PASS Protocol	
Active substance	Benralizumab
Product reference	D3250R00042
Version number	1.0
Date	PPD

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

Sponsor: AstraZeneca
Principal Investigator: Trung N. Tran, MD, PhD

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Approved by:

PPD

Deputy EU QPPV
As delegated by
PPD EU QPPV

PASS INFORMATION

Title	Descriptive Study of the Incidence of Malignancy in Patients with Severe Asthma Overall and Among Those Receiving Benralizumab and Other Biologic Therapy, a Post Authorization Safety Study
Protocol version identifier	1.0
Date of last version of protocol	PPD
EU PAS register number	TBD
Active substance	Benralizumab
Medicinal product	Fasenra ™
Product reference	Benralizumab
Procedure number	Not applicable
Marketing authorisation holder(s)	AstraZeneca AB
Joint PASS	No
Research question and objectives	The primary objective of this study is to measure the incidence of malignancy in the overall severe asthma population and its subgroups including patients receiving benralizumab, those receiving non-benralizumab biologics or other steroid-sparing agents, and those not receiving biologics or steroid-sparing agents. The study also aims to describe the clinical characteristics of the new malignancy cases in patients with severe asthma.
Country (-ies) of study	United States, Canada, UK, Spain, Italy, Denmark, Finland, Iceland, South Korea, Japan, Bulgaria, Ireland, Greece.

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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

Abbreviation or special term	Explanation
NAEPP	National Asthma Education and Prevention Program
OCS	Oral Corticosteroids
OPC	Optimum Patient Care
PAM	Post-authorisation Measure
PASS	Post Authorization Safety Study
PRO	Patient Reported Outcome
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.

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4. ABSTRACT

Title: Descriptive Study of The Incidence of Malignancy in Patients with Severe Asthma Overall and Among Those Receiving Benralizumab and 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. Few data are available on the occurrence of malignancy in severe asthma patients, including those receiving benralizumab and not receiving benralizumab. The current study will describe the occurrence of malignancy, including the incidence and clinical characteristics of the malignancy cases in patients with severe asthma and its relevant subgroups. 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 measure the incidence of malignancy in the overall severe asthma population and relevant subgroups including patients receiving benralizumab, those receiving non-benralizumab biologics or other steroid-sparing agents, and those not receiving biologics or steroid-sparing agents. The study will also describe in detail the clinical characteristics of the new malignancy cases in patients with severe asthma.

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 person-year will be calculated for severe asthma patients, patients receiving benralizumab, patients receiving non-benralizumab biologics or other steroid-sparing agents, and patients not receiving biologics or other steroid-sparing agents. ISAR and CHRONICLE are prospective cohorts that collect routine specialist care data on severe asthma patients. Crude and standardized incidence rates will be calculated for the overall study population and for each subgroup adjusting for key patient characteristics. 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 main study group includes all patients with severe asthma. Subgroups

will include patients who receive benralizumab, non-benralizumab biologics or other steroid-sparing agents, and those who do not receive biologics or steroid-sparing agents.

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 more than 14 countries, including the United States, Canada, UK, Spain, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, and Greece (http://www.encepp.eu/encepp/viewResource.htm?id=23721). Almost 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: ISAR and CHRONICLE are targeted to recruit at least 10,000 and 4,000 severe asthma patients respectively by PPD respectively. The current projections for ISAR and CHRONICLE recruitment, which assume 20% loss to follow-up, suggests that by PPD (with 2 to 6 years of follow-up on study participants) both registries may provide up to a total of 34,000 person-years of follow-up for the overall severe asthma population; approximately 17,300 for biologic users, and 5,800 for benralizumab users.

Data analysis: The incidence rate for malignancies in the overall severe asthma population and its relevant subgroups will be estimated in the pooled data from ISAR and CHRONICLE, as well as by each registry separately as a supportive analysis. No formal comparative statistical tests are pre-defined. Unadjusted incidence rates, 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. Age- and sex-standardized incidence rates for new malignancies in the overall study population and across subcohorts will also be calculated using weights from the general population (US general population, https://seer.cancer.gov/popdata/). Standardized morbidity ratios for all malignancies of the overall study population and each study cohort in reference to the general population can be estimated. 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 to PPD There will be three annual interim reports, conducted in PPD (for data accrued by PPD i.e. one year before the planned recruitment completion in 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
None				

6. MILESTONES

Table 2 Study milestones

Milestone	Planned date
Start of data collection	PPD
End of data collection	PPD
Annual interim reports	PPD
Registration in the EU PAS register	TBD
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 -longacting- 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 7857 patients were enrolled in the study from 445 sites (omalizumab cohort, n=55007; nonomalizumab cohort, n=52829). The omalizumab cohort had a higher proportion of patients with severe asthma compared with the nonomalizumab cohort (50.0% vs 23.0%). Crude malignancy rates were similar in the omalizumab and nonomalizumab 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 nonomalizumab) 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 effect that biologics may have on development of malignancies when used 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:

- To measure the incidence of malignancy in the overall severe asthma population as well as its relevant subgroups, including patients receiving benralizumab, patients receiving non-benralizumab biologics or steroid-sparing agents, and patients not receiving biologics or other steroid-sparing agents
- 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 the International Severe Asthma Registry (ISAR) and the US severe asthma registry (CHRONICLE). The study analyses 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 will be calculated for severe asthma patients and patients receiving benralizumab, patients receiving non-benralizumab

biologics or other steroid-sparing agents, and patients not receiving biologics or steroid-sparing agents.

Crude and standardized incidence rates by key patient characteristics, such as age, gender will be calculated for the overall severe asthma population and for each subgroup. 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 PPD. In CHRONICLE, data on malignancies will be 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 PPD, although recruitment may be extended. Both ISAR and CHRONICLE will follow the patients for the occurrence of new malignancies until PPD. 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 PPD or until the patient withdraws from the registry or death, whichever occurs first.

The index date of the overall study cohort (pooling data from ISAR and CHRONICLE) is the date of study entry (i.e. baseline visit). For the benralizumab cohort, the index date will be the date of the first benralizumab use for those enrolled prior to receiving benralizumab and study entry for those enrolled while receiving benralizumab. The same approach will be applied to the cohort of non-benralizaumab biologics or other steroid-sparing agents. For those who do not receive biologics or other steroid-sparing agents (i.e. those who receive chronic OCS or are uncontrolled GINA 4), the index date will be study entry. 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 PPD through PPD 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 of enrolled patients by PPD will be conducted in PPD (using follow-up data accrued by PPD allowing for 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 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 PPD 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 analytic dataset. Annual interim analyses are planned for PPD for data accrued by PPD respectively. The final analysis and report is planned for PPD for data accrued by the end of follow-up in PPD

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)

    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, height, weight, BMI, smoking status, pack years
- Clinical characteristics: GINA step; age at asthma onset; number of exacerbations, hospitalizations, ED 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

- Asthma medication: Specific medication, i.e. ICS, LABA, ICS+LABA, LAMA, theophylline, LTRA, anti-IgE, anti-IL5, macrolide antibiotic, other biologics, other steroid-sparing agents, start and end date of use.

Details of the collected variables are included in Annex 1, Appendix 1, 2, and 4.

9.4 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

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.

9.5 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 14 countries, including the Unites States, Canada, UK, Spain, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, and Greece. ISAR is targeted to recruit at least 10,000 severe asthma patients by PPD starting in PPD (http://www.encepp.eu/encepp/viewResource.htm?id=23721). As of PPD , 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 (https://clinicaltrials.gov/ct2/show/NCT03373045). CHRONICLE is targeted to recruit 4,000 severe asthma patients within 3 years, starting in PPD

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. Together by the end of PPD we expect to have 14000 severe asthma patients 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. Overall, no problems are anticipated with merging data from ISAR and CHRONICLE.

9.6 Study size

The primary objective of this study is to estimate the incidence of malignancy in the overall asthma population and in particular in patients receiving benralizumab, patients receiving non-benralizumab biologics and/or steroid-sparing agents, and patients not receiving biologics or steroid-sparing agents.

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 person-years.

It is estimated that ISAR will recruit approximately 10,000 patients after 5 years whereof 5,850 are estimated to be treated with biologics. Assuming 35% of the biologics users are on treatment with benralizumab, approximately 2,050 patients will be benralizumab users. By PPD assuming ~20% of loss to follow-up, we expect 22,000 person-years of follow-up for the overall severe asthma population, 13,000 for biologic users, and 4,600 for benralizumab users.

CHRONICLE will recruit approximately 4,000 patients by the end of PPD We expect ~35% of all patients will receive biologics (N=1,400) and ~10% of all patients will receive benralizumab (N=400). By PPD assuming 20% of loss to follow-up, we expect 12,000 person-years of follow-up for the overall severe asthma population, 4,300 for biologic users, and 1,200 for benralizumab users. Thus, the current projection of ISAR's and CHRONICLE's recruitment suggests that together ISAR and CHRONICLE may provide up to a total of 34,000 person-years of follow-up for the overall severe asthma population, 17,300 for biologic

users, and 5,800 for benralizumab users.

Table 3 below shows the expected number of events, and width of 95% confidence intervals (CI) for considered true incidence rates and different number of patient years of follow-up.

Table 3 Expected number of events, and width of 95% confidence intervals for different number of patient-years

True incidence rate (events/patient-year)	Patient years	Expected number of observed events	Expected observed rate (events/patient-year)	Expected lower 95% CI	Expected upper 95% CI
0.003	1500	4	0.003	0.0013	0.0062
	5000	15	0.003	0.0018	0.0047
	7000	21	0.003	0.0020	0.0044
	10000	30	0.003	0.0021	0.0042
	15000	45	0.003	0.0022	0.0039
	20000	60	0.003	0.0023	0.0038
	30000	90	0.003	0.0024	0.0036
	40000	120	0.003	0.0025	0.0036
0.006	1500	9	0.006	0.0032	0.0104
	5000	30	0.006	0.0042	0.0083
	7000	42	0.006	0.0045	0.0079
	10000	60	0.006	0.0047	0.0076
	15000	90	0.006	0.0049	0.0073
	20000	120	0.006	0.0050	0.0071
	30000	180	0.006	0.0052	0.0069
	40000	240	0.006	0.0053	0.0068

*Table based on 100,000 simulated studies using exact Poisson Confidence intervals (CI)

9.7 Data management

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 analytic dataset prior to statistical analyses.

Missing values for the critical data are expected to be less than 10%. There is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses may be conducted. These will be specified in the SAP.

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.

9.8 Data analysis

This is a descriptive study estimating the incidence rate for malignancies in the overall severe asthma population and its relevant subgroups including patients

- receiving benralizumab,
- patients receiving non-benralizumab biologics and/or other steroid-sparing agents,
- patients not receiving any biologics or steroid-sparing agents (e.g. those on maintenance OCS or high dose ICS/LABA).

The incidence rate for malignancy will be assessed in the pooled data from ISAR and CHRONICLE, and separately in ISAR and CHRONICLE. No formal statistical tests are pre-defined. All confidence intervals will be presented as nominal 95% confidence intervals.

Unadjusted incidence rates per 1,000 patient-years, together with nominal 95% confidence intervals, will be presented for all new malignancies with and without NMSC. Absolute differences in incidence rates and crude ratio of rates between the study cohorts (i.e. patients receiving benralizumab versus patients receiving non-benralizumab biologics or steroid-sparing agents, and those receiving benralizumab versus those not receiving biologics or steroid-sparing agents) will be presented together with 95% CIs.

The person-time at risk for the benralizumab cohort is from the index date to diagnosis of a new malignancy, death, loss to follow-up, or end of study whichever comes first, regardless of whether benralizumab use has been discontinued or not. For the other two non-benralizumab cohorts, some patients may switch to benralizumab during the study. For these patients, person-time at risk ceases at the time of switch to benralizumab and only new malignancies with onset prior to switching are counted as non-benralizumab malignancies. For new malignancies with onset after switching to benralizumab will be summarized separately.

In order to understand what factors may potentially influence the incidence rates of malignancy in severe asthma, a literature review was conducted to identify potential risk factors for malignancy in severe asthma. Few studies were found. In the EXCELS study among moderate to severe asthma, Long et al (2014) suggested lack of any important confounding. We expect that risk factors for malignancy are similar between severe asthma and the general population.

Time from the index date to first new malignancy will be explored using Kaplan-Meier plots. Age- and sex-standardized incidence rates for all new malignancies in the overall study population and across cohorts using weights from the general population (US general population, https://seer.cancer.gov/popdata/) will also be calculated. In addition, standardized morbidity ratios (SMR) of the overall study population and each study cohort in reference to the SEER population can be estimated for all malignancies (except NMSC which is not captured in the SEER database). The SMR is calculated as the ratio of observed and the expected number of cases in the study group had it experienced the incidence rates of the general population.

Given the heterogeneity of ISAR participating countries, differences of patient characteristics across ISAR participating countries and between ISAR and CHRONICLE are expected. In order to evaluate this potential heterogeneity, distribution of demographic characteristics, asthma features, comorbidities, and asthma treatment of patients with focus on potential risk factors for malignancy will be presented descriptively overall and by key subgroups.

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.

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

9.9 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 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.

9.10 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.

9.11 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, PPD). 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 analytic data sets 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 PPD (for data accrued by PPD i.e. one year before the planned recruitment completion in PPD through PPD (for data accrued by PPD i.e. one year before the end of follow-up) describing the incidence of malignancy in the overall severe asthma population including the subgroups of patients receiving benralizumab, patients receiving non-benralizumab biologics or steroid-sparing agents, and patients not receiving biologics or other steroid-sparing agents.

A final report describing the study endpoints according to the SAP will be prepared by the MAH at the end of the study (PPD for data accrued at the end of follow-up in PPD 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).

13. REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 4 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*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

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 Patients with Severe Asthma Overall and Among Those 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:

Registration in the EU PAS register will be updated to the protocol after protocol approval by EMA

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, 9.8
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)	☒	☐	☐	9.8
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?	☒	☐	☐	9.5
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.6
	4.2.2 Age and sex?	☒	☐	☐	9.2.2
	4.2.3 Country of origin?	☒	☐	☐	9.5
	4.2.4 Disease/indication?	☒	☐	☐	7, 8, 9
	4.2.5 Duration of follow-up?	☒	☐	☐	9.1, 9.6
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

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, 9.8
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.10
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.8
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?	☒	☐	☐	9.4
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)	☒	☐	☐	9.10
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, 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?	☒	☐	☐	9.8

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.8
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.10
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.10

Comments:

The main objective of this descriptive study is to describe the incidence and characteristics of malignancy in the overall severe asthma population and its subgroups. It adjusts for differences in key patient characteristics such as age and sex between study groups.

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)	☒	☐	☐	9.4
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))	☐	☐	☒	
9.3.3 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 to a CRF for both ISAR and CHRONICLE. Therefore, no coding system for the variables or linkage between data sources is needed.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.8
10.2 Are descriptive analyses included?	☒	☐	☐	9.8
10.3 Are stratified analyses included?	☒	☐	☐	9.8
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.6

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?	☒	☐	☐	9.9

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
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)	☒	☐	☐	9.10

Comments:

This is a descriptive and not a comparative study.

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: Trung Tran PPD

Date: dd/Month/year

Signature: PPD