of the past year (37). The identification steps of patients with severe asthma within the cohort of patients with asthma receiving high-intensity treatment is illustrated below in Figure 2. The same approach is used for both adults and adolescent patients.

Figure 2 Identification of patients with severe asthma among adult and adolescent asthmatic patients receiving high-intensity treatment

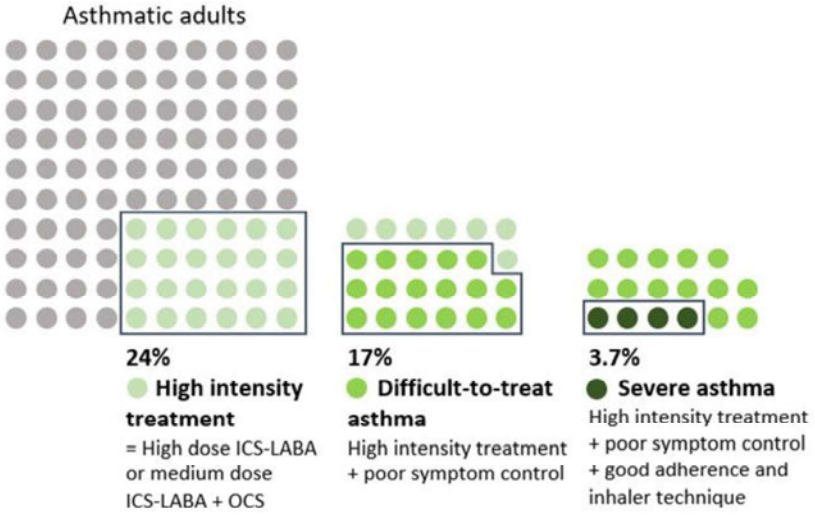


Figure from GINA Main report 2022 (38)
Abbreviations: ICS-LABA, Inhaled Corticosteroid-Long-acting β2-agonist; OCS, Oral Corticosteroid.

In this study, **high-intensity treatments** are defined as any of below combinations:

- Concomitant use of high dose ICS + LABA
- Concomitant use of medium to high dose ICS + low dose OCS at least 50% of the past year
- Concomitant use of medium to high dose ICS + LABA + low dose OCS at least 50% of the past year
- Concomitant use of medium to high dose ICS + LABA + third controller other than low dose OCS
- Biologics

The criterion of concomitant use of medium to high dose ICS plus LABA plus a third controller was added to the criteria listed in Figure 2 above to include a broader definition reflecting clinical practice. Given their indication, exposure to biologics can also be considered as an indicator of severe asthma.

SOC for severe asthma includes high-intensity treatments (non-biologic high-intensity treatments for the comparative analyses) which are further detailed in Section 9.3.1.2.

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 (37): 1) poor symptom control (not available in data), 2) frequent severe exacerbations, 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). Given the use of secondary data sources, in this study, **uncontrolled asthma** is defined as any of the below definitions in the 12 months before index date:

- Frequent severe exacerbations
    - 2 or more prescriptions of high dose 'burst' OCS (dose ≥40 mg for 5-7 days)
    - SABA over-use, defined as the use of three or more 200-dose cannisters
- Hospitalisation for asthma
- Low dose OCS (≤7.5 mg/day prednisone equivalent) for >50% (proportion of days covered).

Each component used to define uncontrolled asthma is part of the list of covariates to be included in the PS (Section 9.3.3).

9.2.5 Source population and study populations

To address the research questions, eligible patients with asthma will be identified through a nested selection process. The *source population* will consist of patients with a diagnosis of asthma receiving tezepelumab or high-intensity SOC treatment for severe asthma (as described above in Section 9.2.4) at any point during the study period. From this source population, the *exposed study population* will be identified as patients who initiate tezepelumab treatment and the *unexposed study population* will be identified as comparable patients who are unexposed to tezepelumab. The unexposed population will be selected from a pool of patients (in the source population) who could become exposed to tezepelumab in the future.

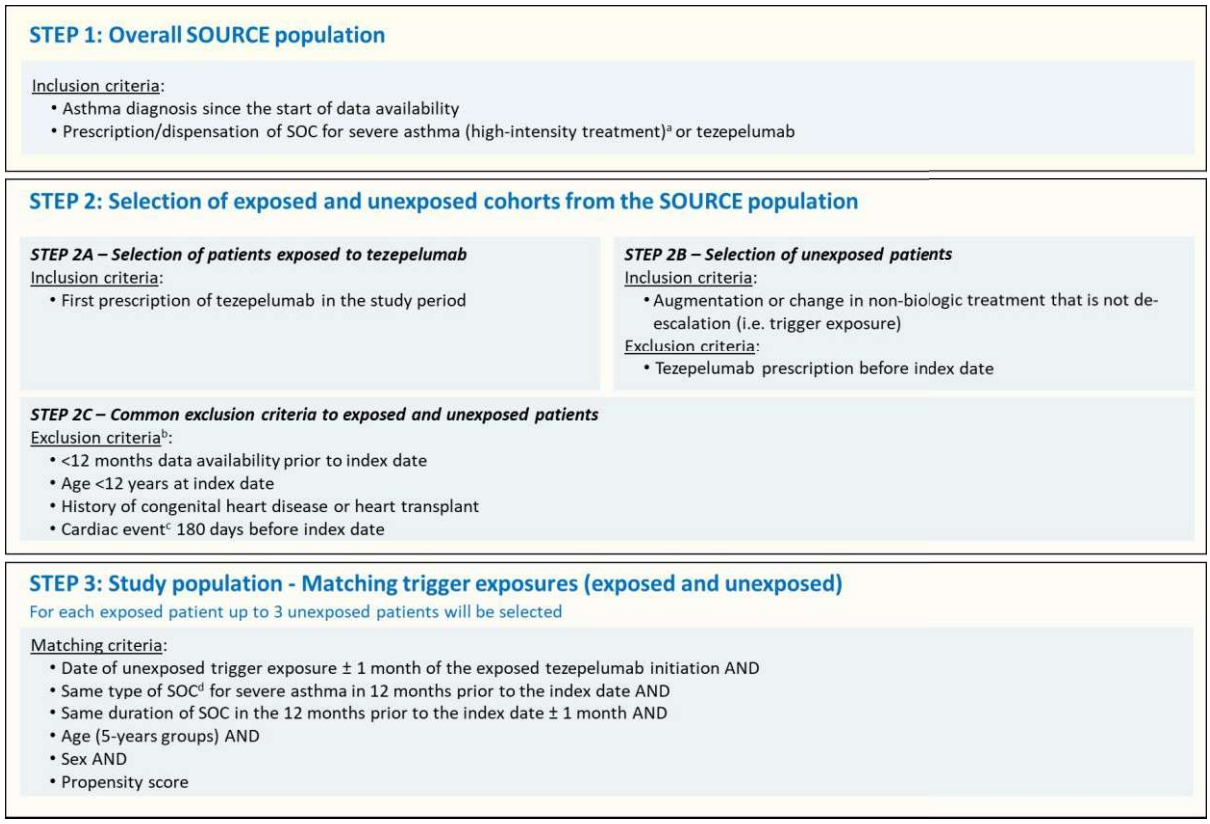
The selection of comparable unexposed patients will be based on the following criteria:

1. Unexposed patients will be required to have a trigger exposure (as defined in Section 9.3.1.4) that mirrors tezepelumab initiation. This treatment exposure is defined as an augmentation or change in severe asthma treatment that does not represent treatment de-escalation.
2. Unexposed patients are required to have matching clinical and treatment characteristics to the exposed patients in the 12-month baseline period before the

trigger exposure date. Additionally, unexposed patients will be those who have a similar baseline risk of cardiovascular events. The parameters considered are detailed in Section 9.3.3.

The selection process is outlined in Figure 3 and detailed in below sections.

Figure 3 Overview of the data extraction and definition of the study population



[a] High-intensity treatment: concomitant use of high dose ICS + LABA; concomitant use of medium to high dose ICS + low dose OCS at least 50% of the past year; concomitant use of medium dose ICS + LABA + low dose OCS at least 50% of the past year; concomitant use of medium dose ICS + LABA + third controller not low dose OCS; biologics

[b] Additional exclusion criteria will be considered for comparative analyses (i.e. exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic)

[c] Non-fatal myocardial infarction or non-fatal stroke and outcome-specific serious cardiovascular events

[d] Type of baseline SOC defined in Section 9.3.1.3.

Abbreviations: SOC, standard of care; ICS, Inhaled corticosteroids; LABA, Long-acting β2-agonist; OCS, Oral corticosteroid

9.2.5.1 Overall Source population inclusion criteria (STEP 1, Data extraction)

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

- Patients with asthma diagnosis (10th Revision International classification of diseases [ICD-10] codes described in Table 16, Appendix E) during the study period

- Patients with high-intensity treatment during the study period (as defined in Section 9.3.1.2)

9.2.5.2 Selection of exposed and unexposed cohorts from the SOURCE population (STEP 2)

From the source population, a cohort of patients exposed to tezepelumab will be identified. Unexposed cohort will be selected from the pool of patients on high-intensity SOC treatment. Eligible patients will be those with an augmentation or change in non-biologic high-intensity treatment that does not represent treatment de-escalation (i.e. trigger exposure). Trigger exposures are designed to mirror tezepelumab initiation, as detailed in Sections 9.3.1.4 and 9.2.5.3.

At STEP 2, the unit of observation will be the trigger exposure: first tezepelumab prescription for exposed patients (one per patient) and the trigger exposure for unexposed patients (one or more triggers per patient). Selection of patients in the exposed and unexposed cohort will be based on the following steps:

Selection of patients exposed to tezepelumab (STEP 2A)

Patients will be eligible for inclusion in the *exposed cohort* if they have:

- A first prescription or administration of tezepelumab during the inclusion period (index date)

Selection of unexposed patients (STEP 2B)

Patients will be eligible for inclusion in the *unexposed cohort* if they have:

- Any trigger exposure, defined as treatment augmentation with a non-biologic in addition to baseline high-intensity treatment during the inclusion period or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation. The date of each trigger will be defined as a potential index date (each patient can have multiple trigger exposures).

Patients will be excluded if they have:

- One or more tezepelumab prescriptions prior to index date

Common exclusion criteria to exposed and unexposed patients (STEP 2C)

- <12 months of data availability prior to index date
- Age <12 years at index date
- Presence of a cardiac event (non-fatal myocardial infarction, non-fatal stroke and the outcome of interest) in the 180 days prior to index date
- A history of congenital heart disease
- A history of heart transplant

Patients with a diagnosis code for non-fatal myocardial infarction or non-fatal stroke in the 180 days[2] prior to index date will be excluded. For each specific outcome, the presence of the outcome of interest in the 180-days before index date will be considered an additional exclusion criterion (described in Section 9.3.2).

9.2.5.3 Study population - Matching trigger exposures (exposed and unexposed) (STEP 3)

To ensure similar baseline risk of cardiovascular events, time-conditional matching criteria will be applied to identify unexposed patients who are comparable to exposed patients in terms of baseline SOC type, SOC duration, age, sex, and PSs. An exposure set will be created for each exposed patient consisting of unexposed patients having a trigger exposure. Inclusion, exclusion, and matching criteria will be evaluated at the date of each trigger exposure (potential index date). Unexposed patients may contribute to multiple exposure sets.

Matching will be done within each exposure set chronologically starting with the first exposed patient. Once an unexposed patient has been matched, they will no longer be considered a potential comparator for another exposed patient (i.e. matching without replacement). However, the unexposed patient can become an exposed patient later during follow-up.

Matching criteria are defined as (all criteria are considered):

- **Date of trigger exposure in unexposed patients ± 1 month** of the exposed index date
    - Wider assessment intervals may be considered if comparators are not identifiable within ± 1 month. With this approach, unexposed patients will be identified around tezepelumab initiation in comparable exposed patients, minimising potential bias due to time trends and assuring broadly similar durations of follow-up between exposed and unexposed cohorts.
- **Type of SOC** for severe asthma in 12 months prior to the index date (as described in Section 9.3.1.3)
- **Duration of the above type of SOC** (± 1 month, wider assessment intervals may be considered up to ± 3 months if comparators are not identifiable within ± 1 month) for severe asthma in the 12 months prior to the index date
- **Age** (5-years groups)
- **Sex**
- **PS**, including prior disease characteristics and other potential confounders (as described in Section 9.3.3)

[2] The time period of 180 days was defined to account for possible delay in recording diagnosis and maximise capturing incident events. A sensitivity analysis (Section 9.7.4) is planned to exclude patients with a history of the outcome of interest (ever).

9.2.5.4 Objective-specific study cohorts

Outcome-specific study cohorts for the main analyses of primary and secondary objectives are described in Table 3. Outcome-specific exclusion criteria will be applied for each objective.

Table 3 Cohorts definition, by objective

Objective	Outcome	Input population	Additional exclusion criteria to be applied at STEP 2C
Primary objective 1	Composite – MACE	Study population	• No additional exclusion criteria
Primary objective 2	Composite – MACE	SOURCE population	• Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
Secondary objective 3	Composite – arrhythmias, coronary artery disease, heart failure, or myocardial disorders	SOURCE population	• Diagnosis of arrhythmias, coronary artery disease, heart failure, or myocardial disorders in the 180 days prior to index date
Secondary objective 4	Composite – arrhythmias, coronary artery disease, heart failure, or myocardial disorders	SOURCE population	• Diagnosis of arrhythmias, coronary artery disease, heart failure, or myocardial disorders in the 180 days prior to index date • Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
Secondary objective 5	Non-fatal myocardial infarction	Study population	• No additional exclusion criteria
	Non-fatal stroke	Study population	• No additional exclusion criteria
	Arrhythmias	SOURCE population	• Presence of arrhythmias in the 180 days prior to index date
	Coronary artery disease	SOURCE population	• Presence of coronary artery disease in the 180 days prior to index date
	Heart failure	SOURCE population	• Presence of heart failure in the 180 days prior to index date
	Myocardial disorders	SOURCE population	• Presence of myocardial disorders in the 180 days prior to index date
	Cardiovascular death	SOURCE population	• No additional exclusion criteria
Secondary objective 6	Non-fatal myocardial infarction	SOURCE population	• Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
	Non-fatal stroke	SOURCE population	• Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic

Objective	Outcome	Input population	Additional exclusion criteria to be applied at STEP 2C
	Arrhythmias	SOURCE population	• Presence of arrhythmias in the 180 days prior to index date • Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
	Coronary artery disease	SOURCE population	• Presence of coronary artery disease in the 180 days prior to index date • Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
	Heart failure	SOURCE population	• Presence of heart failure in the 180 days prior to index date • Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
	Myocardial disorders	SOURCE population	• Presence of myocardial disorders in the 180 days prior to index date • Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic
	Cardiovascular death	SOURCE population	• Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic

Abbreviation: MACE, Major adverse cardiovascular events.

9.2.5.5 Study cohorts for sensitivity analysis

Sensitivity analyses described in Section 9.7.4 will be performed on the study cohorts created for the main analyses, except the analysis excluding patients with a history of the outcome of interest ever since data availability. The cohort for this sensitivity analysis is defined in Table 4.

Table 4 Cohort for sensitivity analysis excluding any history of outcome

Sensitivity analysis	Objective	Input population	Exclusion criteria to be applied at STEP 2C
Exclusion of patients with a history of the outcome of interest (ever)	Primary objective 1	SOURCE population	• Any history of non-fatal myocardial infarction or non-fatal stroke (beyond 180 days)

Sensitivity analysis	Objective	Input population	Exclusion criteria to be applied at STEP 2C
	Primary objective 2	SOURCE population	• Any history of non-fatal myocardial infarction or non-fatal stroke (beyond 180 days) • Exposure to non-tezepelumab biologics on index date or within the 5- half-life clearance period of the biologic
	Secondary objective 3	SOURCE population	• Any history of non-fatal myocardial infarction or non-fatal stroke (beyond 180 days) AND • Any history of arrhythmias, coronary artery disease, heart failure, or myocardial disorders (beyond 180 days)
	Secondary objective 4	SOURCE population	• Any history of non-fatal myocardial infarction or non-fatal stroke (beyond 180 days) AND • Any history of arrhythmias, coronary artery disease, heart failure, or myocardial disorders (beyond 180 days) • Exposure to non-tezepelumab biologics on index date or within the 5- half-life clearance period of the biologic

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 covariates, which include participants' characteristics and other potential confounding variables and risk factors (Section 9.3.3).

In this protocol, ICD-10 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 Organization's (WHO) Anatomical Therapeutic Chemical (ATC) classification system will be used for all prescription drugs in this protocol. The ICD-10 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 ICD-10 to identify Clinical Modifications, ICD10-CM) and will be provided in the statistical analysis plan (SAP). The ICD-10 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 ICD-10-CM) and will be provided in the SAP.

Appendix E provides an exemplar list of codes for exposure, outcome, and other variables for which either ATC codes and/or ICD-10 codes are used. List of codes will be finalised in the SAP.

9.3.1 Exposure

Exposure to tezepelumab and other SOC drugs for severe asthma will be ascertained from registries of outpatient visits, procedures, prescriptions dispensed at community pharmacies, and insurance claims registrations as available in the different data sources.

9.3.1.1 Exposed patients (tezepelumab)

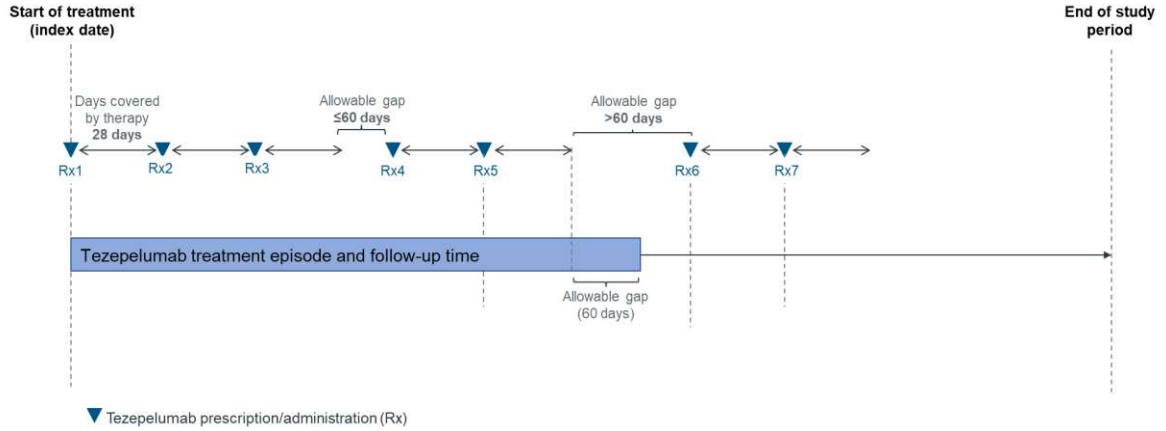
The exposure of primary interest is tezepelumab. According to the current drug indication, tezepelumab is expected to be prescribed as an add-on maintenance treatment in patients with severe asthma who are inadequately controlled despite high dose ICS and other SOC maintenance drugs for severe asthma. It is possible that the therapeutic indication for tezepelumab and its method of administration may change over the course of the study period. 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.

Tezepelumab is expected to be administered every 4 weeks (every 28 days). **Treatment episodes** will start at the date of the first prescription/administration and subsequent prescriptions/administrations will be combined into treatment episodes following below assumptions.

To mitigate the impact of irregular administrations or missing data of continuously treated patients, an allowable gap of 28 + 60 days between administrations will be considered continuous treatment (due to the chronic nature of treatment), as detailed in Figure 4. Exposure assessment (and exposed follow-time) will stop at the end of the treatment episode, or any other censoring criteria as defined in Section 9.2.3. This approach is based on the assumption that any possible increased risk of cardiovascular outcomes is substantially reduced after the end of the treatment.

Further details on the definition of exposure time, including rules for stockpiling, overlap and gaps in treatment will be further detailed in the SAP.

Figure 4 Exposure assessment for patients exposed to tezepelumab



Abbreviation: Rx, Medical prescription.

9.3.1.2 SOC for severe asthma

The identification of treatment combinations and dosage of SOC for severe asthma is based on the 2023 GINA Global Strategy for Asthma Management and Prevention (1), defined as high-intensity treatment, as described in Section 9.2.4.

As SOC for severe asthma may change during the study period, the initial list of SOC treatments shown in Table 5 will be finalised during the SAP development and updated in subsequent study reports. Exemplar code list of the drugs considered for SOC is detailed in Table 17, Appendix E.

Table 5 Drugs included in the SOC treatment for severe asthma

Non-biologic treatments
ICS
High dose ICS (i.e. beclomethasone dipropionate, budesonide, ciclesonide, fluticasone, mometasone)
Medium dose ICS (i.e. beclomethasone dipropionate, budesonide, ciclesonide, fluticasone, mometasone)
Second controllers
LABA (i.e. formoterol, salmeterol, vilanterol, indacaterol)
OCS low dose (≤7.5 mg/day prednisone equivalent) (i.e. dexamethasone, prednisone)
Third controllers
LABA (if not used already)
OCS low dose (≤7.5 mg/day prednisone equivalent) (i.e. dexamethasone, prednisone) (if not used already)
LAMA (i.e. tiotropium bromide, glycopyrronium bromide, umeclidinium bromide)
LTRA (i.e. montelukast, zafirlukast, pranlukast, zileuton)

Non-biologic treatments
Others (i.e. theophylline, azithromycin 500 mg three times a week)
Biologic treatments [a]
Anti-immunoglobulin E (anti-IgE) (i.e. omalizumab)
Anti-interleukin 5/5R (anti-IL5/5R) (i.e. reslizumab, mepolizumab, benralizumab)
Anti-interleukin 4Rα (anti-IL4R) (i.e. dupilumab)

[a] For comparative analyses, only non-biologic high-intensity treatments will be considered as standard of care
Abbreviations: ICS, Inhaled corticosteroid; LABA, Long-acting β2-agonist; LAMA, Long-acting muscarinic antagonists; LTRA, Leukotriene receptor antagonist; OCS, Oral corticosteroids.

ICS dosage is defined in Table 6 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 6 Definition of high daily dose of various ICS for patients aged 12 years or more (38)

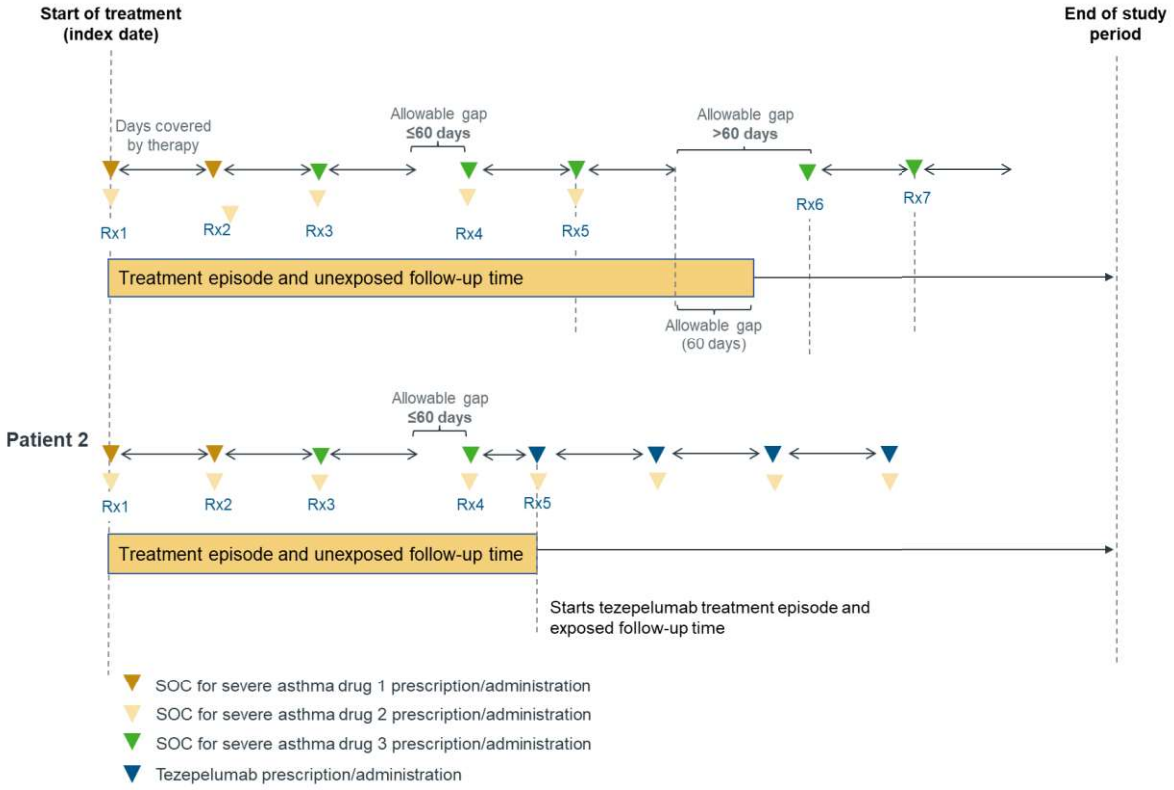
ICS	Preparation	Threshold daily dose in µg	
		Medium	High
Beclomethasone dipropionate	DPI or pMDI, extrafine particle, HFA	>200-400	>400
	pMDI, standard particle, HFA	>500-1000	>1000
Budesonide	DPI, or pMDI, standard particle, HFA	>400-800	>800
Ciclesonide	pMDI, extrafine particle, HFA	>160-320	>320
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.

Exposure assessment in unexposed patients

Exposure assessment will follow the overall approach described for tezepelumab exposure assessment (Section 9.3.1.1). SOC treatment episodes will consist of sequential treatment as long as the minimum criteria of high-intensity SOC treatment for severe asthma is maintained (outlined in Section 9.2.4). The end of a treatment episode will be defined as the final date of the days covered by the forementioned SOC treatments that indicate the end of high-intensity treatment. Any changes within the SOC (switching, addition or reduction of drugs) will not influence the duration of treatment, however patients will be censored if they initiate tezepelumab or any other biologic (see patient 2 in Figure 5; further details on follow-up and censoring are available in Section 9.2.3). Different SOC drugs will not be counted as a different treatment episode if prescribed/administered within the allowable gap of 60 days after the days covered by the last drug (Figure 5).

Figure 5 Exposure assessment for patients unexposed to tezepelumab – exposed to SOC for severe asthma



Abbreviation: Rx, Medical prescription; SOC, Standard of care.

9.3.1.3 Type of baseline SOC

The categories of baseline SOC during the 12-month baseline period will be data-driven (i.e. informed by the most frequently observed treatment patterns in each data source), but

supported by clinical considerations and available knowledge on the importance of each drug to represent asthma severity and drug's cardiovascular safety. Type of SOC may include the following categories:

a) ICS-LABA

b) ICS-LABA-third controller

c) ICS-OCS

d) Biologics [3]

For comparative analyses patients with biologics exposure at index date or within five half-lives of the biologic drug will be excluded. Additionally, a sensitivity analysis is planned to stratify exposed and unexposed patients based on the type of baseline SOC, as detailed in Section 9.7.4.

9.3.1.4 Trigger exposure definition

Augmentation or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation will be considered as trigger exposures in the unexposed patient cohort. Trigger exposures are designed to mirror the start of tezepelumab in the exposed patient cohort and will be captured in the -/+ 1 months' time interval around the tezepelumab initiation date. Triggers will be defined as follows:

- Baseline SOC + start of *additional* controller (e.g. ICS-LABA + *OCS*)
- Baseline SOC + *switching* controller (e.g. ICS-LABA-*OCS*→ICS-LABA-*LTRA*)

Non-biologic treatments are defined in Section 9.3.1.2. The date of treatment start or switch within the time interval will define the index date.

9.3.2 Outcomes

Overall, outcomes in the study refer to serious adverse cardiovascular events that will be identified from hospitalisations using ICD-10 diagnosis codes available in participating data sources. Availability of the codes in each country and their accuracy was assessed in the feasibility assessment and described in Section 9.4.1. Limitations on the availability and accuracy of the codes are described in Section 9.9.

Table 7 presents the operational definitions of the study outcomes for each of the objectives. Diagnosis codes for each outcome are presented in Table 18 and Table 19 in Appendix E.

[3] Biologics will be captured during the 12-month baseline period to categorise type of SOC but will not be used to define a trigger exposure.

Table 7 Study outcomes definition

Objective	Outcome	Definition
Primary (Table 18 in Appendix E)	MACE, composite of: non-fatal myocardial infarction non-fatal stroke Cardiovascular death	First hospitalisation after index date with a recorded diagnosis of myocardial infarction OR stroke, with a discharge status alive and no record of death in the following 30 days. OR any death caused by a cardiovascular event (if cause of death available) OR death occurring during a hospitalisation with a recorded primary diagnosis related to cardiovascular condition (discharge status death) OR death within 30 days of hospitalisation (of discharge date) with a recorded primary diagnosis related to cardiovascular condition.
Secondary (Table 19 in Appendix E)	Composite of four serious adverse cardiovascular events: Arrhythmias coronary artery disease heart failure myocardial disorders	First hospitalisation after index date with a recorded diagnosis of: arrhythmia OR coronary artery disease OR heart failure OR myocardial disorders AND no records of death related to the named cardiovascular events (discharged alive and no records of death in the following 30 days)
	Serious adverse cardiovascular events individually:	
	Arrhythmia	First hospitalisation after index date with a diagnosis of arrhythmia with a discharge status alive and no record of death in the following 30 days.
	Coronary artery disease	First hospitalisation after index date with a recorded diagnosis of coronary artery disease with a discharge status alive and no record of death in the following 30 days.
	Heart failure	First hospitalisation after index date with a recorded diagnosis of heart failure with a discharge status alive and no record of death in the following 30 days.
	Myocardial disorders	First hospitalisation after index date with a recorded diagnosis of myocardial disorder with a discharge status alive and no record of death in the following 30 days.
	Myocardial infarction	First hospitalisation after index date with a recorded diagnosis of myocardial infarction with a discharge status alive and no record of death in the following 30 days.

Objective	Outcome	Definition
	Stroke	First hospitalisation after index date with a recorded diagnosis of stroke with a discharge status alive and no record of death in the following 30 days.
	Cardiovascular death	Any death caused by a cardiovascular event (if cause of death available) OR death occurring during a hospitalisation with a recorded primary diagnosis related to cardiovascular condition (discharge status death) OR death within 30 days of a hospitalisation (of discharge date) with a recorded primary diagnosis related to cardiovascular condition.

Abbreviation: MACE, Major adverse cardiovascular events.

9.3.2.1 Primary outcome: MACE

MACE is a recognised relevant cardiovascular endpoint (39). In this study, the composite will consist of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death which is comparable with definitions used in other studies using secondary data (40). Regarding stroke, all types will be considered to minimise misclassification due to heterogeneity on coding practices, namely on distinguishing between ischaemic and subarachnoid and intracerebral haemorrhages (40).

Events considered for MACE (objectives 1 and 2) will be identified using diagnosis codes from hospitalisations. A cardiovascular death will be defined as any death caused by a cardiovascular event as specified in death certificates if suitable data on underlying cause are available within data source. Otherwise, fatal events will be assumed to occur when the patient dies during a hospitalisation related to the event of interest (discharge status) or within 30 days of the discharge (41). Fatal cardiovascular events will be aggregated under cardiovascular death category as a component of MACE (objectives 1 and 2) or quantified in a separate category (objectives 3 and 4).

9.3.2.2 Secondary outcomes: serious adverse cardiovascular events

As for primary outcomes, the secondary composite outcome of four SAEs (objectives 3 and 4) will be identified using diagnosis codes from hospitalisations. Thus, the first hospitalisation due to arrhythmias, coronary artery disease, heart failure or myocardial disorders will define the secondary composite outcome.

Additionally, individual components of primary and secondary composite outcomes will be evaluated separately (objective 5 and 6).

9.3.3 Covariates

An initial assessment of the types of covariates to be included in this study as baseline characteristics are presented in Table 8. These include sociodemographic and clinical

characteristics (including asthma characteristics and comorbidities), HCRU and prior concomitant use of drugs. These variables will be considered for characterising exposed and unexposed cohorts at baseline and are potential candidates for inclusion in the PS.

Within asthma characteristics, potential proxies for disease severity based on treatment history may be considered, including exacerbations in the previous 12 months. As previously described in Section 9.2.4, severe asthma patients may increase the use of OCS (i.e. two or more prescriptions of high dose OCS) and over-use of SABA (i.e. more than three SABA cannisters) in addition to high-intensity treatment to relieve their symptoms and treat exacerbations.

The initial selection of covariates was based on clinical relevance, possible confounder role identified in observational longitudinal studies included in a meta-analysis on the association of asthma and cardiovascular disease, additional literature, and key opinion leader input. The rationale for covariate selection and exemplar list of ICD-10 codes is detailed in Table 20 in Appendix E. The availability of covariates in the data sources is described in Section 9.4.1 and Table 15 in Appendix D. Recorded diagnoses in primary care or outpatient settings may not be available in all data sources which can limit the ability to capture some baseline comorbidities. Whenever feasible, proxy measures using prescribed medications may be considered to define the comorbidity and minimise missingness (e.g. prescription of anti-hypertensives to define the existence of hypertension). More details will be provided in the SAP.

Table 8 Initial list of covariates at baseline

Characteristics	Measurement period	Potential variables of interest
Sociodemographic characteristics	Index date (closest to)	• Gender • Age at index date • Race/ethnicity • Socioeconomic status (e.g. educational attainment, income level or deprivation index of the city of residence) • Calendar year of index date
Lifestyle characteristics	Index date (closest to)	• Smoking status • Alcohol abuse or dependence • Substance abuse or dependence • Obesity
Clinical Characteristics		

Characteristics	Measurement period	Potential variables of interest
Asthma characteristics	12 months preceding the index date	• High-intensity asthma treatments, including biologics (for patients' characterisation) • Exposure to (any) OCS • Number of exacerbations • ≥2 prescriptions for high dose OCS • More than 50% of days covered by low dose OCS • SABA over-use (≥3 cannisters, 200 doses each) • Number of hospitalisations due to asthma • Number of emergency room visit, or outpatient visit due to asthma • Number of admissions in intensive care unit
Respiratory diseases (other than asthma)	12 months preceding the index date (inclusive)	• Bronchiectasis • Allergies (e.g. mites, fungus, pollen) • Chronic obstructive pulmonary disease (COPD), including emphysema • Pulmonary arterial hypertension • Lower respiratory tract infections • SARS-CoV-2
Cardiovascular disease [a]	Database availability to index date (inclusive)	• Hypertension • Hyperlipidaemia • Myocardial infarction • Acute coronary syndrome or unstable angina • Stable angina • Coronary atherosclerosis and other forms of chronic ischaemic heart disease • Other atherosclerosis • Previous cardiac procedure • Congestive heart failure • Peripheral vascular disease or surgery • Atrial fibrillation • Other cardiac dysrhythmia • Cardiac conduction disorders • Stroke
History of malignancies	Database availability to index date (inclusive)	• Any malignancy

Characteristics	Measurement period	Potential variables of interest
Other comorbidities	12 months preceding the index date (inclusive)	• Diabetes • Charlson Comorbidity Index
HCRU	12 months preceding the index date (inclusive)	• Outpatient and primary care visits • Use of emergency department • Hospitalisations (number of days, number of hospitalisations)
Prior and concomitant use of drugs	12 months preceding the index date (inclusive)	• Any relevant medication (for any other reason than asthma)

[a] The list of comorbidities will depend on the outcome of interest being evaluated.
Abbreviations: HCRU, Health care resource utilisation; OCS, Oral corticosteroids; SABA, Short-acting beta2-agonist; SARS-COV-2, Severe acute respiratory syndrome coronavirus 2.

9.4 Data sources

A feasibility assessment was conducted between July and November 2023 to assess the suitability of the proposed data sources to address the study's research question and objectives.

Thirty-six data sources were investigated during the feasibility assessment across nine countries in Europe (Belgium, Denmark, Finland, France, Germany, Italy, Portugal, Spain, and the UK) and in the USA. In addition, eleven severe asthma registries were investigated but none was suitable to be included in current study. A summary of the rationale for inclusion/exclusion of each evaluated data source is presented in Table 14 in Appendix D.

Of the ten countries evaluated, four were selected: Denmark, France, Germany, and USA.

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

- Characteristics of the data sources
- Logistics and access requirements
- Availability and coding systems of drugs, diagnoses, and procedures
- Availability and completeness of variables (exposures, outcomes, and covariates)
- Estimated number of patients with severe asthma

The number of patients with severe asthma was estimated by multiplying the number of patients with asthma provided by the data holders by the prevalence of severe asthma among

asthmatic patients reported in the literature: varying from 3% to 8% among adults (7, 42) and 0.2% and 2% in childhood (9, 42).

Tezepelumab was approved in the US in December 2021, and by the EMA in September 2022. Tezepelumab is administered subcutaneously 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 include prescriptions for self-administration- at home, with one dose/vial per prescription, to be filled/administered every four weeks as prescribed.

The final list of data sources was based on the results of the feasibility assessment, including the ability of the data sources to meet the requirements (estimated size of patient population, ability to capture SOC for severe asthma (including biologics), and ability to capture study outcomes). The protocol will be amended if it is determined that additional data sources are warranted to meet study enrolment and endpoint requirements.

9.4.1 Overall description of the databases

A summary of the selected data sources, including the availability of exposure and outcome variables is presented in Table 9, below.

Table 9 Summary of feasibility of selected data sources

Country	Start of data availability	Country coverage	Data lag, months	Availability of exposure		Availability of outcomes[1]		
						Primary outcomes		Secondary outcomes
				Tezepelumab	SOC	Coded diagnoses	Cause of death	
Denmark, National Registers	1977[2]	100%	13	Yes	Yes	Yes	Yes	Yes
France, SNDS	2008	99%	12	Yes, except for inpatients[3]	Yes, except for inpatients[3] and reslizumab	Yes	No, but proxy can be derived	Yes
Germany, SHI	2008	5.4%	16	Yes, except for inpatients	Yes, except for inpatients	Yes	No, but proxy can be derived	Yes
USA Carelon	2006	4.9%	3	Yes[4]	Yes[4], except chromones	Yes	Yes[5]	Yes

[1] Diagnoses will not be available if recorded in primary care (Denmark) or in the outpatient care (France).
[2] Considering the Danish National Patient Register-Denmark (DNPR-Den). National Hospital Medication Register (SMR) only available since 2018.
[3] Drugs administered during hospitalisation can be captured if part of the high-cost drugs list (as of October 2023, omalizumab and mepolizumab are part of that list).
[4] For inpatient drugs, chart reviews on a subset of the population (for which the charts are available) can be considered with additional contracting.
[5] Cause of death available through linkage, but percentage of linkage is only known after contract is signed.

Abbreviations: SHI, Statutory Health Insurance; SNDS, French National Health Data System (Système National des Données de Santé); SOC, Standard of care; USA, United Stated of America.

9.4.1.1 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. 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*

  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 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)*

  Danish National Patient Register-Denmark (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 (ICD-10), examinations and treatment information – including surgery coded with Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures codes, as well as supplementary information regarding births.

- *Danish Cause of Death Registry (CDR)*

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

- *Register for udvalgte kroniske sygdomme (Register of Selected Chronic Diseases and Severe Mental Disorders) (RUKS)*

  The RUKS contains information on individuals in Denmark with type 1 diabetes, type 2 diabetes, COPD, asthma, osteoporosis, rheumatoid arthritis, schizophrenia, and dementia. In 2022, RUKS included 459,975 patients with asthma. RUKS contains information about individuals that are resident in Denmark and who meet the criteria for a given disease. RUKS is based on an algorithm using data from RPS as well as diagnosis codes registered in connection with hospital contact in NPR. It can, for example, be redemption of a specific type of medication or a diagnosis in connection with treatment at the Danish hospitals. The register is updated for the entire reporting period with each update, as the disease criteria are continuously evaluated and adjusted in relation to the latest knowledge.

  RUKS has data from 1995 onwards. The period is limited to the date of discharge from NPR and the purchase date from the Medicines Statistics Register. The register is updated once a year when updated source data is available. Every January, the register is updated for people who have been diagnosed with the selected chronic diseases/severe mental disorders up to and including January of the previous year.

Study-specific data availability for Denmark

In the RUKS registry, the number of patients with asthma (defined by recorded diagnoses in secondary care and/or the use of asthma drugs among patients aged 12 or more years) was 251,075 in 2022. Among these, between 7,532 to 20,086 patients with severe asthma are expected to be identified. If the number of severe asthma patients is estimated from the number of patients with an asthma diagnosis in secondary care only (26,579 in 2022), between

797 and 2,126 patients with severe asthma would be expected. However, this population of asthma patients may represent those with more severe disease because it only includes diagnosis in secondary care. If so, the actual number of patients with severe asthma is likely to be higher.

In Denmark, a public report showed that 1,040 patients with severe asthma were on biologic treatment in 2022 (43). Considering the expected number of patients with severe asthma in the RUKS, this number represents 5-15% of severe asthma patients on biologics.

In Denmark, tezepelumab received marketing authorisation in September 2022. A pre-reimbursement programme with tezepelumab available for health care professionals to prescribe when a specific request is submitted to the hospital was in action between November 2022 and April 2023. The actual date of tezepelumab launch with reimbursement was 26 April 2023 and this is the anticipated start of the study period for Denmark. Since then, tezepelumab is recommended as maintenance treatment for adults with severe asthma with signs of type 2 inflammation that is not adequately controlled despite optimised standard treatment (high dose ICS and another asthma drug for maintenance treatment).

Information on drugs dispensed in community pharmacies is available through RPS, drugs prescribed in hospital, other institutional care or drugs administered in hospital are available through SMR. ATC codes and Danish brand names allow the distinction between biologics.

Diagnoses for primary and secondary outcomes can be captured. Additionally, date and cause of death are available through CDR. Cardiovascular diagnoses in the NPR showed high positive predictive values (PPV), if captured from hospitalisations, and taking into account only primary or primary and secondary diagnoses. However, sensitivity is not known. PPV varied from 82% to 97% for myocardial infarction and from 74% to 97% for stroke (44-47). PPV for unstable angina as a primary diagnosis of hospitalisation was 88%, increasing to 95% when including secondary diagnoses and those in the outpatient setting (45). For heart failure, PPV of primary hospitalisation discharge diagnosis was 88%, decreasing to 76-80% if the diagnosis was recorded in the outpatient setting (45, 47, 48).

MACE has been considered in previous studies using the Danish national registries, although with slightly different definitions: all-cause mortality instead of cardiovascular mortality and inclusion of other adverse events such as events requiring revascularisation or cardiovascular events requiring hospitalisation (49, 50) . The quality of the data on causes of death relies mainly upon the correctness of the physicians' notification and the coding in the National Board of Health (51). For events with myocardial infarction as the primary diagnosis (from hospitalisations) or underlying cause of death, the sensitivity was 77.6% but increased when including secondary diagnosis and contributory cause of death (52).

Covariates are available (Table 15) except for ethnicity. Most lifestyle variables are available to the extent they are captured from coded diagnoses. Comorbidities are expected to be

available unless diagnosed solely by primary care, in which case they will be missing. Admission to ICU or emergency department (with dates and diagnoses) is possible to capture, but it is based on department unit codes that exist in every hospital and may be more complex to define.

9.4.1.2 France

The French National Health Data System (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 (53). 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 expected data application process for France is about 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.

SNIIRAM collects healthcare information generated through the reimbursement scheme of the French national health insurance. The database provides data on sociodemographic, diagnoses of chronic conditions – the long-term disease (LTD) codes and dates of their first registration, health care encounters such as physician or paramedical visits, medicines, medical devices, and lab tests (without results); outpatient medical expenses including dispensed medication, medical visits and procedures, date and duration of hospitalisations, inpatient diagnoses and procedures (54). However, some health care consumptions cannot be seen, such as consumptions not claimed for reimbursement, not reimbursable health services, and self-medication. Moreover, the only in-hospital prescriptions included are those of expensive drugs that are excluded of the hospital diagnosis related groups (e.g. targeted cancer therapies and some biologics (53)).

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 diagnostic data are encoded according to the ICD-10. Date of death is available within SNDS through a linkage to the national death registry, but information on underlying cause is missing.

Study-specific data availability for France

For SNDS counts, asthma population was defined by the LTD code within the outpatient setting, capturing those with severe persistent asthma. In 2021, 150,810 patients were identified. Additionally, it was possible to identify 63,033 hospital stays in 2022 using asthma ICD-10 codes. No counts for the number of patients on biologics was available, but in 2022, 830,912 boxes of the five considered biologics for asthma were dispensed.

In France, tezepelumab was available for compassionate use, a special authorisation provided by the French National Authority for Health, between 24 August 2022 and 17 February 2023. Tezepelumab was approved in the outpatient setting on 15 May 2023. Data on tezepelumab use (since 2022) will be collected.

Drugs (biologics and non-biologics) dispensed through retail pharmacies are recorded in the *Données de Consommation Interrégimes* (DCIR) (which is part of the SNDS) when they are reimbursed. Data are available from 2008 for outpatient (DCIR) and inpatient (PMSI) settings. Drugs administered during hospitalisation are only captured in the SNDS if they are included in a high-cost drug list (in October 2023, the list includes omalizumab and mepolizumab). If tezepelumab is included in the high-cost drug list, hospital administration of the drug will be captured in the SNDS. Reslizumab was withdrawn from the market in 2019.

In France, study outcomes of interest are available from diagnoses during hospitalisation. A proxy measure for cardiovascular death needs to be defined as described in Table 7.

In a previous study from 2013, the sensitivity of SNDS hospitalisation codes for acute ischaemic stroke was 67% (55). More recent studies have used validated algorithms for MACE using SNDS, including stroke, myocardial infarction, all-cause mortality (56-58) and also cardiovascular mortality (59). Acute coronary syndrome, including ICD-10 codes I20 to I25 (excluding I23 and I25.2), showed high PPV. Additionally, all events were assumed to be captured (suggesting high sensitivity), considering that acute coronary syndrome is a serious event requiring contact with the healthcare system and it is unlikely to be recorded with other ICD-10 codes (60). Most covariates are available (Table 15) except for ethnicity. Most lifestyle variables are available to the extent they are captured from coded diagnoses. Comorbidities are expected to be available if recorded during hospitalisations (primary and/or secondary diagnoses) or as a LTD. Admission to ICU and emergency department can be captured with the respective dates and ICD-10 codes.

9.4.1.3 Germany

In Germany, insurance claims from up to ten different SHIs providers are collected by Team Gesundheit. This is an established research institute which has been working for more than 1,000 health insurance companies, organisations, and ministries since 1997. With branches in Essen, Hamburg, Bielefeld, Berlin, Frankfurt and Munich, they are active in German health management nationwide. Since an SHI is a requirement for individuals with a permanent

place of residence in Germany, even for short-term stays, the general population coverage in the SHI is considered nationwide. The SHIs also allow insurance coverage for children and spouses within a family insurance policy. The population size available through Team Gesundheit is approximately 5 million individuals which represents an estimated 5.4% of the SHI insured population in Germany. Historical data is available from January 2011. All patients are anonymised on a unified identification number, so longitudinal analyses are possible. The update is performed once per year in Q1 of the following year, with an average lag time of approximately 16 months.

The database contains information from primary care, in- and outpatient hospital care, as well as sick leaves. Data on medical encounters encompasses details of general practitioners' and specialists' visits, including dates, diagnoses (available per quarter, limiting ability to accurately define the date of the event if recorded in this setting) and speciality of the treating physician (e.g. pulmonologist). Inpatient care claim data include assigned diagnoses (up to three principal and 30 secondary diagnoses per episode), billed diagnosis related groups (German classification), data on surgical and medical procedures, and duration of the stay among others.

Data on medications includes both reimbursed and non-reimbursed drugs prescribed in primary care for outpatient use and community pharmacy dispensing, and medication administered in hospital outpatient settings. Data on biologics have been available since 2010. Medication use in hospital inpatient settings is not available.

Diagnoses are recorded in the ICD-10 coding system with German modification (GM). Data on surgical and medical procedures are recorded using Operation and Procedure Code (OPS) which is the GM of the international classification of procedures in medicine. Due to the nature of claims data, information on data that is not subject to reimbursement is not available in the database. For example, information on symptoms captured by ICD-10 coding would have little or no coverage as they are usually not subject to reimbursement. Similarly, information on a conducted diagnostic test is only available if being subject to reimbursement. Test results are not available in claims data.

Data on medications includes prescriptions in primary care and community pharmacy dispensing, and medication administered in hospital outpatient settings. Medication use in hospital inpatient settings is not available.

Study-specific data availability for Germany

The number of adult patients with severe asthma in 2022 was expected to vary between 9,231 and 24,616 and between 32 and 324 among children aged 12-17 years. Among the population aged 12 years or more, 3,460 patients had at least one prescription of omalizumab, reslizumab, mepolizumab, benralizumab, or dupilumab between 2019 and 2021, of which 126 were expected to be between the ages of 12-17 years.

In Germany, tezepelumab received marketing authorisation in September 2022. It received approval for reimbursement on 15 November 2022. Asthma biologics, including tezepelumab, are expected to be used in the outpatient setting and thus, will be captured.

In Germany, study outcomes of interest are available. A proxy measure for cardiovascular death will be utilized as described in Table 7. MACE has been considered in other studies using German claims databases (57, 61, 62) and its components were previously validated in a German claims database (63). Cardiovascular death was defined as death within 60 days of a cardiovascular hospitalisation. PPV for myocardial infarction and stroke were above 90% and for cardiovascular death, the PPV was 75%.

Most covariates are available (Table 15) except for ethnicity. Information on socioeconomic status can be derived from other characteristics (highest school-leaving qualification, status in the profession). However, this information is available on a yearly basis only. Lifestyle variables are available to the extent they are captured from coded diagnoses. Comorbidities are expected to be available. Admission to ICU during hospitalisation can be captured. An admission that started with an emergency visit is not trackable, it will be absorbed in the hospital stay. An emergency visit without admission can be tracked and ICD-10 codes are available.

9.4.1.4 USA

Carelon is a large administrative healthcare database maintained by Carelon Research 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. In 2023, the active population was about 16,8 million individuals (around 4.9% of the USA population). 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 ICD-10 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.

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. Carelon is a part of the Sentinel Network utilised by the FDA and as such validates the data as stipulated by the FDA.

Study-specific data availability for the USA

Between 25,773 and 68,728 patients in Carelon are expected to have severe asthma. In 2022, Carelon data included 17,800 patients 12 years of age or older with a record of biologic analogue use, with 1,044 of those occurring within the 12-17 years of age population.

In the USA, tezepelumab received FDA approval in December 2021 and entered the market in January 2022. The first record of tezepelumab in the database occurred in May 2022 and 768 patients were exposed to tezepelumab in the 2022 calendar year, 7 of which were between the ages of 12-17 years.

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. However, inpatient drugs might be missed as inpatient admission claims often bundle drugs administered. Data on drugs administered may be captured via abstraction from requested medical records (available for a subset of patients) However, drugs taken by oral route may not be available.

Study outcomes of interest are available. Cause of death is available through linkage, but percentage of linkage is currently unknown. If linkage is found to be insufficient, a proxy measure for cardiovascular death can be defined as described in Table 7.

A validation study using the HealthCore Integrated Research Database^{SM} (HIRD, currently curated by Carelon Research) and including ICD-9 codes for myocardial infarction and ischaemic stroke in hospitalisations between 2002-2004, showed high PPVs – 84% and 92%, respectively (64). Another study, although using other insurance claims data, concluded that both primary and secondary diagnoses should be considered in the hospitalisation discharge data to increase the sensitivity of the algorithm to capture acute myocardial infarction (65). Other study showed that the PPV of acute myocardial infarction or stroke decreased from 81% when considering principal diagnoses to 62% when considering non-principal diagnoses. PPVs were lower for individuals younger than 65 years of age (66).

All key covariates are expected to be available (Table 15), except for body mass index (BMI) and lifestyle habits which are available to the extent they are captured from coded diagnoses. Admissions to ICU and to the emergency department can be captured.

9.5 Study size

In this study, both sample size and power calculations were carried out separately for the primary outcome (MACE) 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 hazard ratio (HR) (i.e. have it outside the 95% CI) of 1.8 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 patients exposed to tezepelumab by the end of study period:

- Approach 1: **Minimum detectable HR** that could be ruled out with 80% power (see Section 9.5.4);
- Approach 2: **Expected power** to rule out a HR of 1.8 (see Section 9.5.5).

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

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

To assess impact of between-country heterogeneity of HRs, all study size calculations were performed and presented at varying levels of between-country heterogeneity (see Section 9.5.2).

All study size calculations consider number of patients after accounting for potential confounding via matching (i.e. after exact and PS matching has been applied).

9.5.1 Assumptions for the study size calculations

- **A baseline rate of 0.45 events per 100 person-years for MACE events**.

Estimates for MACE in adult patients with severe uncontrolled asthma range from 0.4 to 3.9 per 100 person-years, with the lowest and highest rates observed among those who would be eligible for inclusion in clinical trials and those with comorbid COPD, respectively. These age- and sex-standardised rates were derived from real-world data spanning the period between 2009 and 2018 in the US (IBM MarketScan claims) with a **mean follow-up duration of 2.3 years**, which was also assumed in calculations for this study (67).

- **Uptake of tezepelumab among patients with severe asthma** according to projected number of patients treated with tezepelumab.

First, the number of severe asthma patients was estimated by multiplying the number of adult patients with asthma available in each data source by the expected prevalence of severe disease among asthma patients. Based on a recent study in the Nordic countries, it was assumed that 3.5% of patients with asthma may present severe asthma (42) This frequency is considered a conservative estimate, as some studies show that it might increase up to around 8% of asthma patients (7). The number of severe asthma patients was considered constant during the study period (considering the short period of time (2023-2027), new cases and drop-outs are expected to result in a relatively stable number of severe asthma patients).

Then, tezepelumab uptake in the first year after market launch was based on Marketing Authorisation Holder (MAH) sales projections for patients treated with tezepelumab (in Germany, France, and USA) and the estimated number of severe asthma patients in each country. The average tezepelumab uptake in the first year after market launch in Germany,

France, and USA was used to estimate the expected first year uptake in all countries (including Denmark, for which the MAH sales projections were not available).

The estimated number of patients initiating tezepelumab in the subsequent study years is based on an assumption of 10% increase of tezepelumab uptake year on year for all study countries. It is likely that the actual tezepelumab numbers throughout the years are higher, but the proposed conservative approach represents a base case scenario for the purpose of sample size calculations.

- **A non-inferiority margin of HR of 1.8 (target effect size).**

The HR of 1.8 was based on the HR value suggested as appropriate by EMA to provide a reasonable basis for regulatory assessment of the cardiovascular safety in reflection paper on assessment of cardiovascular safety profile of medicinal products (39).

- **Exposed to unexposed patient ratios of 1:1, 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, although it might depend on exact definition of the comparator cohort at the time of analysis. Thus, the least demanding (in terms of matches) allocation ratio 1:1, as well as allocation ratios of 1:2 and 1:3 were used, as matching each patient in the exposed cohort to more than one patient in unexposed cohort will increase statistical power.

Using the derived uptake projections and the timing of patient inclusion periods within countries (see Table 2), the total number of new patients exposed to tezepelumab identified during the inclusion period in each study country was estimated as the number of severe asthma patients multiplied by tezepelumab uptake proportion for each study year (see Table 10). As discussed above, the number of patients initiating tezepelumab was based on an increase of 10% each year in all study countries.

Table 10 Expected number of patients exposed to tezepelumab in the data sources by final study reporting year under the assumed uptake scenario

Country, data source	Expected number of patients initiating tezepelumab (Inclusion period: 2022-2027)	Country contribution, %
Denmark, National Registers	3,792	4.0%
Germany, SHI	4,498	4.7%
France, SNDS	65,637	68.7%
USA, Carelon	21,647	22.6%
All	**95,574**	**100%**

Abbreviations: SHI, Statutory Health Insurance; SNDS, French National Health Data System (Système National des Données de Santé); USA, United Stated of America.

9.5.2 Methods for the study size calculations

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

The sample size and power calculations were performed using simulations under the assumption that the true mean HR is 1.0 (39). It was assumed that true HRs may fluctuate around the true mean HR in individual countries, e.g. due to varying levels of ability to adjust for confounders
The following steps constitute a single simulation and are the same for all study size calculations:

1. For a given overall sample size, a fixed proportion of the overall sample was assigned to each of the data sources included in the meta-analysis, corresponding to expected distribution of sample across the data sources by the final study reporting year (see Table 10).
2. For each data source, the true log-HR was drawn from normal distribution $N(0, \sigma^2)$, where σ was selected to provide the specified standard deviation, σ_{HR}, for the sampled true HRs (i.e. exponentiated log-HRs). The following values for σ_{HR} were used: 0, 0.1, 0.2, 0.3. Corresponding values for σ were 0, 0.099, 0.194, 0.282, which were obtained using the relationship between parameters of the normal and log-normal distributions.
3. The survival times for primary outcome events in each exposure group were simulated using *simsurv* package in R (68). Survival times were simulated for each data source from an exponential distribution with scale parameter λ=-log(1- baseline rate), which was assumed constant across all countries. Simulations were conducted using the true HR in each country as obtained in step 2. The maximum follow-up time at which subjects were censored was set to 2.3 years.
4. The estimated data source level log-HRs, their standard errors, and their 95% CIs were computed using a Cox proportional hazards (CPH) regression.
5. The data source level log-HRs and their standard errors were entered into a fixed-effect (when simulating under no between-study heterogeneity, σ_{HR}=0) or a random-effects (when simulating with between-study heterogeneity, σ_{HR}>0) meta-analysis model, where pooled effect estimates and their 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 (69).

For **minimum required sample size**, the steps 2-4 were repeated 1,000 times on a sequence of sample sizes. For each sample size, the proportion (which represents the power) of the 1,000 simulated 95% CI upper bounds that were smaller than the target HR of 1.8 (the smallest among HRs considered) was computed. The sample size for which this proportion was the closest to 80% was selected (rounded to nearest ten).

For **minimum detectable HR**, the steps 2-4 were repeated 1,000 times for the sample size equal to expected number of tezepelumab exposed patients in total across the data sources at the end of study period. For all HRs in a grid with precision of 0.01, the proportion (which represents the power) of the 1,000 simulated 95% CI upper bounds that were smaller than the corresponding HR was computed. The HR for which this proportion was the closest to 80% was selected.

For **expected power**, the steps 2-4 were repeated 1,000 times for the sample size equal to expected number of tezepelumab exposed patients in total across the data sources at the end of study period. The proportion (which represents the power) of the 1,000 simulated 95% CI upper bounds that were smaller than the target HR of 1.8 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 HR 1.8 for the primary outcome (MACE). 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 (Table 10).

The minimum required overall sample sizes at different levels of between-study heterogeneity are presented in Table 11 (sample sizes per data source are presented in Table 21 in Appendix F).

Table 11 Minimum required sample size in tezepelumab exposed group for meta-analysis of MACE at different matching ratios and between-country heterogeneity levels

Between-country heterogeneity (σ_{HR})	Minimum required sample size in tezepelumab exposed group for meta-analysis of MACE		
	1:1	1:2	1:3
0	4,530	3,430	3,100
0.1	6,020	5,140	4,750
0.2	8,550	6,960	6,300
0.3	16,640	13,410	11,890

Abbreviations: MACE, Major adverse cardiovascular event.

9.5.4 Minimum detectable risk ratio

While the above calculation shows the sample size required to rule out a HR of 1.8 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 9.5.3. Therefore, the minimum detectable HR for 80% power was computed at the meta-analysis level based on the expected number of 95,574 severe asthma patients exposed to tezepelumab in total across the data sources at the end of

study period (Table 10). The minimum detectable HR was at least (depending on the matching scenario) 1.14 for no-heterogeneity case (σ_{HR}=0) up to at least 1.58 for considerable heterogeneity case (σ_{HR}=0.3) (Table 12). These minimum detectable HRs, which are lower than non-inferiority margin of 1.8, will provide a more conservative value when examining the safety of the drug.

Table 12 Minimum detectable HR in the meta-analysis of MACE outcome for patients with severe asthma exposed to tezepelumab at different matching ratios and between-country heterogeneity levels

Between-country heterogeneity (σ_{HR})	Minimum detectable HR for the meta-analysis of MACE		
	1:1	1:2	1:3
0	1.14	1.12	1.11
0.1	1.26	1.24	1.24
0.2	1.42	1.39	1.39
0.3	1.58	1.56	1.56

Abbreviations: HR, Hazard ratio; MACE, Major adverse cardiovascular event.

9.5.5 Expected power

The expected power was computed at the meta-analysis level based on the expected number of 95,574 patients exposed to tezepelumab in the data sources under the assumed uptake scenario during the study period (Table 10). The expected power to rule out a HR of 1.8 varied from >99% (in all matching scenarios) for no-heterogeneity case (σ_{HR}=0) up to at least 93% for considerable heterogeneity case (σ_{HR}=0.3) (Table 13).

Table 13 Expected power in the meta-analysis of MACE outcome for patients with severe asthma exposed to tezepelumab at different matching ratios and between-country heterogeneity levels

Between-country heterogeneity (σ_{HR})	Expected power for the meta-analysis of MACE		
	1:1	1:2	1:3
0	>99%	>99%	>99%
0.1	>99%	>99%	>99%
0.2	99%	>99%	>99%
0.3	93%	94%	94%

Abbreviation: MACE, Major adverse cardiovascular event.

9.6 Data management

9.6.1 Data collection, harmonisation and management

Following ethics submissions and data source contracting, IQVIA will secure the collected data, from up to five target sources, according to data source-specific general data protection regulation (GDPR)/Data Privacy rules and regulations. Data will be stored at servers that satisfies the country specific security requirements for processing personal health data: two factor- authentication, offline when data is being accessed and analysed, appropriate firewalls, etc. Data analysis is expected to be conducted at the data source within each country. The aggregated data, i.e. the descriptive tables and comparative analyses, will be transferred to IQVIA for meta-analysis if applicable considering data source-specific masking rules. If needed, due the masking rules, the meta-analysis may be conducted at a country specific server.

IQVIA statistical programmers will develop a study common data model (CDM) and accompanying data management plan (DMP) to guide the collection of standardised data elements across all participating sources, aligned to the tezepelumab pregnancy PASS CDM process for efficiencies. Specific activities include:

- Creation of a study data specification as part of the DMP
- Mapping of raw data to the CDM
- Completion of all derivations / transformations to create the analytical dataset
- Running analysis using common centralised analysis code (R or SAS as needed) for each source
- Data source-specific analysis datasets

Data management for this study will be conducted using standard IQVIA processes. Further details on the data handling procedures will be provided in the SAP and/or in the DMP. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

9.6.2 Data Management plan adaptations

DMP adaptations will cover the same content as the DMP, localised for each data source. The DMP will include:

- DMP (including data specifications document, data source-specific dictionary mapping, data flow, Quality Control (QC) requirements, quality indicators)
- CDM

- Single analytic-ready dataset (interim analysis datasets & 1 final analysis dataset) The IQVIA DMP template aligns with expectations from FDA guidance for provenance and traceability.

9.7 Data analysis

9.7.1 Methods

A full description of the analytical approach will be developed and described in the SAP. Details on data derivations, category definitions, analyses, handling of missing data, 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.

Data analysis for each study objective will be performed separately for each data source. All study results will be presented separately for each country in the study reports, as appropriate when data become available. The final study report will include all descriptive, comparative and sensitivity analyses for all the data sources as well as the meta-analysis combining the results from individual data sources, as applicable.

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 (70). 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.

Analysis specifically addressing each study objective is described in Sections 9.7.2 and 9.7.3.

9.7.1.1 Accounting for potential confounding

Time-based exposure sets

Time-based exposure sets will be used to form a set of potential matches for each patient initiating tezepelumab.

The **base cohort**, from which the time-based exposure sets will be formed, will comprise of an exposed and unexposed cohort as defined in Section 9.2.5.2.

For each exposed patient in the base cohort, an **exposure set** will be created by adding unexposed trigger exposure that satisfy the exact matching criteria provided in Section 9.2.5.3. For trigger exposures, criteria will be evaluated at the date of trigger exposure.

Patients contributing multiple trigger exposures to the base cohort might be included in multiple exposure sets (with potentially different matching criteria values in each exposure set). Patients contributing to unexposed pool of triggers who subsequently become exposed to tezepelumab during their follow-up will be censored as comparators at the time of tezepelumab initiation and may contribute to the exposed group starting from their index date (with their own exposure set constructed).

Propensity score estimation

The time-conditional PS model will be fitted on a dataset that combines all time-based exposure sets (71). A single time-dependent CPH regression or conditional logistic regression model will be used as the PS model, using either time to tezepelumab initiation or binary tezepelumab initiation indicator as an outcome variable, respectively, and selected time-varying and fixed variables as covariates, separately for each data source. The list of variables considered for inclusion in the time-conditional PS are presented in Table 8. Values for time-varying PS covariates (for example, age, smoking status, asthma characteristics, HCRU etc.) will be assessed at the date of trigger exposure corresponding to the respective time-based exposure set (i.e. at index date).

The fitted model will be used to compute time-conditional PS values for all study units in each exposure set.

To assess the comparability of the exposed and unexposed cohort, the area under the curve (AUC) from the PS logistic model will be estimated. The AUC computed for a predictive model is considered a measure of overall predictive accuracy, or discriminative ability of the model. It describes how well the predicted probabilities from the PS model classify patients into exposure groups the AUC from the PS reflects the covariates' distribution among the exposure groups; hence, it reflects the degree of the association between the covariates and the exposure of primary interest. A high AUC suggests substantial nonoverlapping of the covariates across exposure groups and hence separation of the two exposure groups, leading to potentially fewer subjects available to be matched. The overlap and distributions of PS of the two exposure groups will be investigated descriptively and graphically. Number of exposed patients that lack appropriate comparators (and therefore must be excluded) will be assessed. A comparative analysis is recommended only if there is sufficient overlap as indicated by the AUC and descriptive analyses of the PS distributions (72, 73).

Matching

PS matching will be performed separately for each country. To ensure comparability, within each time-based exposure set, the time-conditional PS value of the exposed patient should be

within the range of the time-conditional PS values of the unexposed patients. If this is not the case, the exposure set is eliminated (74).

Matching will be done chronologically based on the calendar time starting from the first tezepelumab initiator. Up to three matches will be selected amongst the unexposed trigger exposures within the time-based exposure set with PS scores closest to the score of the tezepelumab initiator. Further trigger exposures of the matched comparators will be removed from all subsequent time-based exposure sets (i.e. matching without replacement). The final choice of the matching ratio will depend on characteristics of the actual study data such as total sample size, available unexposed controls, and comparability of exposed and unexposed patients.

The effectiveness of this matching will be assessed. Covariate distributions before and after matching and the associated balance diagnostics will be reported. Covariate balance will be assessed by examining the distribution of variables in the exposed and unexposed cohorts and estimating standardised differences for each variable between the exposed and unexposed cohort. In case large differences in standardised differences are present, modifications to the time-conditional PS or to the matching algorithm will be considered (e.g. using alternative model for fitting the PS model or specifying a caliper for PS matching).

Further details regarding the PS computation and matching procedure will be provided in the SAP.

9.7.1.2 Descriptive analysis

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 counts and percentages of observations for each of the categories will be presented in descriptive analysis. The count of patients and percentages with missing data for each variable will be reported.

In the descriptive analysis of study outcomes, the total number of study units, the descriptive statistics of the follow-up time and the number of outcome events for each study outcome in the exposed and unexposed matched cohorts will be presented.

Further details on methodology will be provided in the SAP.

Kaplan-Meier curves

Complement of Kaplan-Meier (KM) curves, i.e. 1 – KM, will be used to estimate the risk of primary and secondary outcome events in the exposed and unexposed cohorts after matching. An event will be defined as the first occurrence of the respective outcome event, time from the index date will be used as the underlying time scale and censoring events as described in Section 9.2.3 will be used for the estimation. Number of patients at risk and cumulative event

probabilities with 95% CIs will be calculated and presented at relevant time points during the follow-up time.

In case a considerable number of competing risk events (in particular, death for any reason) are observed during the follow-up, a more appropriate event risk estimator might be considered (e.g. cumulative incidence function (75)).

9.7.1.3 Comparative analysis

CPH regression models will be used to estimate the HRs for each primary and secondary outcome event within the matched population for each of the relevant study outcomes. HRs and the corresponding 95% CIs will be reported. CIs will be based on appropriate standard errors which account for potentially the same patient contributing person-time to both exposed and unexposed cohorts (e.g. obtained using a robust sandwich covariance matrix (76)).

If covariate balance is not achieved through matching, additional adjustment by using unbalanced covariates in the CPH 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 and model assessment 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 for the comparative primary and secondary study objective. The meta-analysis will be performed using effect size estimates from all study countries for which HR were estimated, as long as HR 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, I^2 and the τ^2 statistics.

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 (77), 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 sample size and outcome events to conduct the comparative analysis. 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 a composite of MACE in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma) will be performed using the objective-specific cohort as defined in Section 9.2.5.4. The KM curve will be estimated as described in Section 9.7.1.2 in matched cohorts separately for patients with severe asthma who were exposed or unexposed to tezepelumab.

Objective 2

To compare the risk of MACE in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab, (treated with SOC for severe asthma), the HR (with corresponding 95% CI) will be estimated using the objective-specific cohort as defined in Section 9.2.5.4. The HR and its 95% CI will be estimated using a CPH regression model as specified in Section 9.7.1.3. The meta-analysis on the data source-specific HRs of MACE will be conducted as described in Section 9.7.1.4.

9.7.3 Secondary objectives

Objective 3

The analysis to estimate the risk of a composite of serious adverse cardiovascular events (see Table 7) in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma) will be performed using the objective-specific cohort as defined in Section 9.2.5.4. The KM curve will be estimated as described in Section 9.7.1.2 in matched cohorts separately for patients with severe asthma who were exposed or unexposed to tezepelumab.

Objective 4

To compare the risk of a composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with SOC for severe asthma) the HR (with corresponding 95% CI) will be estimated using the objective-specific cohort as defined in Section 9.2.5.4. The HR and its 95% CI will be estimated using a CPH regression model as specified in Section 9.7.1.3. The meta-analysis on the data source-specific HRs of a composite of serious adverse cardiovascular events will be conducted as described in Section 9.7.1.4.

Objective 5

The analysis to estimate the risk of each of the individual serious adverse cardiovascular cardiac events included in either MACE or the composite of serious adverse cardiovascular

events (see Table 7), in adolescent and adult patients with severe asthma who initiated tezepelumab and in matched patients unexposed to tezepelumab (treated with SOC for severe asthma) will be performed using the objective-specific cohorts as defined in Section 9.2.5.4. The KM curves will be estimated for each individual outcome event as described in Section 9.7.1.2 in matched cohort separately for patients with severe asthma who were exposed or unexposed to tezepelumab.

Objective 6

To compare the risk of each of the individual serious adverse cardiovascular cardiac events included in either MACE or the composite of serious adverse cardiovascular events in adolescent and adult patients with severe asthma who initiated tezepelumab versus matched patients unexposed to tezepelumab (treated with SOC for severe asthma) the HRs (with corresponding 95% CIs) will be estimated using the objective-specific cohorts as defined in Section 9.2.5.4. The HRs and their 95% CIs will be estimated using a CPH regression model as specified in Section 9.7.1.3. The meta-analysis on the data source-specific HRs of each of the individual serious adverse cardiovascular cardiac events included in either MACE or the composite of serious adverse cardiovascular events will be conducted as described in Section 9.7.1.4.

9.7.4 Sensitivity analysis

Stratification by previous exposure to biologics [objectives 1 and 3]

To estimate the risk of the primary and secondary composite outcomes, patients will be stratified based on their prior history of exposure to biologics. The stratification will allow patients initiating tezepelumab with no prior exposure to other biologics (new users of any biologic) to be compared with unexposed patients without prior exposure to other biologics.

Exclusion of patients with a history of the outcome of interest (ever) [objectives 1 to 4]

Outcomes of interest may include diagnosis records of prevalent events that had occurred more than 180 days before the index date. This sensitivity analysis will maximise the probability of all outcomes being incident cases after index date. It aims to estimate and compare the risk of the primary and secondary composite outcomes, excluding patients with any history of the outcome of interest since start of data availability.

Stratification by type of baseline SOC during the 12-month baseline period [objectives 1 to 4]

A stratification according to type of baseline SOC (based on data-driven categories, which may include the use of biologics at baseline, as detailed in Section 9.3.1.3) will be applied to the primary and secondary composite outcomes. This sensitivity analysis will address effect modifications of prior exposure to SOC on the tezepelumab cardiovascular risk.

Quantitative Bias Assessment to examine the impact of unmeasured confounding

Unmeasured confounding related to asthma severity may potentially threaten the validity of the comparative assessment of tezepelumab and SOC. A quantitative bias assessment (QBA) could be performed as a sensitivity analysis to quantify the uncertainty of the study findings due to unmeasured confounding. QBA modelling methods utilises what is known about the unmeasured confounder to model plausible scenarios to provide corrected effect estimates. The array approach is a QBA modelling method that takes into consideration what is known about the unmeasured confounder to model a range of plausible assumptions likely to be more meaningful. This approach will be used to examine a range of plausible assumptions related to the unmeasured confounder on the impact of the effect estimates (78). Details of the operationalisation of this sensitivity analysis will be outlined in the SAP.

9.8 Quality control

9.8.1 IQVIA quality management system (QMS)

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work-frame of IQVIA QMS and in accordance with the following manual, policies and work instructions.

According to the policies and procedures above, a QC plan for the study will be developed and executed, which will include QC on study methodology, SAP, programming, data management and analysis, study results, conclusions, and study report. Furthermore, the study QC plan will establish ownership for the execution of the individual QC steps. The principles of the independence of QC applies as follows:

- The Principal-in-Charge of the study 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.
- The executed QC plan will be subjected to a final review and approval for sufficiency and completeness from the Principal-in-Charge of the study Also, the Principal-in-Charge of the study will verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure PM0035 “Real-World Project Specific Training and Staff Transition”.

9.8.2 Risk management

Risk management will follow IQVIA working instruction: RWI_WI_PM0034 - Managing Real-World Project Risks. The study risk log will be maintained in the IQVIA Resource and

Portfolio Management System, and an Excel will be extracted for Astra Zeneca review in bi-monthly frequency.

9.9 Limitations of the research methods

The use of secondary data collected and maintained in electronic databases offers several scientific and operational advantages for conducting post-authorisation safety studies. Specifically, it eliminates the need for informed consent and optimises statistical efficiency. However, because such data are collected primarily for the management, billing and /or reimbursement of patients care, their utility in comparative analyses or drug safety studies may be limited by the completeness and accuracy of records in the data sources to be utilised.

Data availability

Information bias due to not registered variables is common in observational studies and can impact the estimation and interpretation of study findings. Consequently, some outcomes of interest (e.g. data on specific cause of death) or enrolee characteristics (e.g. severity of asthma) may not be available or be incomplete in all eligible databases in the proposed study. Efforts are made to effectively respond to unavailable or incomplete data defining relevant proxies and building algorithms based on sound assumptions. Additionally, sensitivity analyses will help understand the impact of unavailable data. Strategies to mitigate missing data, and data imputation will be considered where possible.

Specifically, data may be incomplete for:

- Drugs administered during hospitalisation in France, Germany and the USA. In Denmark, the Danish SMR is a recent registry and coverage is not yet known. This limitation may have minimal impact as SOC and tezepelumab are expected to be prescribed and administered in the outpatient setting.
- Cause of death in France and Germany. Cause of death is available through linkage in Carelon, but percentage of linkage is currently unknown. However, a proxy measure can be defined taking into account deaths occurring during a cardiovascular-related hospitalisation or deaths within 30 days of a cardiovascular-related hospitalisation. Proxy measures were already implemented for other studies in most data sources, assuring comparability (41, 59, 63).
- Some covariates, taking into account the availability of drugs and coded diagnoses according to care setting. Proxy measures using prescribed medications may be considered to define comorbidities and minimise missingness, whenever feasible (i.e. when treatments are disease-specific). Lifestyle variables (smoking, alcohol/substance abuse and obesity) are available to the extent they are captured from coded diagnoses. Patients with heavier consumptions (e.g. heavy smokers) or more obese patients are more likely to be captured. Additionally, ethnicity is only available in Carelon.

Identification of severe asthma

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. The algorithm includes requirements to controller and reliever treatments used in high-intensity treatment, combined with additional information on exacerbations proxied by OCS usage, as well as any over-use of SABA treatment. Patients treated with biologics for severe asthma will be included regardless of other asthma treatment, OCS or SABA use.

Exposure to asthma treatment

Data on medication dispensing or prescription available in data sources do not necessarily reflect medication use/consumption, therefore misclassification of exposure to tezepelumab and other drugs offered in SOC is a potential study limitation.

An inherent limitation of this study is the comparability of exposed and unexposed patients. To enhance the comparability of the cohorts, the selection of unexposed patients will be based on a trigger exposure defined as augmentation or change of the non-biologic high-intensity treatment that does not represent treatment de-escalation. However, it should be acknowledged that this will not entirely reflect current SOC for severe asthma, particularly treatment with biologics. Additionally, for some patients, tezepelumab is the only biologic available as tezepelumab has a broader indication. This may result in more severe disease among exposed patients than in the unexposed.

Study design limitations

Confounding by indication, based on disease severity, is a common limitation in comparative observational studies that might not be fully addressed using secondary data. To reduce such potential bias, all included patients had to have high-intensity non-biologic asthma treatment or biologic treatment. Additionally, patients unexposed to tezepelumab had to have an equivalent trigger exposure and were matched on the type of treatment 12 months prior the index date. However, not considering the full duration and detail of treatment history (difficult due to likely left censoring) may result in some residual bias.

Further matching on sex, age, and a host of other potential confounders through PS analysis are likely to control for confounding by measured variables, including other variables that might be associated with treatment change and outcomes' risk.

Definition of outcomes

In clinical practice, a serious event is identified based upon appropriate medical judgement and may refer to events ranging from a death or hospitalisation to a medically important condition requiring intervention to prevent from its deterioration.

In this study, the occurrence of serious cardiovascular events will be narrowed to events requiring inpatient care and identified using relevant diagnosis codes assigned to the hospitalisation. Accuracy of detected events will depend largely on the availability and accuracy of diagnosis codes as well as local coding practices, thus there is a room for potential misclassification. In addition, this strategy comes down to identifying serious cases requiring specialist outpatient hospital care. Patients with a serious condition but treated in the outpatient setting will not be considered. The potential misclassification of outcomes seems to be non-differential, thus would bias the risk estimates toward the null and attenuate any true effect of tezepelumab in terms of cardiovascular safety. Additionally, restricting to inpatient diagnosis promotes comparability between data sources, as some data sources are not able to capture outcomes in the outpatient setting: in Germany diagnoses in outpatient settings are only available on a quarterly basis, limiting the ability to accurately identify the date of the event; in Denmark, primary care diagnoses are not available; in France only hospitalisation diagnosis or those recorded as a LTD are available. Information on the underlying cause of death is not available in all data sources, therefore cardiovascular death will be proxied by a death during or shortly after hospitalisation related to a cardiovascular event of interest. This may lead to flawed identification of cases with a possible misclassification towards underestimated mortality rate due to cardiovascular events (79).

Evolving time trends

Long-term exposure may be necessary to observe serious adverse cardiovascular events. Patient characteristics, SOC and tezepelumab indication may evolve over time and influence patients' risk profile and comparability. Matching on calendar time is designed to limit the influence of evolving alternative treatments and the knowledge on safety of drugs which could drive the probability of exposure.

9.10 Other aspects

None

10. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the guidelines for good pharmacovigilance practices (GVPs) and good pharmacoepidemiology practices issued by the international Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws, and regulations.

10.1 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. The progress report will be submitted to Ethics Review Boards (ERBs) and/or other regulatory authorities as required by local laws and regulations. When 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. This study is non-interventional, and analysis is based on secondary data use. No identifying data is collected or stored by IQVIA in any of the planned approaches. Consideration of the patient view can sometimes be an item ERBs like to observe within an application. As a result, IQVIA would recommend considering the inclusion of a patient representative within the steering committee for this study.

10.2 Regulatory and ethics considerations

The study guarantees patient confidentiality and will follow applicable data protection laws. Per design, non-interventional studies do not affect the treatment of the patients, and analyses are based on secondary data use. No identifiable data will be collected. Detail considerations of the data sources will be further assessed during the feasibility study.

Nordics –ERB and National Board of Welfare and Health

The application process varies between the Nordic countries. In some countries, using Nordic national registries requires an Ethics Committee review. In Denmark, only applications to the data holders are necessary. The applications to the Ethics Committees must include a protocol, application form, and code lists. Curricula vitae and conflict of interest statements are also required for all researchers named on the application. 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. Timelines for the approval are driven by the general demand for access to registry data for research projects and cannot be influenced by IQVIA.

Upon approval of ethics/data holder applications, IQVIA will get access to pseudonymised data including dummy study identification numbers only. The Sponsor will not have access to the patient-level data at any time of the study. Although approval of the protocol is likely

given the scientific merits of this study, IQVIA cannot guarantee the acceptance of ethics/data holder submission applications nor the time it takes for approval. Additional fees will apply for multiple submission to any given Ethics Committee or data holder. According to the regulations regarding the use of data from national registers in the Nordics, the main results of the study must be published, whether positive or negative. To fully comply with this requirement, publication plans of the results must be included in the protocol of the study before requesting the data.

Germany – SHI Claims Data

SHI Claims Data accessed through collaboration with Team Gesundheit is frequently used for research purposes. Data extracted from the German SHIs cannot leave the country and thus require local access and analysis. A formal data application includes communication of a research proposal and a purchase order to Team Gesundheit through IQVIA Germany. Thus, access to the claims data can be granted through the collaboration with the research institute Team Gesundheit and a local IQVIA Team in Germany. Extracted data from Team Gesundheit will subsequently be delivered to IQVIA Germany for local analysis.

France - SNDS

The study protocol is to be submitted to CESREES for validating the study method and to verify that there is a public health benefit. Then, once this approval is obtained, the second phase of the process is a submission to CNIL to ensure GDPR compliance and French requirements in terms of data privacy and data protection using healthcare database (response within 4-8 months). IQVIA cannot guarantee approval of projects submitted to those official and independent national committees. Once those approvals are obtained, a tripartite contract between the client, IQVIA and CNAM (French SNDS data access body) should be signed before accessing the data.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study design which is based on secondary data use, as such there is no requirement to collect adverse event data. Expedited reporting of Adverse Events and Adverse Drug Reactions is not required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Progress reports

A progress report is planned for April 2025 which is 12 months after Pharmacovigilance Risk Assessment Committee (PRAC) endorsement of the protocol which is currently assumed to happen Q2 2024. It will contain a status update of database applications and relevant amendments pertaining to database applications, if applicable. Database access may take between 7 to 18 months; therefore, the progress report may not include tezepelumab user numbers from each data source. Study population counts will not be included.

12.2 Interim analyses and reporting

The two interim reports will be submitted 24 (April 2026) and 48 (April 2028) months after PRAC endorsement of the protocol. The first interim report will contain descriptive analyses relevant to primary and secondary objectives, using all available data at the time of reporting. The second interim report will in addition inform the full analysis of the signal evaluation for the final study report. It will contain 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 incidence rates, comparative analyses, sensitivity analyses, or meta-analyses.

12.3 Final analyses and reporting

The final study report is planned for May 2030.

The interim/progress report(s) and the final study report will be written in accordance with the GVP guidelines module VIII (80), and the RECORD-PE Checklist (81). 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 Post-Authorisation Studies (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. According to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (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 2 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 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: An Observational Multi-Country Post-Authorisation Safety Study to Evaluate the Risk of Serious Adverse Cardiovascular Events in Adolescent and Adult Patients with Severe Asthma taking Tezepelumab

EU PAS Register® number: Study not registered **Study reference number (if applicable): D5180R00024**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[4]	☒	☐	☐	6, 9.2.1
1.1.2 End of data collection[5]	☒	☐	☐	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, 12.3
1.1.6 Final report of study results.	☒	☐	☐	6, 12.3

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1, 8.2
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	9.2.5
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

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

[4] 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.
[5] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4
3.3	Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	9.7.1.2
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?	☒	☐	☐	9.2.5
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	☒	☐	☐	9.2.5
	4.2.3 Country of origin	☒	☐	☐	9.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.4, 9.2.5
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.5

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
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
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.5.2, 9.2.5.3

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (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)	☒	☐	☐	9.7.4, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
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, comorbidity, 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, 9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☐	9.4, 9.3.2
9.3.3 Covariates and other characteristics?	☐	☐	☐	9.4, 9.3.3
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?	☒	☐	☐	9.7.1
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?	☒	☐	☐	9.7.4
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?	☐	☒	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
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?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

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)?	☒	☐	☐	12.1, 12.2, 12.3
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.4

Comments:

Name of the main author of the protocol: [redacted]

Date: 30/January/2024

Signature: _____

Appendix C Summary of objectives, study design and main analysis

Objective	Population (key inclusion and exclusion criteria)	Exposure	Comparator	Outcome	Time (start and end of follow-up)	Setting	Main measures of effect
Primary objective 1	**Inclusion criteria** Patients (≥12 years), with asthma diagnosis and high-intensity treatment **Exclusion criteria** Diagnosis of non-fatal myocardial infarction or non-fatal stroke in the 180 days prior to index date A history of congenital heart disease or heart transplant	Patients initiating tezepelumab	Patients with a trigger exposure matched with exposed patients on: duration of SOC treatment, type of SOC 12 months prior index date, age group, sex propensity score (at index date, no prior exposure to tezepelumab)	MACE (i.e. non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death)	**Start of follow-up**: First Rx of tezepelumab (exposed) and trigger exposure (unexposed) **End of follow-up**: End of tezepelumab (exposed) or SOC (unexposed) treatment Start of tezepelumab (unexposed) or any other biologic First occurrence of the outcome of interest Death, exit from cohort end of study period	Countries and study period: Denmark: 01 May 2023 to 30 April 2028 France: 01 June 2023 to 31 December 2027 Germany: 15 November 2022 to 31 May 2028 USA: 01 January 2022 to 28 February 2029	Kaplan-Meier survival curve
Primary objective 2	**Inclusion criteria** Same as prior objectives **Exclusion criteria** Same as prior objective in addition to: Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic	Same as prior objectives	Same as prior objectives	Same as prior objectives	Same as prior objectives	Same as prior objectives	Hazard Ratio (Cox Model)

Objective	Population (key inclusion and exclusion criteria)	Exposure	Comparator	Outcome	Time (start and end of follow-up)	Setting	Main measures of effect
Secondary objective 3	**Inclusion criteria** Same as prior objectives **Exclusion criteria** Diagnosis of non-fatal myocardial infarction or non-fatal stroke and diagnosis of arrhythmias, coronary artery disease, heart failure, or myocardial disorders in the 180 days prior to index date A history of congenital heart disease or heart transplant	Same as prior objectives	Same as prior objectives	Composite (i.e. arrhythmias, coronary artery disease, heart failure, or myocardial disorders)	Same as prior objectives	Same as prior objectives	Kaplan-Meier survival curve
Secondary objective 4	**Inclusion criteria** Same as prior objectives **Exclusion criteria** Same as prior objective in addition to: Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic	Same as prior objectives	Same as prior objectives	Composite (i.e. arrhythmias, coronary artery disease, heart failure, or myocardial disorders)	Same as prior objectives	Same as prior objectives	Hazard Ratio (Cox Model)

Objective	Population (key inclusion and exclusion criteria)	Exposure	Comparator	Outcome	Time (start and end of follow-up)	Setting	Main measures of effect
Secondary objective 5	**Inclusion criteria** Same as prior objectives **Exclusion criteria** Diagnosis of non-fatal myocardial infarction or non-fatal stroke and diagnosis of the following serious adverse cardiovascular events in the 180 days prior to index date (assessed separately): arrhythmias, coronary artery disease, heart failure, myocardial disorders A history of congenital heart disease or heart transplant	Same as prior objectives	Same as prior objectives	Separately: Non-fatal myocardial infarction Non-fatal stroke Arrhythmias Coronary artery disease Heart failure Myocardial disorders Cardiovascular death	Same as prior objectives	Same as prior objectives	Kaplan-Meier survival curve
Secondary objectives 6	**Inclusion criteria** Same as prior objectives **Exclusion criteria** Same as prior objective in addition to: Exposure to non-tezepelumab biologics on index date or within the 5-half-life clearance period of the biologic	Same as prior objectives	Same as prior objectives	Same as for objective 5	Same as prior objectives	Same as prior objectives	Hazard Ratio (Cox Model)

Abbreviations: MACE, Major adverse cardiovascular events; USA, United Stated of America; SOC, Standard of care.

Appendix D Details of the data sources

Table 14 Data sources included in the feasibility assessment

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / considerations
Suitable data sources				
Denmark	National Registers and Register of Selected Chronic Diseases and Severe Mental Disorders (RUKS)	Yes	Yes	- Tezepelumab recommended for adults (18+) with signs of type 2 inflammation. - Hospital administration of drugs has been captured since 2018 and has been available for research since 2022, although coverage is not known - Study outcomes are available (if coded in secondary care) - Available linkage to the cause of death registry
France	National Health Data System (SNDS)	Yes	Yes	- Tezepelumab approved for reimbursement and confirmed to be observable in the SNDS - Severe asthma patients may be fully captured using Long-term disease (LTD) status codes - Outcomes expected to be available but mostly limited to hospital discharge diagnoses; cause of death available by proxy - Drugs administered during inpatient admissions are not captured (with exception of innovative and expensive drugs) - Potential to provide a large number of tezepelumab users (largest European/US data source)
Germany	Statutory Health Insurance Claims (SHI)	Yes	Yes	- Tezepelumab approved in Germany since 2022. Expected to be observable in the SHI databases in 2025 - Outpatient drugs expected to be captured; inpatient drugs not available - Diagnoses available, but for the outpatient settings in a

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / considerations
				quarterly basis (potential misclassification of the date of the event); cause of death defined by proxy
USA	Carelon	Yes	Yes	- Tezepelumab observable in the database since 2022 - Drugs administered in outpatient settings are available. Drugs administered in inpatient settings are partially available (often bundled with other care items) For inpatient drugs, chart reviews on a subset of the population can be considered with additional contracting - Outcomes expected to be available. Cause of death available through linkage, but percentage of linkage is currently unknown - Large sample size expected
	PharMetrics Plus	Yes	No	- Database only includes individuals until 65 years of age - Tezepelumab observable in the database since 2022 - Drugs administered in outpatient settings available. Inpatient drugs often bundled with other inpatient services and therefore, cannot be separately identified - Outcomes expected to be available, expect cause of death (proxy to be defined) - Large sample size expected - Back-up data source if minimum sample size is not reached
Finland	National Registers	Yes	No	- Tezepelumab not yet approved for reimbursement. If not approved, tezepelumab use is expected to be low due to high costs - Primary, secondary, and private care data available

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / considerations
				- Outcomes are expected to be available but under-record may exist if the event is not the main reason for health care encounter; cause of death is available - Back-up data source if minimum sample size is not reached and tezepelumab is approved for reimbursement
Spain	Information System for the Development of Primary Care Research (SIDIAP)	Yes	No	- Tezepelumab approved and reimbursed since 2023 but not possible to capture in the feasibility assessment (or biologics' use) - Drugs administered during inpatient admissions are not captured, however, it is not expected to impact the ability to capture biologics - Outcomes expected to be available but mostly limited to hospital discharge diagnoses or diagnoses recorded in primary care – outpatient specialist care not available; cause of death defined by proxy - Back-up data source if minimum sample size is not reached
NOT Suitable data sources				
United Kingdom	British Thoracic Society Difficult Asthma Registry	Yes, preliminary	No	- Linkage unavailable
United Kingdom	United Kingdom Severe Asthma Register (UKSAR)	Yes, preliminary	No	- Linkage unavailable - Do not have the resourcing in place to support the study
Denmark	Danish Register for Asthma (DrAstma)	Yes, preliminary	No	- Not allowing use for external research as of 2023
Denmark	Danish Severe Asthma Registry	Yes, preliminary	No	- Small sample size - No response despite multiple outreach attempts
Germany	German Asthma Net Registry	Yes, preliminary	No	- Small sample size - Overlap with national registry
RAMSES	Research on Severe Asthma cohort (RAMSES)	Yes	No	- Patients are only expected to be included in the dataset from 2019 until 2024, so it will not capture entire study period.

Country	Data source	Assessed in feasibility assessment	Selected for this study	Rationale for decision / considerations
				- Data is only available at set timepoints to include baseline, 6, 12, 36, and 60 months from recruitment date.
Belgium	Belgium Severe Asthma Registry (BSAR)	Yes, preliminary	No	- Small sample size - No contact details available - Limited information available
Italy	National Registry of Severe Asthma (RAG)/Italian Registry of Severe Asthma (IRSA)	Yes, preliminary	No	- Strict data sharing policies
Italy	Severe Asthma Registry in Italy (SANI)	Yes, preliminary	No	- Strict data sharing policies
Portugal	Portuguese Severe Asthma Registry (REAG)	Yes, preliminary	No	- Small sample size
Multi-country	Severe Heterogeneous Asthma Research collaboration Patient-centred registry (SHARP)	Yes, preliminary	No	- No contact details available

Abbreviation: USA, United States of America

Table 15 Availability of baseline characteristics and covariates **Covariates**	**Country/Databases**			
	Denmark (National Registries)	**France (SNDS)**	**Germany (SHI)**	**USA (Carelon)**
Sociodemographic characteristics				
Gender	Yes	Yes	Yes	Yes
Age at index date	Yes	Yes	Yes	Yes
Race/Ethnicity	No	No	No	Yes
Socioeconomic status	Yes	Yes	Yes	Yes
Calendar year	Yes	Yes	Yes	Yes
Lifestyle characteristics				
Smoking status	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)
Alcohol abuse or dependence	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)
Substance abuse or dependence	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)
Weight and height or BMI (kg/m^2)	No	No	No	No
Obesity	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)	Partial (diagnosis code)
Clinical characteristics				
High-intensity asthma treatments				
Biologics	Yes, except inpatients	Yes, except inpatients [a]	Yes, except inpatients	Yes, except inpatients [b]
Exposure to (any) OCS	Yes, except inpatients	Yes, except inpatients [a]	Yes, except inpatients	Yes, except inpatients [b]
Number of exacerbations			Yes, except inpatients	
- ≥2 prescriptions for high dose OCS	Yes, except inpatients	Yes, except inpatients [a]	Yes, except inpatients	Yes, except inpatients [b]
- SABA over-use (≥3 cannisters, 200 doses each)	Yes, except inpatients	Yes, except inpatients [a]	Yes, except inpatients	Yes, except inpatients [b]
More than 50% of days covered by low dose OCS	Yes, except inpatients	Yes, except inpatients [a]	Yes, except inpatients	Yes, except inpatients [b]
Number of hospitalisations due to asthma	Yes	Yes	Yes	Yes
Number of emergency room visit, or outpatient visit due to asthma	Yes	Yes	Yes [c]	Yes
Number of admissions in intensive care unit	Yes	Yes	Yes	Yes
Respiratory diseases (other than asthma)				
Bronchiectasis	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes

Table 15 Availability of baseline characteristics and covariates **Covariates**	**Country/Databases**			
	Denmark (National Registries)	**France (SNDS)**	**Germany (SHI)**	**USA (Carelon)**
Allergies (e.g. mites, fungus, pollen)	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Chronic obstructive pulmonary disease (COPD), including emphysema	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Pulmonary arterial hypertension	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Lower respiratory tract infections	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
SARS-CoV-2	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Cardiovascular disease	Partial, except primary care			
Hypertension	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Hyperlipidaemia	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Myocardial infarction	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Acute coronary syndrome or unstable angina	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Stable angina	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Coronary atherosclerosis and other forms of chronic ischaemic heart disease	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Other atherosclerosis	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Previous cardiac procedure	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Congestive heart failure	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Peripheral vascular disease or surgery	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Atrial fibrillation	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Other cardiac dysrhythmia	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Cardiac conduction disorders	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Stroke	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
History of malignancies				
Any malignancy	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Other comorbidities				
Diabetes	Partial, except primary care	Partial, except outpatients [d]	Yes	Yes
Charlson Comorbidity Index	Yes [e]	Yes [e]	Yes [e]	Yes [e]
HCRU				
Outpatient and primary care visits	Yes	Yes	Yes	Yes

Table 15 Availability of baseline characteristics and covariates **Covariates**	**Country/Databases**			
	Denmark (National Registries)	**France (SNDS)**	**Germany (SHI)**	**USA (Carelon)**
Use of emergency department	Yes	Yes	Yes	Yes
Hospitalisations (number of days, number of hospitalisations)	Yes	Yes	Yes	Yes

[a] Except if included in the list of expensive and innovative drugs. For biologics, omalizumab and mepolizumab are part of that list as of October 2023.

[b] For inpatient setting, chart reviews on a subset of the population can be considered with additional contracting.

[c] An admission that started with an emergency visit is not trackable, it will be absorbed in the hospital stay. An emergency visit without admission can be tracked and ICD-10 codes are available.

[d] In outpatient settings diagnoses are restricted to Long-term Disease (LTD) status.

[e] Based on local adaptations whenever available.

Abbreviations: BMI, body mass index; COPD, Chronic obstructive pulmonary disease; HCRU, health care resource utilisation; OCS, Oral corticosteroids; SABA, Short-acting beta$_2$-agonist; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SHI, Statutory Health Insurance; SNDS, French National Health Data System (Système National des Données de Santé); USA, United Stated of America

Appendix E Exemplar code lists

Table 16 Diagnosis codes for asthma

	ICD-10	Definition
Asthma	J45.x	Asthma
	J46.x	Status asthmaticus

Abbreviation: ICD-10, 10th Revision International classification of diseases.

Table 17 ATC codes for drugs in standard of care for severe asthma

Sub-groups according to chemical substance(s)	ATC	Chemical substance(s)
ICS		
Beclomethasone	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		
Fluticasone and salmeterol	R03AK06	ICS-LABA
Budesonide and formoterol	R03AK07	ICS-LABA
Beclomethasone and formoterol	R03AK08	ICS-LABA
Mometasone and formoterol	R03AK09	ICS-LABA
Fluticasone furoate and vilanterol	R03AK10	ICS-LABA
Fluticasone and formoterol	R03AK11	ICS-LABA
Budesonide and salmeterol	R03AK12	ICS-LABA
Mometasone and indacaterol	R03AK14	ICS-LABA
ICS-LABA-LAMA		
Fluticasone furoate, umeclidinium bromide and vilanterol	R03AL08	ICS-LAMA-LABA
Beclomethasone, formoterol, glycopyrronium bromide	R03AL09	ICS-LABA-LAMA
Budesonide, glycopyrronium bromide and formoterol	R03AL11	ICS-LAMA-LABA
Indacaterol, glycopyrronium bromide and mometasone	R03AL12	LABA-LAMA-ICS
LTRA		
Montelukast	R03DC03	LTRA
Montelukast, combinations	R03DC53	LTRA
Pranlukast	R03DC02	LTRA
Zafirlukast	R03DC01	LTRA
Zileuton	-	LTRA
Chromones		

Sub-groups according to chemical substance(s)	ATC	Chemical substance(s)
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
OCS		
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 beclomethasone	R03AK13	ICS-SABA
Fenoterol and ipratropium bromide	R03AL01	LABA-SABA
Salbutamol and ipratropium bromide	R03AL02	SABA
Others		
Theophylline	R03DA04	Xanthines
Azithromycin	J01FA10	Macrolide

Abbreviations: ATC, Anatomical Therapeutic Chemical; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; IL4R, Interleukin-4 receptor; IL5, interleukin-5; L5R, interleukin-5 receptor; LABA, Long-Acting Beta-Agonists; LAMA, Long-acting muscarinic antagonists; LTRA, Leukotriene receptor antagonists; OCS, Oral corticosteroids; SABA, Short-acting beta-agonists; TSLP, Thymic stromal lymphopoietin.

Table 18 Diagnosis codes for MACE components (primary outcome)

MACE components	ICD-10
Myocardial infarction	I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9 I22.0, I22.1, I22.8, I22.9
Stroke	I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9 I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9 I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64.
Cardiovascular death	I01-I99

Abbreviations: MACE, Major adverse cardiovascular events; ICD-10, 10th Revision International classification of diseases.

Table 19 Diagnosis codes for serious adverse cardiovascular events (secondary outcome)

Serious adverse cardiovascular events	ICD-10
Arrhythmias	I48.0, I48.1, I48.2, I48.3, I48.4, I48.9 I49.0, I49.1, I49.2, I49.3, I49.4, I49.5, I49.8, I49.9
Coronary artery disease	I20.0, I20.1, I20.8, I20.9 I24.0, 124.1, I24.8, I24.9 I25.0, I25.1, I25.2, I25.3, I25.4, I25.5, I25.6, I25.8, I25.9
Heart failure	I09.9 I11.0 I13.0, I13.2 I50.0 I50.1, I50.9
Myocardial disorders	I40.0, I40.1, I40.8, I40.9 I41.0, I41.1, I41.2, I41.8 I42.0, I42.1, I42.3, I42.4, I42.5, I42.7, I42.8, I42.9 I43.0, I43.1, I43.2, I43.8

Abbreviation: ICD-10, 10th Revision International classification of diseases.

Table 20 Selection of covariates

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Lifestyle characteristics			
Smoking status	F17.x, T65.2, Z71.6, Z72.0	Specific local codes may be used depending on availability.	Well-established risk factor for cardiovascular disease (1) and associated with more severe asthma symptoms and worse clinical and functional respiratory outcomes in asthma patients (2). Previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3).
Alcohol abuse	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1 Similar approach for coding elsewhere (4,5)		Well-established risk factor for cardiovascular disease (6). Associated with increased morbidity and healthcare use in asthma patients (7). Previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3).
Substance abuse	F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2 Similar approach for coding elsewhere (4,5)		Substance use has been associated with cardiovascular disease, such as heart failure (8), and atherosclerotic cardiovascular diseases in young adults (9). Substance abuse has also been associated with increased risk of severe symptoms in asthma patients (10).

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Obesity	E66.x Similar approach for coding elsewhere (4)	Local procedures codes for surgical procedures and drug dispensations may be considered if relevant	Obesity is a well-established risk factor for cardiovascular disease (11). Obesity has also been associated with more severe symptoms in asthma patients (11). Previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3)
Clinical characteristics			
Respiratory diseases (other than asthma)			
Bronchiectasis	J47		Inclusion recommended by KOL.
Allergies (including hypersensitivity pneumonitis)	D72.1, J30.x, J67.x	Drug dispensations relevant for local contexts may be considered if relevant	Some research suggests a link between allergy (e.g. allergic rhinitis) and cardiovascular disease in asthma patients, but this relationship remains unclear (12). Lung disease and poor lung function are well-established risk factors for cardiovascular disease (13). Previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3)

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Chronic obstructive pulmonary disease (COPD) including emphysema	J41.x, J43.x-J44.x J98.2, J98.3 Similar approach for coding elsewhere (14).		Patients with comorbid asthma and COPD have an increased risk of cardiovascular events (15). Previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3) Emphysema has been associated with greater lung function decline in COPD patients (16).
Pulmonary arterial hypertension	I27.x		Pulmonary arterial hypertension is a common complication of congenital heart disease (17).
Lower respiratory track infections	J09.x-J18.x, J20.x-J22.x Similar approach for coding elsewhere (18)		Lung disease and poor lung function are well-established risk factors for cardiovascular disease (13).
SARS-CoV-2	U07.1 Similar approach for coding elsewhere (18)		SARS-CoV-2 infection has been associated with increased risk of cardiovascular events (19)
Cardiovascular disease			
Hypertension	I10.x, I11.x–I13.x, I15.x Similar approach for coding elsewhere (4,5,20)		Asthma is frequently associated with comorbidities, including cardiovascular disease. These patients tend to experience more severe symptoms (e.g. exacerbation, lower lung function, higher rates of hospitalisation) (21). Some previously used as a confounder in observational studies on the association of asthma and cardiovascular disease morbidity and mortality (3)
Hyperlipidaemia	E78.x Similar approach for coding elsewhere (20)		
Myocardial infarction (including old)	I21.x, I22.x, I25.2 Included in Charlson Comorbidity Index (4).		
Acute coronary syndrome or unstable angina	I20.0, I24.x		
Stable angina	I20.1, I20.8, I20.9		

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Coronary atherosclerosis and other forms of chronic ischaemic heart disease	I25.1x, I25.3x, I25.5x, I25.6x, I25.8x, I25.9x,		
Other atherosclerosis	I70.0, I70.9		
Previous cardiac procedure	Z95.x	Local procedures codes for surgical procedures	
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x Included in Charlson Comorbidity Index (4).		
Peripheral vascular disease or surgery	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, Z95.8, Z95.9 I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x Included in Charlson Comorbidity Index (4).		
Arrhythmia (atrial fibrillation)	I48.x Similar approach for coding elsewhere (20)		
Other cardiac arrhythmias	I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0 Similar approach for coding elsewhere (4,5,22).		
Cardiac conduction disorders	I44.x, I45.x		
Any stroke	I60.x, I61.x, I63.x, I64 Similar approach for coding elsewhere (23)		
Others			

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Diabetes	E10.x, E11.x, E12.x, E13.x, E14.x Similar approach for coding elsewhere (4,5)		Asthma is frequently associated with comorbidities, including diabetes. These tend to experience more severe symptoms (e.g. exacerbations, lower lung function, higher rates of hospitalisation) (21)
History of malignancies			
Solid malignancies and haematological malignancies	C00.x–C26.x, C30.x–C34.x, C37.x-C41.x, C43.x, C45.x–C58.x, C60.x-C76.x, C81.x–C85.x, C88.x, C90.x–C97.x Similar approach for coding elsewhere (4,5)		Asthma patients are at higher risk of different types of cancer (24). An increased risk of cardiovascular disease has been reported in cancer patients (25)
Charlson Comorbidity Index (4,26) (codes for foetus and newborn excluded)			
Myocardial infarction	I21.x, I22.x, I25.2		Comorbidity scores are widely used to adjust for confounding in studies using administrative databases, however, residual confounding cannot be ruled out (27)
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x		
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, Z95.8, Z95.9		
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x		
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1		
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3		
Rheumatologic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0		
Peptic ulcer disease	K25.x–K28.x		

Covariates	**ICD-10**	**Additional codes**	**Rationale for selection (*references within the table are listed below*)**
Mild liver disease	B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4		
Diabetes without chronic complications	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9		
Diabetes with chronic complications	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2E13.5, E13.7, E14.2–E14.5, E14.7		
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9		
Renal disease	I12.0, I13.1, N03, N05, N18.x, N19.x, N25.0, Z49.0, Z49.2, Z94.0, Z99.2		
Any malignancy, including leukaemia and lymphoma	C00.x–C26.x, C30.x–C34.x, C37.x-C41.x, C43.x, C45.x–C58.x, C60.xC76.x, C81.x–C85.x, C88.x, C90.x–C97.x		
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7		
Metastatic solid tumour	C77.x–C80.x		
AIDS/HIV	B20.x–B22.x, B24.x		

Abbreviations: AIDS, Acquired immune deficiency syndrome; HIV, Human immunodeficiency virus; ICD-10, 10th Revision International classification of diseases; KOL, Key opinion leader; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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Appendix F Study size tables

Table 21 Minimum required sample size in tezepelumab exposed group for meta-analysis of MACE at different matching ratios and between-country heterogeneity levels, by country

Data source	Minimum required sample size in tezepelumab exposed group for meta-analysis of MACE		
	1:1	1:2	1:3
Between-country heterogeneity $\sigma_{HR} = 0$			
Denmark	180	136	123
Germany	213	161	146
France	3,111	2,356	2,129
USA	1,026	777	702
In total	**4,530**	**3,430**	**3,100**
Between-country heterogeneity $\sigma_{HR} = 0.1$			
Denmark	239	204	188
Germany	283	242	224
France	4,135	3,530	3,262
USA	1,363	1,164	1,076
In total	**6,020**	**5,140**	**4,750**
Between-country heterogeneity $\sigma_{HR} = 0.2$			
Denmark	339	276	250
Germany	402	328	296
France	5,872	4,780	4,327
USA	1,937	1,576	1,427
In total	**8,550**	**6,960**	**6,300**
Between-country heterogeneity $\sigma_{HR} = 0.3$			
Denmark	660	532	472
Germany	783	631	560
France	11,428	9,210	8,165
USA	3,769	3,037	2,693
In total	**16,640**	**13,410**	**11,890**

Abbreviations: MACE, Major adverse cardiovascular events; USA, United States of America.

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