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Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorization Safety Study

Sponsor: AstraZeneca
Principal Investigator: Peter McMahon, MSc

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Sodertalje SWEDEN
MAH contact person	PPD Regulatory Affairs Director AstraZeneca UK Limited 1 Francis Crick Avenue Cambridge Biomedical Campus Cambridge CB2 0AA, United Kingdom PPD

Approved by:

	PPD Deputy Qualified Person for Pharmacovigilance in the EU, as delegated by PPD, Qualified Person for Pharmacovigilance in the EU	Electronic signature is available at the end of the document

PASS INFORMATION

Title	Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Biologic Therapy, a Post Authorization Safety Study
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Research question and objectives	The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.
Country (-ies) of study	United States, Canada, UK, Spain, Sweden, Germany, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, and Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Singapore, Taiwan, and the UAE

Author(s)	Peter McMahon, MSc Director, Safety Epidemiology Biopharmaceuticals Medical, Respiratory and Immunology Academy House 136 Hills Rd. Cambridge CB2 8PA Email: peter.mcmahon1@astrazeneca.com PPD Senior Director Medical Evidence & Observational Research Center Global Medical Affairs, AstraZeneca 200 Orchard Ridge Gaithersburg, Maryland 20878 PPD PPD Director, Epidemiology Biopharmaceuticals Medical Respiratory and Immunology Global Medical Affairs, AstraZeneca Academy House 136 Hills Rd. Cambridge CB2 8PA PPD

1. TABLE OF CONTENTS

PAGE

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADEPT	Anonymised Data Ethics & Protocol Committee
ADR	Adverse Drug Reaction
ATS	American Thoracic Society
AZ	AstraZeneca
BMI	Body Mass Index
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV^1	Forced Expiratory Volume during 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IgE	Immunoglobulin E
IL5	Interleukin 5
ISAR	International Severe Asthma Registry
ISPE	International Society for Pharmacoepidemiology
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MAH	Marketing Authorisation Holder
NAEPP	National Asthma Education and Prevention Program
NMSC	Non-melanoma skin cancer
OCS	Oral Corticosteroids

Abbreviation or special term	Explanation
OPC	Optimum Patient Care
PAM	Post-authorisation Measure
PASS	Post Authorization Safety Study
PRO	Patient Reported Outcome
PY	Person-Years
SAP	Statistical Analyses Plan
UK	United Kingdom
US	United States

3. RESPONSIBLE PARTIES

The Marketing Authorisation Holder (MAH) is responsible for the design and execution of this study. It is the responsibility of the MAH to ensure review of the study plan, interim reports and final report, and compliance of study materials, reports and protocols to the Post Authorization Safety Studies (PASS) guidance of the European Medicines Agency and other regulatory authorities.

The principal investigator:
Peter McMahon,
Director, Safety Epidemiology,
Biopharmaceuticals Medical, Respiratory and Immunology
Academy House 136 Hills Rd. Cambridge CB2 8PA
Tel: +447513545252
Email: peter.mcmahon1@astrazeneca.com

4. ABSTRACT

Title: Descriptive Study of The Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab or Other Therapies, a Post Authorization Safety Study

Rationale and background: Benralizumab is an eosinophil-depleting monoclonal antibody (IgG1 kappa). In Europe, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists. In the US, it is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. Although there is no current evidence suggesting a causal relationship, malignancy is an important potential risk of eosinophil-lowering therapies such as benralizumab. The

current study will describe the occurrence of malignancy in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those receiving non-biologic treatment only. This will be accomplished through analysis of high quality information from two severe asthma registries among patients with specialist-confirmed severe asthma, including benralizumab and non-benralizumab patients, with confirmation of drug exposures and detailed descriptions of characteristics of malignancy cases.

The Study fulfils a category 3 post-authorisation measure (PAM) to the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC).

Research question and objectives: The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.

Study design: This is a real-world, observational, prospective cohort study in patients with severe asthma recruited into the International Severe Asthma Registry (ISAR) and the US severe asthma registry (CHRONICLE) and followed-up for occurrence of new malignancies. Incidence rates per 1000 person-years will be calculated for severe asthma patients receiving benralizumab and compared with patients receiving non-benralizumab biologics, and patients not receiving biologics. ISAR and CHRONICLE are prospective cohorts that collect routine specialist care data on severe asthma patients. Adjusted incidence rates will be calculated for each study group based on propensity scores and comparison will be made based on the propensity score adjusted estimates of the incidence rates. New malignancy cases developed during the follow-up period will be described with regards to their history of prior malignancy, malignancy type, location, stage, and outcomes. Data from ISAR and CHRONICLE will be pooled to increase the precision of the study.

Population: The study population includes patients with severe asthma recruited into ISAR and CHRONICLE. Severe asthma patients are defined as those receiving treatment consistent with Global Initiative for Asthma (GINA) Step 5 or who are uncontrolled on GINA Step 4 treatment regimens. The three main study groups are: severe asthma patients who receive benralizumab, who receive non-benralizumab biologics, and those who do not receive any biologics.

Variables: The outcome is new malignancy cases, which will be obtained by the treating physicians during office visits. Potential risk factors for malignancies and patient characteristics including demographics, asthma features, comorbidities, asthma treatment are also collected. Details regarding variable definitions will be provided in the Statistical

Analysis Plan (SAP) to be developed separately and submitted to the agency prior to the submission of the first annual interim report.

Data sources: This study will analyse data from ISAR and CHRONICLE. ISAR prospectively collects routine specialist care data on severe asthma patients from at least 14 countries, including the United States, Canada, UK, Spain, Sweden, Germany, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, and Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Singapore, Taiwan, and the UAE (http://www.encepp.eu/encepp/viewResource.htm?id=23721). All of these countries committed to the collection of malignancy data. CHRONICLE is a multi-center, observational, prospective cohort study of adults with severe asthma in the US (https://clinicaltrials.gov/ct2/show/NCT03373045). The US sites in CHRONICLE do not overlap with the US sites in ISAR.

Study size: By the end of PPD approximately 9,000 severe asthma patients were recruited to both ISAR and CHRONICLE.

Data analysis: Both adjusted and unadjusted incidence rates together with difference in incidence rate and incidence rate ratio between the three cohorts will be presented. Incidence rate will be reported as new malignancies incidence rates per 1,000 PY for all new malignancies with and without NMSC. Propensity scores will be used to estimate the adjusted incidence rates, difference in incidence rates, and incidence rate ratios. The incidence rate will be estimated in the pooled data from ISAR and CHRONICLE, as well as by each registry separately as a supportive analysis.

The analyses will be descriptive in nature with no formal comparative statistical tests to rule out pre-defined differences in incidence rates. Incidence rates, rate difference, and rate ratios, together with nominal 95% confidence intervals will be presented. Time from the index date to first new malignancy will be explored using Kaplan-Meier plots. Adjusted analyses based on propensity score weighted cox regression for time to first new malignancy will also be performed. Descriptive statistics will be provided for description of patients who developed new malignancy during the follow-up and those who did not.

Details of the statistical analysis are to be provided in the SAP which will be available prior to the first interim report.

Milestones: The study is planned for 7 years from PPD. There will be three annual interim reports, conducted in PPD (for data accrued by PPD through PPD (for data accrued

by PPD i.e. one year before the end of follow-up). The final report with statistical analysis according to the SAP will be prepared at the end of the study (PPD based on data accrued at the end of follow-up in PPD

5. AMENDMENTS AND UPDATES

Table 1 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
Protocol Version 2.0	PPD	*Section 4 & 8*	Clarified study objectives	Response to comments from EMA
		Section 4 & 9.6	Revised the projection person-years	Response to comments from EMA
		Section 9.7	Added data collection, management, and storage	Response to comments from EMA
		Section 9.8	Added a new section on data pooling	Response to comments from EMA
		Section 9.9	Added more details to data analysis	Response to comments from EMA
Protocol Version 3.0	PPD	*Section 9*	Revised section numbering	Response to comments from EMA
		Section 4, 8, 9.1, & 9.5	Clarified study objectives	Response to comments from EMA
		Section 9.5	Added more details on study size	Response to comments from EMA
		Section 9.6.3	Added more details on data pooling	Response to comments from EMA
		Section 4 & 9.7	Added more details on data analysis	Response to comments from EMA
		Annex 1	Added Appendix 5 and 6	Response to comments from EMA

Number	Date	Section of study protocol	Amendment or update	Reason
Protocol Version 4.0	PPD	*PASS Information*	Added Adrian Rabe as an author	Reflect study structure
		Section 9.1	Change in index date definition	More accurate calculation of incidence rate based on index date
Protocol Version 5.0	PPD	*PASS information*	Added Peter McMahon as an author and Principal Investigator Updated MAH contact person to Ginette Hampshire	Reflect study structure
		Section 6:	Updated submission dates for each interim analysis (IA) from July to Q4	To align with RMP timelines for final submission i.e. submission in Q4 2024. To allow for adequate time for outputting, review outputs and CSR write-up.
		Section 4 & 9.1:	Incidence rate update (expressed per 1000-person years; previously just person-years)	Ease of interpretation
		Section 9.1:	Updates to index date derivation (index date was changed to first use of biologic for benralizumab and non-benralizumab biologic cohorts, and study start date for non-biologic cohort.)	More accurate reflection of the analysis as already captured in the submitted SAP V 4.0

Number	Date	Section of study protocol	Amendment or update	Reason
		Section 9.7.1.	Removal of description of censored patients by year	This originally proposed analysis was deemed not meaningful as there are no fixed visits for ISAR subjects, and no definitive withdrawal or discontinuation dates. Instead, descriptive statistics of overall follow up time by cohort was presented.
		Section 9.7.2:	Updates made to the propensity score wording	More accurate reflection of the analysis
		Section 9.7.2:	Updates made to the outcome: clarification of censoring for patients who switch	More accurate reflection of the analysis
		Section 9.7.2:	Clarified that comparison (benralizumab vs. non-benralizumab biologics, and benralizumab vs. non-biologics) is strata specific - subjects in benralizumab cohort may be in different strata depending on the comparison	More accurate description of the comparison
		Section 4 & 9.1 & 9.4:	Updates to countries included and patient numbers	Latest information added

6. MILESTONES

Table 2 Study milestones

Milestone	Planned date
Start of data collection	PPD
End of data collection	PPD
Annual interim reports	PPD

Milestone	Planned date
Registration in the EU PAS register	PPD
Database lock	PPD
Final report of study results	PPD

7. RATIONALE AND BACKGROUND

Approximately 5 to 10% of asthma patients have severe asthma characterized by a requirement for high-dose inhaled corticosteroid (ICS) plus a second controller (most commonly long-acting beta agonists) to prevent it from becoming uncontrolled [1, 2]. Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients does not adequately respond to current standard therapy. This subset of patients with uncontrolled severe asthma is responsible for a disproportionate percentage of the health care costs associated with asthma. Approximately 30-50% of severe asthma patients are reported to have severe eosinophilic asthma in which their symptoms are associated with increased eosinophils in the blood or sputum [1, 2].

Benralizumab is an eosinophil-depleting monoclonal antibody (IgG1 kappa). In Europe, it is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus -long acting- β-agonists. In the US, it is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. It is administered as a 30 mg subcutaneous (SC) injection given every 4 weeks for the first 3 doses, followed by 30 mg subcutaneous injection every 8 weeks thereafter. Recently, clinical efficacy of benralizumab 30 mg SC in asthma was confirmed in Phase 3 global safety and efficacy trials in patients on moderate to high dose ICS/LABA[3-5]. In patients with blood eosinophil counts ≥ 300 cells/μL, benralizumab, administered every 4 and 8 weeks (Q8W) or every 4 weeks (Q4W) for up to approximately 1 year, produced clinically significant decreases in asthma exacerbations and improvements in lung function and total daily asthma symptoms. Additionally, responses were observed in patients irrespective of blood eosinophil count, particularly among those with other markers of eosinophilic asthma.

Although there is no current evidence suggesting a causal relationship, malignancy is an important potential risk of eosinophil-lowering therapies such as benralizumab. Tumor-associated eosinophilia is well-described, and a role for eosinophils in the immune response to malignancy has been postulated, particularly in light of their known toxic effects on helminthic parasites [6, 7]. Results from several retrospective epidemiological and pathological surveys suggest that higher (versus lower) tissue or blood eosinophil levels in

association with certain solid tumours predict a more favourable prognosis [8, 9]. However, other surveys suggest that tumour-associated eosinophilia may be an epiphenomenon related to elaboration of eosinophil-active factors or tumour stage, without clear influence on the natural history of the disease [10, 11]. Non-clinical models have yielded contrary results, with modelled IL-5 production (and the resultant eosinophilia) or allergic inflammation demonstrating both inhibition and promotion of solid tumour metastasis in animals [12-14]. Although eosinophil infiltration of tumours is common, the cause and consequences (ie, protumorigenic versus antitumorigenic) of this recruitment and accumulation are unclear [15]. In conclusion, while eosinophils have been observed in association with certain solid tumours, especially those of epithelial origin (breast and colon) the role that eosinophils may have in the immune response to malignant neoplasms, if any, remains unclear. While some clinical studies have suggested the presence of eosinophils may be a positive prognostic indicator of patient malignancy survival, a definitive link has not yet been objectively established [16, 17].

Several observational studies have been performed to measure the association of asthma with incidence of malignancies during the last decades. The results have been conflicting and have given rise to two different hypotheses. Some studies have suggested a protective effect of allergies due to the possibility of an enhanced surveillance where stimulated immune systems are able to destroy malignant cells [18-21]. Others have theorized that chronic immune stimulation due to allergy may result in mutations in stem cells and could be associated with an increased risk of malignancy [22-24].

Gonzales-Perez et al. conducted a cohort study with a nested case-control analysis using the General Practitioner Research Database in the UK. Three cohorts were defined: patients with asthma, patients with COPD, and general population. During the follow-up period, a total of 5263 incident cases of malignancies were identified. The nested case-control analysis included all malignancy cases as well as 20,000 non-malignancy controls, frequency-matched on age, sex, and calendar year. Patients with asthma did not exhibit an overall greater risk of malignancy compared with the general population (odds ratio = 0.93, 95% confidence interval (CI): 0.86-1.00). However, they appear to have an elevated risk of experiencing lung cancer (odds ratio = 1.84, 95% CI: 1.58-2.15). Controlling for smoking and other potential confounding factors yielded a lower estimate (odds ratio = 1.35, 95% CI: 1.15-1.59). This was in contrast with the estimate observed for non-smoking related malignancies (0.87, 95% CI: 0.80-0.94). The authors concluded that asthma was not associated with an increased risk of malignancy. They also concluded that the increased risk of lung cancer was probably confounded by aspects such as tobacco smoke and other exposures [25].

Long et al. [26] evaluated the long-term safety in omalizumab-treated and non-omalizumab-treated patients with a primary focus on assessing malignancies. The EXCELS study was a phase IV, prospective, observational cohort study of omalizumab-treated and non-

omalizumab-treated patients enrolled from multiple US centers and followed for up to 5 years. The primary objective of the study was to compare the long-term clinical safety profile of patients treated with omalizumab with that of similar patients who had not been treated with omalizumab. A total of 7,857 patients were enrolled in the study from 445 sites (omalizumab cohort, n=5,007; non-omalizumab cohort, n=2,829). The omalizumab cohort had a higher proportion of patients with severe asthma compared with the non-omalizumab cohort (50.0% vs 23.0%). Crude malignancy rates were similar in the omalizumab and non-omalizumab cohorts, with a rate ratio of 0.84 (95% CI, 0.62-1.13) for all malignancies and 0.98 (95% CI, 0.71-1.36) for all malignancies excluding non-melanoma skin cancer (NMSC). Multivariable analysis, adjusting for confounders and risk factors, resulted in a hazard ratio (omalizumab vs non-omalizumab) of 1.09 (95% CI, 0.87-1.38) for all malignancies and 1.15 (95% CI, 0.83-1.59) for all malignancies excluding NMSC. The results from the EXCELS study suggested that omalizumab therapy is not associated with an increased risk of malignancy.

There are few data regarding the association of asthma with malignancies, but the majority seem to suggest that such a relationship does not exist. Furthermore, there is a greater paucity of data concerning the occurrence of malignancy in patients receiving biologics to treat asthma. The current study will describe the occurrence of malignancy in patients with severe asthma, including those receiving benralizumab and not receiving benralizumab, using data collected on patients enrolled in the International Severe Asthma Registry (ISAR) and an AZ-sponsored US severe asthma registry (CHRONICLE). This approach provides information on the occurrence of malignancies among patients with specialist-confirmed severe asthma, including benralizumab and non-benralizumab patients, with confirmation of drug exposures and detailed characteristics of provider-confirmed malignancy cases. This proposed study will fulfil the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) request for a Category 3 PASS to evaluate the risk of malignancies in benralizumab users.

8. RESEARCH QUESTION AND OBJECTIVES

The objectives of this descriptive study using global registry data are as follows:

Primary objective

- To assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics

Secondary objective

- To describe the clinical characteristics of new malignancy cases that develop in severe asthma patients and relevant subgroups

9. RESEARCH METHODS

9.1 Study design

This is a real-world, observational, prospective cohort study in patients with severe asthma recruited into ISAR and CHRONICLE. The study analyzes secondary data collected by ISAR and CHRONICLE.

All severe asthma patients, defined as those receiving treatment consistent with Global Initiative for Asthma (GINA) Step 5 or who are uncontrolled on GINA Step 4 treatment regimens, recruited to ISAR and CHRONICLE are followed-up for occurrence of new malignancies. Information on the occurrence, type of malignancy, location, date of diagnosis, staging, and outcome is collected prospectively and irrespective of asthma treatment in both ISAR and CHRONICLE. Incidence rates per 1,000 person-years (PY) will be estimated for patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics. Comparisons between groups will be based on propensity score adjusted estimates. The propensity score calculation will take into consideration potential risk factors for malignancy such as age, gender, BMI, smoking, comorbidity, history of malignancy, registry, and country/region.

New malignancy cases developed during the follow-up period will be described with regards to their history of prior malignancy, malignancy type, location, stage, and outcomes. Data from ISAR and CHRONICLE will be pooled to increase the precision.

Both ISAR and CHRONICLE collect data on history of prior malignancy, occurrence of new malignancy and factors that might influence the rate of new malignancy occurrence, such as demographic characteristics, comorbidities, and environmental exposures (e.g., smoking). These may enhance the understanding of malignancy development among severe asthma patients in general, patients receiving benralizumab, and other subgroups, thereby providing greater context for the results.

In ISAR, there are no fixed follow-up visits for patients. Data on malignancies will be collected as part of routine general health assessment in accordance with respiratory care guidelines and/or recommended medical practice guidelines. Patients are being recruited from 1/2018 – 12/2023.

In CHRONICLE, data on malignancies are collected at the baseline visit and every 6 months during follow-up as part of routine general health assessment in accordance with respiratory

care guidelines and/or recommended medical practice guidelines. Patients are being recruited from 2/2018 – 2/2024.

Both ISAR and CHRONICLE will follow the patients for the occurrence of new malignancies until 12/2023. For the current analysis, patients from both registries will be followed for at least 2 and up to 6 years until end of follow-up in 12/2023 or until the patient withdraws from the registry or death, whichever occurs first.

The index date of the benralizumab cohort will be the date of the first benralizumab use on or after 1 Nov 2017. The same approach will be applied to the cohort of non-benralizumab biologics. For those who do not receive biologics, the index date will be registry entry on or after 1 Nov 2017. A patient can contribute person-time to more than one study cohort but can only contribute person-time to one cohort at a time.

Annual interim descriptive analyses of enrolled patients will be conducted from 2021 through 2023. Descriptive interim analyses will be performed on accruing data to gain an understanding of the data collected, the characteristics of the study population and of the newly developed malignancy cases, as well as monitoring the incidence of malignancy in the study cohorts. Final analyses will be conducted in 2024 (using follow-up data accrued by 12/2023) allowing for approximately 2 to 6 years of follow-up for new malignancy occurrences for all enrolled patients.

9.2 Setting

9.2.1 Study Procedures

ISAR is being conducted by Optimum Patient Care (OPC) in collaboration with the Respiratory Effectiveness Group (REG) and AstraZeneca. CHRONICLE is an AstraZeneca-sponsored study with study operations led in collaboration with PARAXEL, a global contract research organization. Recruitment is expected to complete by end of 2021 for both ISAR and CHRONICLE. Longitudinal data on occurrence of malignancy are collected on enrolled patients from study entry, with the exception of ISAR patients enrolled prior to initiation of malignancy data collection. Data from ISAR and CHRONICLE will be pooled to create the analysis dataset. Annual interim analyses are planned for 2021-2023 for data accrued by 2020-2022 respectively. The final analysis and report is planned for 2024 for data accrued by the end of follow-up in 12/2023.

9.2.2 Study Population

9.2.2.1 ISAR

Inclusion Criteria

1. Individuals, 18 years of age or older, with a diagnosis of severe asthma which requires treatment with guidelines suggested medications for GINA step 4 (medium-high dose ICS and LABA or leukotriene modifier/theophylline) and being uncontrolled or GINA step 5 (maintenance systemic corticosteroid, biologics, or other immunosuppressants)

    a. Uncontrolled asthma defined as at least one of the following:

    1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or ‘‘not well controlled’’ by NAEPP/GINA guidelines)

    2) Frequent severe exacerbations: two or more bursts of OCS (>3 days each) in the previous year

    3) Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

    4) Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

Exclusion Criteria

1. Not willing and able to sign written informed consent. Consent can be obtained from having a responsible, legally authorized representative acting on patient’s behalf.

9.2.2.2 CHRONICLE

Inclusion Criteria

1. Individuals, 18 years of age and older, with a diagnosis of severe asthma for at least 12 months prior to enrollment and currently treated by specialist physicians (e.g., pulmonologists and/or allergists) at the Investigator’s or sub-investigators’ site.

2. Meeting at least one of the following three criteria (a, b, or c):

    a. Uncontrolled on asthma treatment consistent with GINA Step 4 or 5, receiving high-dose ICS with additional controllers.

        i. Uncontrolled is defined by meeting at least one of the following (as outlined by ATS/ERS guidelines):

            1. Poor symptom control: Asthma Control Questionnaire consistently >1.5, ACT <20 (or “not well controlled” by NAEPP/GINA guidelines)

2. Frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous 12 months.

3. Serious exacerbations: at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous 12 months.

4. Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).

ii. High-dose ICS will be defined as

1. ICS at a cumulative dose of >500 µg fluticasone propionate equivalents daily or

2. Highest labelled dose of a combination of ICS/LABA.

b. Current use of a Food and Drug Administration (FDA)-approved monoclonal antibody agent for treatment of severe asthma (use is not primarily for an alternative condition).

c. Use of systemic corticosteroids or other systemic immunosuppressants (any dose level) for approximately 50% or more of the prior 12 months for treatment of severe asthma (use is not primarily for an alternative condition).

Exclusion Criteria

1. Not willing and able to sign written informed consent. Consent can be obtained from having a responsible, legally authorized representative acting on patient's behalf.
2. Not fluent in English or Spanish.
3. Inability to complete study follow-up or web-based PROs. If the patient does not have email or web access, minimal assistance from others to access the web-based PRO is permitted (i.e. receiving the email and/or assisting patient in navigating to the web page); PROs must be completed by the patient.
4. Received an investigational therapy for asthma, allergy, atopic disease, or eosinophilic disease as part of a clinical trial during the 6 months prior to enrollment.

9.3 Variables

The following demographic and clinical variables are collected in both ISAR and CHRONICLE and will allow a thorough description of the demographic and clinical characteristics of the severe asthma population, its subgroups, as well as any new malignancy cases that develop in severe asthma patients.

- Demographic: age, gender, race/ethnicity, occupation, height, weight, BMI, smoking status, pack years
- Clinical characteristics: GINA step; age at asthma onset; number of exacerbations, hospitalizations, emergency department admissions; history of invasive ventilation; medication adherence status; maintenance OCS doses; asthma control status
- Laboratory (conducted as part of routine care): Blood eosinophil, IgE, FeNO, allergen sensitization (serum specific IgE or skin prick test)
- Spirometry (conducted as part of routine care): Percent predicted FEV_1 and FVC, pre- and post-bronchodilator FEV_1 and FVC, pre-and post- bronchodilator FEV_1/FVC
- Comorbidities: Allergic rhinitis, chronic rhinosinusitis, eczema, nasal polyps, atopic disease
- Serious infection and anaphylaxis
- Asthma medication: Specific medication, i.e. ICS, LABA, ICS+LABA, LAMA, theophylline, LTRA, anti-IgE, anti-IL5, macrolide antibiotic, other biologics, start and end date of use.

Details of the collected variables are included in Appendices 1-6.

Study Measures (Outcomes)

New onset malignancy data are collected in both ISAR and CHRONICLE at the baseline visit (for the period of one year prior to the baseline visit) and at follow-up visits (i.e. since the last visit for ISAR and during the prior 6 months for CHRONICLE). Both ISAR and CHRONICLE collect information on history of prior malignancy including type, location, date of diagnosis, and whether the malignancy is active or in remission. Collected data of new malignancies include:

- New onset malignancy (Yes/No)
- Date of diagnosis
- Type of malignancy (cell type)
- Location (site) of malignancy
- Stage of malignancy
- Outcome of malignancy

The malignancy diagnoses will be converted to ICD-10 codes. Details of this process is presented in Section 9.6.

ISAR captures whether the patient died because of malignancy. CHRONICLE captures death and cause of death, including a narrative for full context. Details of the malignancy study outcome are included in Annex 1, Appendix 3 and 4.

9.4 Data sources

The study objectives will be assessed using a combined dataset from ISAR and CHRONICLE.

ISAR is a global collaborative initiative to gather anonymous longitudinal real-life data for patients with severe asthma from over 25 countries, including the Unites States, Canada, UK, Spain, Sweden, Germany, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, Greece, Argentina, Colombia, India, Kuwait, Mexico, Saudi Arabia, Singapore, Taiwan, and the UAE. By the end of 2021 , ISAR had recruited approximately 6,000 patients for the safety analysis [27]. As of May 2018, all ISAR participating countries committed to collect malignancy outcome data. The individual countries own, but agree to share, the deidentified data to ISAR, coordinated by Optimum Patient Care in collaboration with the Respiratory Effectiveness Group and AstraZeneca.

CHRONICLE is a multi-centre, observational, prospective cohort study of adults with severe asthma in the US, sponsored by AstraZeneca [28]. CHRONICLE has recruited approximately 3,000 severe asthma patients by the end of 2021.

Both ISAR and CHRONICLE recruit a similar study population of patients with severe asthma (using similar inclusion and exclusion criteria) and follow patients and collect data in a similar fashion. By the end of 2021, approximately 9,000 severe asthma patients were recruited to both ISAR and CHRONICLE. These registries prospectively collect information on patients with severe asthma including patients receiving biologics across many countries. Core variables on demographic characteristics, clinical features of asthma, asthma treatment, and comorbidities are closely aligned between ISAR and CHRONICLE, allowing for data merging between the two datasets. CHRONICLE and all ISAR countries that agree to collect malignancy data will collect data from all participants on history of prior malignancies and occurrences of new malignancy, including pertinent details on malignancy locations, staging, types, and other related information. The malignancy variables and its data collection also closely match between the two registries allowing merging of this data. Mapping of all common variables from ISAR and CHRONICLE was completed suggesting no issues in matching the majority of variables from the two databases (see section 9.6.3 for more details).

9.5 Study size

The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics,

and those not receiving biologics. The calculations below apply to both adjusted and unadjusted estimates.

To estimate the expected background malignancy rates in the general asthma population, we conducted a literature review and data analyses in patients with asthma using the US MarketScan insurance claims database and the UK's Clinical Practice Research Datalink (CPRD). The incidence of malignancy in the general asthma population (of all severity levels combined) was estimated to be between 3 to 6 per 1,000 PY.

At study outset, it was estimated that ISAR would recruit 10,000 patients by PPD and recruit more than 12,000 severe asthma patients by PPD, with 7,300 (60%) patients receiving biologics and 1,800 (15%) receiving benralizumab. By PPD, assuming 20% of loss to follow-up, we expect 26,000 PY of follow-up for the overall severe asthma population, 15,700 PY for biologic users, and 3,900 PY for benralizumab users.

By PPD there were 5385 patients recruited by ISAR to the safety cohort, of which 2526 patients met inclusion criteria for the study. The benralizumab cohort included 190 patients with PY of follow-up of 327.9 years and the non-benralizumab biologic cohort included 1019 patients, with PY follow-up of 2170.4 years. Total PY of follow-up for all ISAR patients in study was 4146.6 years as at PPD. By PPD, there were 5889 patients recruited from ISAR for the study.

CHRONICLE was estimated to recruit approximately 4,000 patients by March 2021, with 2,400 (60%) receiving biologics and 600 (15%) receiving benralizumab. By December 2023, assuming 20% of loss to follow-up, there would be approximately 13,500 PY of follow-up for the overall severe asthma population, 8,100 for biologic users, and 2,000 for benralizumab users.

By December 2020, there were 2694 patients recruited for CHRONICLE, of which 1793 patients met inclusion criteria for the study. The benralizumab cohort included 388 patients with PY of follow-up of 567.8 years and the non-benralizumab biologic cohort 851 patients with PY of follow-up of 1316.6 years. Total PY of follow-up for CHRONICLE patients in study as at 31 December 2020 was 2749.4 years. By December 2021, there were 3131 patients recruited from CHRONICLE for the study.

Table 3 below shows the expected number of events, and width of 95% CI for considered true incidence rates and different number of PY of follow-up.

Table 3 Expected number of events, and width of 95% CI for different number of PY

True incidence rate (events/1,000 PY)	PY	Expected number of observed events	Expected observed rate (events/1,000 PY)	Expected lower 95% CI	Expected upper 95% CI
3	1500	4	3	1.3	6.2
	5000	15	3	1.8	4.7
	7000	21	3	2.0	4.4
	10000	30	3	2.1	4.2
	15000	45	3	2.2	3.9
	20000	60	3	2.3	3.8
	30000	90	3	2.4	3.6
	40000	120	3	2.5	3.6
6	1500	9	6	3.2	10.4
	5000	30	6	4.2	8.3
	7000	42	6	4.5	7.9
	10000	60	6	4.7	7.6
	15000	90	6	4.9	7.3
	20000	120	6	5.0	7.1
	30000	180	6	5.2	6.9
	40000	240	6	5.3	6.8

*Table based on 100,000 simulated studies using exact Poisson CI

In addition, the difference in observed incidence rates between the cohort of patients receiving benralizumab, compared to cohorts of patients receiving non-benralizumab biologics, and patients not receiving biologics will be reported together with 95% CI.

To provide further justification around the expected difference in incidence rate, Table 4 and Table 5 provides the expected width of 95% CI around the observed difference between the benralizumab cohort and the two comparator cohorts. In addition, it also displays the simulated probability of observing a higher incidence rate in the benralizumab cohort (absolute difference greater than 0) compared to the non-benralizumab comparator cohorts, and the probability to observe an absolute difference larger than 1/1000 PY and 3/1000 PY in favour of the comparator.

For example, Table 4 shows that if there is no difference in incidence rate between benralizumab patients and non-biologic patients then there is a 20% or less probability to

observe a difference larger than 0.1 percentage points (12% for true incidence rate of 3/1000 PY in both cohorts, and 20% for true incidence of 6/1000 PY in both cohorts). However, if there is a true increased incidence rate in the benralizumab cohort of 3/1000 PY (e.g. 3/1000 PY vs. 6/1000 PY or 6/1000 PY vs. 9/1000 PY in the two cohorts) there is a >90% (97% or 93% respectively) probability to observe an absolute difference larger than 0.1% in favour of the comparator non-benralizumab cohort. The observed 95% CI around the difference in incidence rate expected to be within 0.3 percentage points in either direction.

Table 5 shows similar results for benralizumab cohort vs. other non-benralizumab biologic comparator cohort.

Table 4 The expected observed difference in incidence rate- benralizumab (5,900[a] PY) vs. non-biologic cohort (15,700[a] PY)

Assumed true incidence rate in non-biologic cohort vs. benralizumab cohort (/1,000 PY)	Probability[b] to observe a difference in incidence rate larger[c] than			Expected half-width of 95% CI[d] for observed difference	
	>0	>0.1%	>0.3%	Lower	Upper
3 vs. 3	49%	12%	0	0.0015	0.0019
3 vs. 4	86%	49%	2%	0.0016	0.0021
3 vs. 6	>99%	97%	49%	0.0020	0.0024
3 vs. 9	>99%	>99%	99%	0.0023	0.0028
6 vs. 6	49%	20%	1%	0.0021	0.0025
6 vs. 7	79%	50%	6%	0.0022	0.0027
6 vs. 9	99%	93%	49%	0.0025	0.0029
6 vs. 12	>99%	>99%	98%	0.0028	0.0033

[a] Expected number of PY observed in cohort
[b] Probability based on 100,000 simulated studies
[c] Larger in favour of comparator
[d] Confidence interval calculated based on the Newcombe approach

Table 5 The expected observed difference in incidence rate- benralizumab (5,900[a] PY) vs. other-biologic cohort (17,900[a] PY)

Assumed true incidence rate in other-biologic cohort vs. benralizumab cohort (/1,000 PY)	Probability[b] to observe a difference in incidence rate larger[c] than			Expected half-width of 95% CI[d] for observed difference	
	>0	>0.1%	>0.3%	Lower	Upper
3 vs. 3	49%	11%	<1%	0.0014	0.0019
3 vs. 4	86%	48%	2%	0.0016	0.0021
3 vs. 6	>99%	97%	49%	0.0019	0.0024
3 vs. 9	>99%	>99%	99%	0.0023	0.0028
6 vs. 6	50%	19%	1%	0.0021	0.0025
6 vs. 7	79%	49%	5%	0.0022	0.0027
6 vs. 9	99%	93%	50%	0.0024	0.0029
6 vs. 12	>99%	>99%	98%	0.0028	0.0033

[a] Expected number of PY observed in cohort
[b] Probability based on 100,000 simulated studies
[c] Larger in favour of comparator
[d] Confidence interval calculated based on the Newcombe approach

Table 6 and Table 7 provides information regarding the expected distribution and confidence interval for the observed incidence rate ratios for the benralizumab group versus the other comparator groups and are consistent with findings from Tables 4 and 5 for the expected observed difference in incidence rate.

Table 6 The expected observed incidence rate ratio - benralizumab (5,900[a] PY) vs. non-biologic cohort (15,700[a] PY)

Assumed true incidence rate in non-biologic cohort vs. benralizumab cohort (/1,000 PY)	Probability[b] to observe a rate ratio[c] larger than			Expected 95% CI[d] for observed rate ratio	
	>1	>1.2	>2	Lower	Upper
3 vs. 3	49%	25%	<1%	0.58	1.73
3 vs. 4	86%	66%	5%	0.81	2.18
3 vs. 6	>99%	99%	49%	1.29	3.09
3 vs. 9	>99%	>99%	98%	2.03	4.44

Assumed true incidence rate in non-biologic cohort vs. benralizumab cohort (/1,000 PY)	Probability[b] to observe a rate ratio[c] larger than			Expected 95% CI[d] for observed rate ratio	
	>1	>1.2	>2	Lower	Upper
6 vs. 6	50%	17%	<1%	0.68	1.47
6 vs. 7	79%	44%	<1%	0.81	1.68
6 vs. 9	99%	90%	4%	1.07	2.10
6 vs. 12	>99%	>99%	50%	1.47	2.72

[a] Expected number of PY observed in cohort

[b] Probability based on 100,000 simulated studies

[c] Larger in favour of comparator

[d] Confidence interval calculated based on a log normal approximation approach without continuity correction by Kotz

Table 7 The expected observed incidence rate ratio - benralizumab (5,900[a] PY) vs. other-biologic cohort (17,900[a] PY)

Assumed true incidence rate in other-biologic cohort vs. benralizumab cohort (/1,000 PY)	Probability[b] to observe a rate ratio[c] larger than			Expected 95% CI[d] for observed rate ratio	
	>1	>1.2	>2	Lower	Upper
3 vs. 3	49%	24%	<1%	0.59	1.71
3 vs. 4	86%	66%	4%	0.82	2.16
3 vs. 6	>99%	99%	50%	1.31	3.05
3 vs. 9	>99%	>99%	98%	2.06	4.38
6 vs. 6	50%	16%	<1%	0.68	1.46
6 vs. 7	79%	44%	<1%	0.82	1.67
6 vs. 9	99%	90%	4%	1.08	2.08
6 vs. 12	>99%	>99%	50%	1.48	2.70

[a] Expected number of PY observed in cohort

[b] Probability based on 100,000 simulated studies

[c] Larger in favour of comparator

[d] Confidence interval calculated based on a log normal approximation approach without continuity correction by Kotz

9.6 Data management

9.6.1 ISAR

9.6.1.1 Data Collection

ISAR data are routinely collected at secondary or tertiary care severe asthma sites in all participating countries. Patients are enrolled by a health care provider and the patient consent form is signed at the baseline visit. Follow-up data are collected at least once a year.

Data are entered via a web-based electronic data captured (EDC) system using eCRFs. The EDC system automatically keeps track of any changes to the data via an audit trail. Edit checks at the point of entry enhances data quality. The data entry personnel (the 'data collector') can raise queries or leave notes by each variable that the country data manager will be notified of.

Data collectors and country data managers are thoroughly trained on the EDC system features, all the variables, the OpenClinica Guide, as well as the Data Collection Standard Operating Procedure during the site initiation visit and via a teleconference post the initiation visit. Ad-hoc training sessions are provided at the discretion of the country lead.

Data collectors can only enter and edit data, and data can be extracted only by the site investigator and/or the central or country data managers. Therefore, access to the EDC system is role based and each personnel receives an individual username and password to access the site.

ISAR collects patient demographics, medical history, current clinical asthma management, and adherence. Clinical information from a patient's medical history and medical management, such as asthma exacerbations, asthma related healthcare utilization, laboratory diagnostics, and asthma treatment will be updated at least every 6 months by each site.

Patient-reported asthma control (Global Initiative for Asthma [GINA] assessment of asthma) is also reported at least every six months.

9.6.1.2 Conversion of malignancy diagnoses to ICD-10 codes

All medical malignancy data are mapped to ICD-10 codes; this is part of the central data processing step of ISAR to further standardize incoming data from various sources. This is initiated immediately following the quarterly data transfer from participating countries.

The medical coding (ICD-10) will be completed by the ISAR central data manager.

All data fields in the malignancy section of the ISAR safety CRF are mandatory; this prevents missing fields. A cancer diagnosis is confirmed and captured in the database via the

Diagnosis_Confirmation variable in the safety CRF. Prior to the data processing step, where ICD-10 coding is applied, all data provided by sites undergo a rigorous data quality assessment procedure at Optimum Patient Care. Each data quality or validation query is shared with the country-specific data manager and must attain a 'resolved' status before a dataset is fully accepted for data processing by ISAR. Data quality control communication is systematically logged and delivered to each country via the *ISAR Central Data Manager Log* workbook. Additionally, malignancy related data fields must be reviewed for accuracy and completion and electronically signed in the electronic data capture system by a practicing physician at the site before safety eCRF data can be accepted by ISAR. Once malignancy data are received, if there are any further questions or clarifications on the information received, the central data manager can escalate the query to initiate the physician at the site to follow-up with the patient. This is again logged in the *ISAR Central Data Manager Log* workbook. Upon successful completion of the above-mentioned steps, the data are then ready to reside in the ISAR central data repository.

9.6.1.3 Data management

Data Format and Scale

All primary data will be collected via electronic Case Record Form (eCRF) and captured in the Electronic Data Capture (EDC) system OpenClinica. Data can be received in common data formats, such as txt, csv.

Data Quality Assurance and Control

Quality Assurance:

Data quality will be ushered via a series of pre-programmed data quality checks that will automatically detect out-of-range or anomalous data on the data collection instrument: the eCRF. In order to minimize data entry errors, the majority of the fields requested on the ISAR eCRF are numeric.

Preprogramed data quality checks in the eCRF:

- Edit checks, e.g. range, length, and between fields checks
- 'No Data' option to distinguish missing from unknown
- Point and click controls (drop down list or radio button in contrast to free text)
- Guided entry for free text

Data entry training workshops, the OpenClinica Guide, data collection standard operating procedures attribute to sustaining high data quality.

Quality Control:

Data quality will be further enhanced through a series of data cleaning and validation programs by utilising robust data management programs (v9.4, SAS Institute, Cary, NC) to detect discrepancies or implausible data. This is communicated in a systematic manner using the *ISAR Central Data Management Log* (DML). The DML lists each data quality issue/query raised by the central data manager and is shared with the country data manager. Details of the discrepancy/query, such as the priority level (high/medium/low) of the query, the variable involved, and status (open/close), help to log and actualise the highest data quality possible. A batch of data received is not processed for integration into the central ISAR data repository unless all 'high' priority data quality queries on a DML gains the 'resolved' status. Any changes to the central database is logged.

Data Transfer

Existing Registries:

Data will continue to be collected in existing data collection platforms (e.g. UK: Dendrite Clinical Systems or Italy: REDCap). Data within the registry will be "hashed" so that it can only link back to a particular patient at the patient's local registry site. Anonymized data will be extracted, indexed and transferred safely to OPC regularly via Secure File Transfer Protocol (SFTP). The data packages are to be 256-bit encrypted to add an extra layer of security to the file transfer operation.

Prior to the transfer of data to the ISAR central repository, the country data managers will make sure all datasets of any sources are fully anonymised and duly indexed. The coding protocols used in the anonymization data processing will be robust and respect the strictest data protection standards. For each country, the indexation system will be unique and consistent along the whole timespan of ISAR.

The data anonymisation will eliminate all information that can make possible the tracing or identification of patients, such as:

- Sensitive information, e.g., surnames, postcodes, health care or national ID identifiers
- Combinations of fields that make the patient identifiable (house number + date of birth etc.)
- Any information considered personal or sensitive in the country legal framework.

New Registries:

The web-based platform OpenClinica will be the location of comprehensive data collection via eCRFs. Data collected will be transferred to a secured server located at OPC Global in Cambridge, UK via the secured method of Secure Socket Layer (SSL).

9.6.1.4 Data Storage

ISAR has set-up a quarterly data transfer. Upon receipt of fully anonymized data from countries. For a transferred batch of data, all data quality items on the DML must be resolved before data processing is initiated. Data processing further standardizes the data from all countries so that it is ready for analysis. Finally, data are integrated into the central ISAR repository in the UK.

The anonymized data will be stored on secure servers hosted at OPC Global. The servers will be firewall-protected, with a UPS source and a user-controlled authentication protocol will be implemented. Mirroring will be used as the main method to replicate the ISAR database/s. Backup procedures will be in place on the main database, at least daily, to preserve the integrity of the data.

9.6.2 CHRONICLE

9.6.2.1 Data collection

This study is observational, and data are to be collected in a naturalistic manner so that patient management is not influenced by the study protocol. The study measures to be collected at each data collection point (baseline and during study follow-up) are provided sections 9.3 and 9.4.

Patients will be enrolled by their healthcare providers who will collect and enter data at baseline and for every subsequent 6-month interval during study follow-up. At the enrolment visit, the informed consent is obtained. Prior to completing each 6-month data entry, healthcare providers will contact the patient's primary care provider to collect additional information regarding the patient's medical history for each 6-month interval.

Patient questionnaires for data collection will be sent at enrolment and every month, every 3 months or every 6 months depending on the survey.

Data will be collected from the patient and healthcare provider in a uniform manner for every patient enrolled using an electronic case report form (eCRF). Basic de-identified information will be collected for all patients meeting study inclusion criteria, including those not approached for enrolment or who decline enrolment, to enable an assessment of the enrolled and non-enrolled populations. This information will include age, sex, insurance status, age at asthma diagnosis, class of asthma treatment per study inclusion criteria, number of asthma exacerbations in the past 12 months, study eligibility, whether the patient was approached for

enrolment, study enrolment status, and reason for not enrolling for those who are approached but do not enrol.

After enrolment, the healthcare provider will collect detailed information on the patient's demographics, medical history, and current asthma management. Relevant portions of the patient's medical history and medical management, including asthma exacerbations, asthma-related healthcare utilization, laboratory and radiographic testing, asthma treatment, and major medical events of interest, will be updated every 6 months by the healthcare provider along with the Investigator's global evaluation of treatment effectiveness (GETE).

Patient-reported asthma control (Asthma Control Test [ACT]), asthma exacerbations, and treatment adherence will be solicited monthly. Patient-reported information on asthma related healthcare utilization, GETE, and work productivity (Work Productivity and Activity Impairment Asthma questionnaire [WPAI-Asthma]) will be collected at baseline and approximately every 3 months. Detailed information on asthma-related quality of life (Saint George's Respiratory Questionnaire [SGRQ]) as well as presence of an asthma treatment plan will be collected from patients approximately every 6 months. All of the questionnaires will be collected via web-based surveys.

Data monitoring will be accomplished largely through automated edit checks within the electronic data capture (EDC) system and remote monitoring of site performance and aggregated data. In-person site monitoring will only be performed if a specific cause requires investigation.

In addition to data collected from healthcare providers and patients, consent will also be obtained to directly collect information from medical, hospital, and pharmacy records to provide a supplementary comprehensive assessment of each patient's healthcare utilization during the study period. A patient's source of prescription medications (pharmacy, mail order, HCP samples, other sources of free medication) will be collected from patients at baseline and every 6 months to inform which patients will be expected to have pharmacy claims (which do not exist for free medications).

Data are collected in the Rave EDC module and access to this is role based. General study roles are as follows:

1. Clinical Research Coordinator - enter or edit data and respond to edit checks
2. Investigator – view, enter and sign the data.
3. Clinical Research Associate – Review and SDV the data (if applicable)
4. Data Manager – Review the data, raise edit checks

5. Outputs role – extracts the data

9.6.2.2 Conversion of malignancy diagnoses to ICD-10 codes

All malignancy diagnoses recorded in the electronic case report form (eCRF) will be mapped to ICD-10 by a PAREXEL oncologist every six months, based on a line listing of clinical information entered in the Diagnosed Malignancy Log (MALIG) section of the eCRF. PAREXEL Data Management will programmatically identify patients with reported malignancies in the study database (using SAS) and generate a line listing for medical review and ICD-10 coding. Malignancy related variables / data fields in the eCRF will be designated as mandatory fields and therefore, the line listing will comprise all variables in MALIG, including Location/Site and Cell Type which are critical data fields for coding to ICD-10 codes. During the mapping of malignancy diagnoses to ICD-10, if there are any further questions or clarifications on the information received, the oncologist medical reviewer can request that the site be queried for additional information.

To ensure comparability of ICD-10 coding between ISAR and CHRONICLE, the PAREXEL oncologist will also review the ICD-10 coding of reported malignancies in ISAR every six months. If the PAREXEL oncologist determines that Cell Type is discordant with the ICD-10 code within the ISAR database or, that a different ICD-10 code should have been coded, then a listing of those discrepancies will be provided to the MAH, along with the ICD-10 code proposed by the PAREXEL oncologist, for resolution with the ISAR central data manager. A master list of all putative discrepancies and how they were resolved will be maintained by the MAH.

9.6.2.3 Data Management

A data management plan was created describing all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out-of-range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. All the modifications to the data will be recorded in an audit trail.

Data Entry/Electronic Data Capture

All prospective data reported by healthcare providers will be entered directly into an EDC system. All data will be linked with a unique patient identification number but stored in a pseudo-anonymized way.

All participating sites will have access to the data entered for patients enrolled at their site. All sites will be fully trained on using the EDC system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC database via eCRFs. Data entered in the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. Healthcare providers and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. When data have been entered, reviewed and edited, the eCRFs should be reviewed, electronically signed, and dated by the healthcare provider. Data will then be locked to prevent further editing. A copy of the eCRF will be archived at the site.

Data Format and Scale

All data are collected in eCRF which is captured in Electronic Data Capture (EDC) system, Medidata RAVE. Data extracts (Datasets, SDTM, ADaM) will be delivered/transferred in XPT format.

Quality Assurance/Control

As per the data validation/cleaning specification and CRF completion guidelines, data quality is handled with database system checks, programmed edit checks and manual offline listing reviews. These cleaning components identify data entry errors, data out of range (outliers) and any data anomalies.

Each study as applicable undergoes process review and dataset/statistical reviews prior to deliverable to maintain high quality data.

Data Transfer

The statistical programming group will extract and execute transfer using a secure FTP server or Client preferred server if applicable. GDO plan details the method of transfer (e.g. PAREXEL secure FTP or client specific).

9.6.2.4 Data storage

Data stored on the Medidata secure server in a third-party hosting environment which is SSAE 16 certified facility and is HIPAA compliant. Direct data access is restricted to identified Medidata IT staff. Log-monitoring and intrusion detection system (IDS) appliances as well as firewalls are installed on the production network. The hosting facility access controls for

physical access are documented, audited and have multiple fail safes for intrusion detection and access logs. Electronic records and signatures have audit trails, as required by 21CFR §1 and ICH/GCP and all data in the database is audit trailed in compliance with FDA and ICH guidelines.

9.6.3 Data Pooling

Clean ISAR and CHRONICLE datasets will be delivered from OPC and PARAXEL respectively to AstraZeneca. Data from the two datasets will be pooled to create the analysis dataset prior to statistical analyses.

Details of the collected variables are included in the Case Report Forms for the study (a list of the CRFs is included in Annex 1 of this protocol). There is no coding system for the exposure or the covariates as information is entered directly to the clinical research form which is standard across sites and countries for ISAR and across sites for CHRONICLE.

All variables from the following domains from both ISAR and CHRONICLE have been mapped and their values assessed for the ability to pool results for combined analysis. No major issues were identified and variables from the following domains can be mapped directly. This means that the exposure, the outcome, and all key covariates for generating the propensity scores align between ISAR and CHRONICLE databases allowing for a smooth data pooling.

- Demography
- Relevant Medical History
- Laboratory test results of interest
- Diagnostic procedures
- Lung function testing
- Presence of confirmed allergy
- Asthma control
- Asthma medications
- Serious infection
- Malignancies
- Anaphylaxis

One variable that will be difficult to match is ‘occupation’. In CHRONICLE, patient occupation is collected in defined occupational categories, which is feasible because of a consistent nomenclature for occupations in the United States. However, in ISAR, occupation is collected as free text data because occupations are labelled differently across participating countries and hence are not feasible to codify consistently, which limits the ability to pool

with CHRONICLE. Also, matching of race/ethnicity will be incomplete; while categories covering the majority of patients can be matched (e.g., Caucasian/White and African/Black) there is incomplete overlap (e.g., the category "Mixed" only appears in ISAR and "American Indian" only appears in CHRONICLE).

Data from the ISAR and CHRONICLE databases is expected to be received in the CDISC SDTM standard format and will be mapped according to the findings from the assessment process as outlined above. Certain transformations, like date formatting or character to numeric transformations and vice-versa will be completed and analysis datasets will be created and documented for all pooling and analytic activities.

There is very little chance of duplication of patients between ISAR and CHRONICLE as none of the CHRONICLE sites participates in ISAR (and vice versa). As a reminder, CHRONICLE is a US only registry while ISAR includes mostly ex-US countries. The only one US site in ISAR is National Jewish Health, which does not participate in CHRONICLE. However, within each registry, there may be a small number of patients that could be managed by more than one tertiary clinic. If this is observed, potential duplicates will be further investigated before including in the study cohort. Date of birth, gender, race/ethnicity, and age at asthma onset will be examined to identify duplicates within each registry.

9.7 Data analysis

This is an observational study with the primary objective to assess the incidence rates for malignancies in 3 asthma cohorts; patients receiving benralizumab, patients receiving non-benralizumab biologics, and patients not receiving any biologics. The focus being on comparison between patients receiving benralizumab with the two other cohorts using descriptive statistics rather than hypothesis testing.

Analyses will be made based on the pooled data from ISAR and CHRONICLE, and separately in ISAR and CHRONICLE data sets.

Incidence rate will be reported as new malignancies incidence rates per 1,000 PY for all new malignancies with and without NMSC together with 95% nominal confidence intervals. No adjustments will be made for multiplicity. Observed incidence rates will be presented together with nominal 95% exact CI (Clopper-Pearson). Differences in incidence rates between the cohorts will be presented with nominal 95% CI (Newcombe, R. "Interval Estimation for the Difference Between Independent Proportions Comparison of Eleven Methods". Statist. Med 17, 873-890 (1998)).

Details of the statistical analysis are to be provided in a statistical analysis plan (SAP) which will be available prior to the first study interim report.

9.7.1 Disposition, demographics and baseline characteristics

The number of eligible patients and descriptive statistics of person-years of follow-up will be displayed by cohort and data source. The number and percentage of patients censored from follow-up in each cohort will be tabulated by data source, and overall for each of the following censoring events:

1. disenrollment from the healthcare system,
2. treatment discontinuation or switch to another treatment group,
3. death, or
4. end of the study period.

Demographic and baseline characteristics will similarly be descriptively displayed to compare characteristics between cohorts, subgroups, and data sources.

9.7.2 Primary analysis

The primary analysis is to assess the incidence rate together with difference in incidence rate and incidence rate ratio between the three cohorts. Both adjusted and unadjusted estimates will be presented. Incidence rate will be reported as new malignancies incidence rates per 1,000 PY for all new malignancies with and without NMSC.

Estimates for incidence rates, difference in incidence rates, and incidence rate ratios will be adjusted based on propensity scores. Overall estimates will be calculated using a weighted regression model with weights based on inverse propensity scores. In addition, the patients will be subclassified into strata, based on their propensity scores and estimates will be derived within each stratum and comparison (benralizumab vs. non-benralizumab biologics, and benralizumab vs. non-biologics). The subclassification will be into propensity score strata reflecting the probability the patient is treated with benralizumab. Further specification of these analyses is to be made in the SAP.

The propensity scores will be derived for each patient and will assess the probability of receiving benralizumab, given patients' measured baseline characteristics, and will be calculated for each comparison (benralizumab vs. non-benralizumab biologics, and benralizumab vs. non-biologics) using a logistic regression model. The propensity score model will include potential important risk factors for malignancy such as age, gender, BMI, smoking, comorbidities, history of malignancy. Included in the model will also be covariates reflecting patient's registry (ISAR and CHRONICLE) and region/country for the patient.

Time from the index date to first new malignancy will be explored using Kaplan-Meier plots. In addition, adjusted analyses based on propensity score weighted cox regression for time to first new malignancy will also be performed. A patient's time at risk is calculated from the index date until date of diagnosis of a new malignancy or censoring due to death, loss to follow-up, or end of study whichever comes first. Lost-to-follow-up status is designated if a participant withdraws from ISAR or CHRONICLE before the malignancy outcome is known or reported. Participants who are lost-to-follow-up will be censored from the last visit with available data. The person-year at risk for the benralizumab cohort is calculated regardless of whether benralizumab use has been discontinued or not.

For patients in the non-benralizumab biologic cohort who switch to benralizumab during the study, the person-year at risk is censored at the time of switch to benralizumab and only new malignancies with diagnosis date prior to switching are counted as non-benralizumab malignancies. A similar approach is adopted for patients switching from benralizumab to the non-benralizumab biologic cohort. New malignancies with diagnosis date after switching to benralizumab will be summarized separately.

Characteristics of new malignancy cases developed during the follow-up with regards to their history of prior malignancies, malignancy type, location, stage, and outcomes will be described using descriptive statistics.

To assess signs of potential imbalances differences between cohorts with regards to potential risk factors for malignancy will be explored using descriptive summaries. If during the enrolment, there is indication that there is an important risk factor present that needs to be considered, additional analysis will be specified in the SAP.

9.7.3 Missing data

Missing values for the critical data are expected to be less than 10%. However, depending on the prevalence of missingness, sensitivity analyses may be conducted. Any analyses to assess the influence of missing data will be pre-specified in the SAP.

9.8 Quality control

All patients enrolled in ISAR and CHRONICLE will be followed by asthma specialists, who will confirm the diagnosis of severe uncontrolled asthma prior to patient enrolment. All countries participating in ISAR will abide to data quality control operating procedures. CHRONICLE will be monitored by AstraZeneca to ensure data quality. Data monitoring will be accomplished largely through automated edit checks within the EDC system and remote monitoring of site performance and aggregated data. In-person site monitoring will only be performed if a specific cause requires investigation.

9.9 Limitations of the research methods

The study precision is dependent on the real-world uptake of benralizumab and the study may require longer time than expected to recruit and follow a sufficient number of exposed patients. However, both ISAR and CHRONICLE are registries of the severe asthma population that is the most likely to use add-on biologic maintenance therapy such as benralizumab. Additionally, these registries have a greater ability than secondary databases (e.g. insurance claims databases or other databases of healthcare utilization) to provide a meaningful sample size and high data quality regarding use of biologic therapy and malignancy incidence and characteristics.

A difference in data quality, including missing data and outcome misclassification, between ISAR and CHRONICLE and among participating countries and/or sites, is a potential limitation. In addition to the post-collection quality control efforts, both registries standardize data collection via the use of electronic case report forms that have integrated quality control measures. We expect asthma related data including asthma medications to be of good quality given it is reported by the treating physicians (i.e. asthma specialists). The malignancy (i.e. outcome) data are reported by the treating physicians and its accuracy depends on the patient's history and medical records which may have misdiagnoses. Patients with more severe asthma (who are also more likely to be on biologics) may be seen more frequently by the treating physicians increasing the chance of detecting new malignancies. Potential increased surveillance for malignancies in biologic recipients may also increase the likelihood of detection bias. The EXCELS study did not find evidence of such biases (Long et al 2014).

It is expected that patients recruited to different registries may be different from each other, reflecting differences in inherent patient characteristics, standard of cares etc. Given malignancy is a rare outcome and the potentially low number of benralizumab recipients, the ability to analyse data separately by countries/registries or stratify by/standardize for multiple patient characteristics can be limited. A previous study in moderate to severe asthma patients suggested that differences in distribution of various characteristics and risk factors for malignancies (i.e. confounding factors) at baseline are not likely to play any important role on the association between Xolair and malignancy [26].

According to the same study [26], loss to follow-up may be substantial, limiting the ability to follow and study patients for a long period of time and therefore limiting the ability to study malignancies with a long latency period.

9.10 Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical conduct

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) (2015) *Guidelines for Good Epidemiology Practices* and applicable regulatory requirements including European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies* (EMA, 2016).

The individual registries involved in ISAR have all received IRB or Ethics Committee approval for their data collection. The CHRONICLE registry has also received IRB approval (Schulman IRB, 3-Nov-2017). No additional IRB or EC approvals are required for the current study, as it will be limited to deidentified data already collected under the ISAR and CHRONICLE protocols.

The study concept has been approved by the ISAR Steering Committee and the study protocol will be reviewed and approved by the ADEPT committee prior to first data extraction. This is a requirement for all studies using ISAR data.

10.2 Registration of Study on Public Website

The study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS Register (ENCePP, 2016) and ClinicalTrials.gov, after protocol approval and before the study implementation commences. The study sponsor will adhere to the general principles of transparency and independence in the ENCePP code of conduct (ENCePP, 2014).

10.3 Database Retention and Archiving of Study Documents

The location of analysis datasets and supporting documentation will be outlined in the final observational study report.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is an observational study analysing secondary data that are being collected through the ISAR and CHRONICLE registries. Adverse Event reporting is not required for this secondary data collection study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The MAH will prepare three annual interim reports in 2021 (for data accrued by 2020, i.e. one year before the planned recruitment completion in 2021) through 2023 (for data accrued by 2022, i.e. one year before the end of follow-up) describing the incidence of malignancy in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics.

A final report describing the study endpoints according to the SAP will be prepared by the MAH at the end of the study (2024) for data accrued at the end of follow-up in 12/2023. The Sponsor will communicate the interim and final results to the FDA, the European Medicines Agency (EMA), and any other relevant regulatory authorities as soon as they are available.

12.1.1 Ownership and Use of Data and Study Results

The individual level study data is owned by ISAR and CHRONICLE and may not be shared. Aggregated data will be shared with the Regulatory Health Authorities (e.g. EMA, FDA). The MAH will do its best to provide as much context to the data as possible following the rules and regulations by the participating registries and local laws.

12.1.2 Scientific Advisory Committee

An independent group of external experts serves as the scientific advisory committee to provide scientific input to this study, including protocol and statistical analysis plan development and interpretation of study findings. The experts will have full access to the annual interim report and the final report. Specific requests from the advisory committee for additional analyses or clarifying questions will be addressed by AstraZeneca.

The advisory committee consists of severe asthma experts from several ISAR participating countries including the UK, Spain, Netherland, and the US.

12.1.3 Publications

AstraZeneca reserve the right to submit the results from these analyses for publication and commit that they will publish at least the final results. The authorship of publications shall be in accordance with standards as described in the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* (International Committee of Medical Journal Editors, 2016).

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 8 List of stand-alone documents.

Number	Document reference number	Date	Title
1	*Appendix 1*	PPD	*ISAR Baseline Case Report Form*
2	*Appendix 2*	PPD	*ISAR Follow-up Case Report Form*
3	*Appendix 3*	PPD	*ISAR Baseline and Follow-up Safety bolt-on Case Report Form*
4	*Appendix 4*	PPD	*CHRONICLE Case Report Form*
5	*Appendix 5*	PPD	*ISAR Baseline and Follow-up Effectiveness bolt-on Case Report Form*
6	*Appendix 6*	PPD	*ISAR and CHRONICLE List of Variables*
7	*Appendix 7*	PPD	*ISAR CORE VARIABLES BASELINE CRF_PPD_Hard Copy V1.2*

Number	Document reference number	Date	Title
8	*Appendix 8*	PPD	*ISAR CORE VARIABLES FOLLOW_UP CRF_PPD Hard Copy V0.8*
9	*Appendix 9*	PPD	*ISAR SAFETY BOLT ON BASELINE_FOLLOW-UP_CRF_PPD _Hard Copy_V2.8*
10	*Appendix 10*	PPD	*234262_Mock CRF_V10.0_PPD*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/PPD

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on PPD

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: *Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorization Safety Study*

Study reference number: D3250R00042

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☒	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	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
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7, 9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

This is a descriptive study of the incidence of malignancy in severe asthma and its subgroups without hypothesis testing.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.1, 9.7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7
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?	☒	☐	☐	9.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.1
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.4
4.2.4 Disease/indication?	☒	☐	☐	7, 8, 9.3
4.2.5 Duration of follow-up?	☒	☐	☐	9.1, 9.5
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1, 9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1-9.3, 9.5
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.6, 9.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1-9.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

The subgroups of severe asthma were classified based on major groups of medications of interest. Malignancy is observed post any exposure, so pharmacokinetics and pharmacodynamics is not relevant

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?	☒	☐	☐	9.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.6
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease, disease management)	☐	☒	☐	

Comments:

HTA endpoints are not study outcomes in this study

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.6-9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.6-9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.6-9.9

Comments:

The main objective of this descriptive study is to assess the incidence and characteristics of malignancies in severe asthma patients receiving benralizumab compared with other comparator groups. Potential differences between study groups are balanced by adjusting for the propensity scores.

Section 8: Effect 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:

This is a descriptive study. There are no known effect modifiers for benralizumab and malignancy.

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)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates?	☒	☐	☐	9.3
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)	☒	☐	☐	Annex 1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Annex 1
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Annex 1
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)		☐	☒	

Comments:

The exposure, outcomes, and covariates are primarily collected by treating physicians and information is entered directly to the CRFs for both ISAR and CHRONICLE. The malignancy outcomes are mapped to ICD-10 diagnosis codes.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☒	☐	☐	10.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.1.2

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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.7

Comments:

Section 13: Ethical 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?	☐	☐	☒	

Comments:

This study analyzes de-identified, secondary data collected for the ISAR and CHRONICLE registries and does not require additional IRB or EC approval beyond those required for ISAR and CHRONICLE.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Peter McMahon

Date: dd/Month/year

Signature: _____

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