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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

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EU Qualified Person for
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PASS INFORMATION

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Country (-ies) of study	United States, Canada, UK, Spain, Italy, Germany, 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
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.

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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 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, Italy, Germany, Denmark, Finland, Iceland, Ireland, Bulgaria, South Korea, Japan, and Greece (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: ISAR and CHRONICLE are targeted to recruit at least 10,000 and 4,000 severe asthma patients 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 combined total of 5,900 person-years for benralizumab users, 17,900 person-years for non-benralizumab biologic users, and 15,700 person-years for non-biologic patients.

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

Number	Date	Section of study protocol	Amendment or update	Reason
		Annex 1	Added Appendix 5 and 6	Response to comments from EMA

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	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 -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 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 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 (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 PPD and may be extended through 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 benralizumab cohort 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-benralizumab biologics. For those who do not receive biologics, 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 will be conducted in PPD (using follow-up data accrued by PPD) 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 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 analysis dataset. Annual interim analyses are planned for PPD for data accrued by PPD 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)

    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 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 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 14,000 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. 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.

It is estimated that ISAR will recruit 10,000 patients by PPD and may 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.

CHRONICLE will recruit approximately 4,000 patients by PPD, with 2,400 (60%) receiving biologics and 600 (15%) receiving benralizumab. By PPD, assuming 20% of loss to follow-up, there will 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.

Thus, the current projection of ISAR's and CHRONICLE's recruitment suggests the potential for a combined total of 39,500 PY of follow-up for the overall severe asthma population

including 15,700 PY for non-biologic users and 23,800 PY for biologic users which includes 5,900 PY for benralizumab users and 17,900 PY for non-benralizumb biologic users.

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 person-years of follow-up will be displayed by cohort, data source and year. The number and percentage of patients censored from follow-up in each cohort will be tabulated by year, 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. The subclassification will be into propensity score strata reflecting the probability the patient treated with the different treatments. Further specification of these analyses is to be made in the SAP.

The propensity scores will be derived for each patient using a multinomial model modelling the probability that the patient receiving benralizumab treatment, non-benralizumab biologic treatment, and non-biologic treatment. 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 two non-benralizumab cohorts 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 onset prior to switching are counted as non-benralizumab malignancies. For new malignancies with onset 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, 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 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 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 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 (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).

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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*

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 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: Trung Tran

Date: dd/Month/year

Signature: _____

Patient ID: _____ Date of Visit: _____ Centre ID: _____

INTERNATIONAL SEVERE ASTHMA REGISTRY

Baseline Questionnaire
Data Collection Form

Patient ID: _____ Date of Visit: _____ Centre ID: _____

GENERAL GUIDE TO COMPLETE THE CRF

Completing the CRF

- Use a ballpoint pen to fill in the CRF, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the CRF are consistent with the source documents.
- Do not leave questions unanswered. If data is not available for a field, check the "No Data" box and move to the next question.
- Sign and date the CRF each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the CRF

- Each correction in the CRF must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Indicator	Field
–	**This secondary branch question is probed when the primary trunk question is filled**
+	**This tertiary branch question is probed when the primary trunk and secondary branch questions are filled**
Greyed Out Text	**This greyed out question is auto-calculated and does not require data input.**

Form Completed By: _____

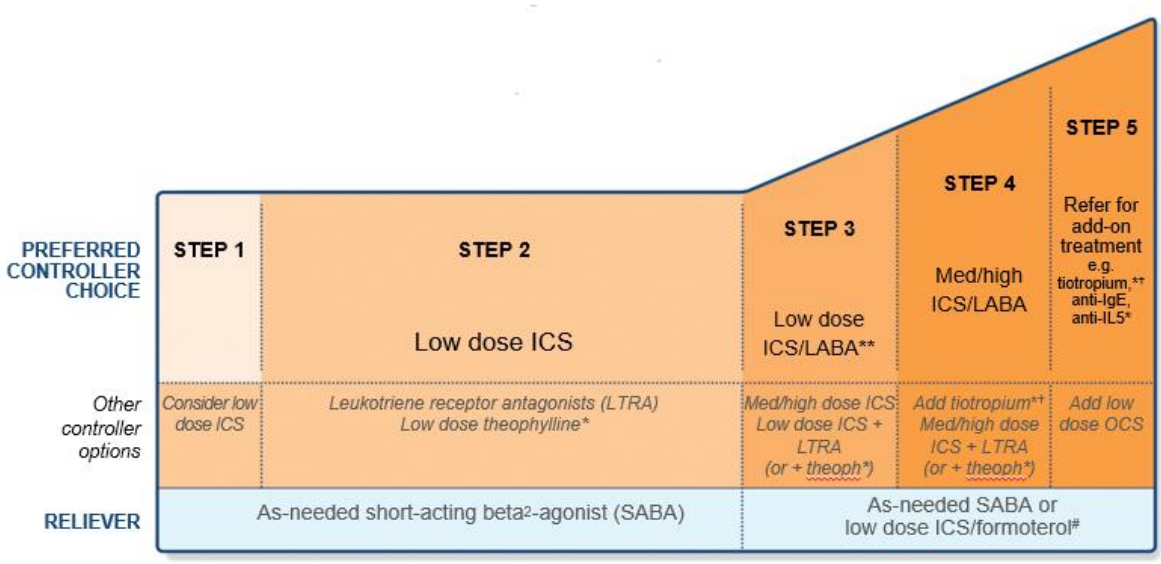
Date: _____

Signature: _____

Patient ID: _____ Date of Visit: _____ Centre ID: _____

INCLUSION GUIDELINES

GINA[1] guidelines for Asthma treatment (1)



*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Figure 1. GINA stepwise approach for asthma control

Note: tiotropium by soft mist inhaler is indicated in adults aged ≥18 years in the EU.

1) Please check all that apply (For adults ≥ 18 years old)

i) On GINA Step 5 treatment:	☐ Yes ☐ No
ii) Uncontrolled on GINA Step 4 treatment: Uncontrolled defined as: a. **Having severe asthma symptoms [2]** b. **Frequent severe asthma exacerbations[3] requiring systemic corticosteroids**	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No

Does the patient have severe asthma in accordance with the guidelines for ISAR above? *(Auto-Populated)*

[1] GINA: Global Initiative for Asthma

[2] Severe asthma symptoms (ERS/ATS Guidelines) (2):
(a) Poor symptom control where Asthma Control Questionnaire consistently >1.5, Asthma Control Test <20 (or "not well controlled" by NAEPP/GINA guidelines)
(b) Airflow limitation: FEV1< 80% predicted (in the face of reduced FEV1/FVC following a withhold of short and long acting bronchodilators, i.e. Pre-bronchodilator)
(c) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year

[3] Frequent severe asthma exacerbations (ERS/ATS Guidelines) (2):
Two or more bursts of systemic Corticosteroids (>3 days course each) in the previous year

Patient ID: _____ Date of Visit: _____ Centre ID: _____

PATIENT DETAILS

Please record the patient's demographic data collected at the baseline visit

2) Date of Visit

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY)

3) Date of Birth

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY)

Age at Assessment (Years)
(Auto-Calculated)

4) Gender:

Female ☐

Male ☐

5) Ethnicity:
(Please select from list)

Caucasian ☐

South East Asian ☐

North East Asian ☐

African ☐

Mixed ☐

Other, please specify: _____ ☐

Unknown ☐

☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

6) Height: ☐.☐☐ m ☐ No data

7) Weight: ☐☐☐.☐ kg ☐ No data

Patient Body Mass Index (BMI) kg/m^2
(Auto-Calculated)

Patient Body Surface Area (BSA) m^2
(Auto-Calculated)

8) Has the patient ever had Bronchial Thermoplasty[4]?

○ No ○ Yes ○ No Data

9) What is the current occupation of the patient?

☐ No data

(Please input job description)

[4] Bronchial Thermoplasty (Alair™ System): FDA approved treatment(2010) for severe asthma where controlled therapeutic radiofrequency energy is supplied to the airway wall, inducing heat and damaging smooth muscle tissue present in the airway wall to alleviate smooth muscle constriction during an asthma attack (5)

Patient ID: _____ Date of Visit: _____ Centre ID: _____

MEDICAL HISTORY

Please record the patient's medical history collected at the baseline visit

Smoking History

10) What is the current smoking status of the patient?

- ○ Never smoked
- ○ Ex-Smoker
- ○ Current Smoker ☐ No data

-Number of cigarettes smoked per day? *(if indicated for Ex-Smoker, Current Smoker)*

☐☐☐ cigarettes/day ☐ No data

-Number of smoking years? *(if indicated for Ex-Smoker, Current Smoker)*

☐☐.☐ smoking years ☐ No data

-Pack Years[5]? (if indicated for Ex-Smoker, Current Smoker)
(Auto-Calculated)

-Date when the patient quit smoking *(if indicated for Ex-Smoker)*
(Please input at least the year if the exact date is not available)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

[5] Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Exacerbation History

11) Date when the patient's asthma symptoms started.

(Please input at least the year if the exact date is not available)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

12) Total number of exacerbations requiring rescue steroids within the last year?

(Severe asthma exacerbations are defined as events that require urgent action (rescue steroids) on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma)(3)(4)

☐☐☐ exacerbations ☐ No data

- For each exacerbation since the last 12 months, please specify the date of exacerbation, starting from the most recent:

Number	(a) Date of Exacerbation	(b) Rescue Steroid Used	(c) Label Dose	(d) Frequency per day	(e) Start & End date
1	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
2	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Number	(a) Date of Exacerbation	(b) Rescue Steroid Used	(c) Label Dose	(d) Frequency per day	(e) Start & End date
3	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
4	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
5	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
6	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data

12 (c) Please input the label indicated dose of the rescue steroid administered.
12 (d) Please indicate the frequency of rescue steroid administered per day.
12 (a) and (e) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Exacerbation and Start/Diagnosis date should be within 12 months prior to the baseline visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Date of Visit: _____ Centre ID: _____

13) Total number of episodes of invasive ventilation ever?

☐☐☐ episodes ☐ No data

14) Total number of A&E attendances (Emergency room visit) for asthma within the last year?

☐☐☐ attendances ☐ No data

15) Total number of hospital admissions for asthma within the last year?

☐☐☐ admissions ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

RELEVANT COMORBIDITIES

COMORBIDITY

Please record the patient's comorbidity details collected at the baseline visit.

Does the patient have an indication of the following:

16) Allergic Rhinitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

17) Chronic Rhinosinusitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

18) Atopic dermatitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

19) Nasal Polyps

- ○ Never
- ○ Current
- ○ Past ☐ No data

Current Atopic Disease? (if indicated current for Eczema and/or Allergic Rhinitis)
(Auto-Populated)

Patient ID: _____ Date of Visit: _____ Centre ID: _____

BLOOD AND SPUTUM

Please record highest patient blood and sputum test details within the last year.

20) What is the highest blood eosinophil count within the last year?

☐☐☐.☐☐☐ (Unit: 10^9/L, µL) ☐ No data

-Date of highest blood eosinophil count within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

-Was the highest blood Eosinophil count during an exacerbation event within the last year?

(This Question will only populate if Q20 is indicated)

◯ No ◯ Yes ◯ No Data

+What is the Highest Blood Eosinophil count?
(within the last year AND NOT during exacerbation)

(This Question will only populate if Yes is indicated)

☐☐☐.☐☐☐ (Unit: 10^9/L, µL) ☐ No data

+Date of highest blood eosinophil count
(within the last year AND NOT during exacerbation) (DD/MM/YYYY or UNK/UNK/YYYY)

(This Question will only populate if Yes is indicated)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY)

☐ No data

21) What is the highest sputum eosinophil count within the last year?

☐☐.☐ % ☐ No data

-Date of highest sputum eosinophil count within the last year:
(DD/MM/YYYY or UNK/UNK/YYYY)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

BLOOD LOG

Please record all available patient blood test details within the last year

22) Blood eosinophil count

Please provide all available patient blood eosinophil test results within the last year

Number	Blood Eosinophil Counts	Unit of measurement (Please select)	Date of blood eosinophil count (DD/MM/YYYY or UNK/UNK/YYYY)
1.	☐ No data	10^9/L, Cells/µL	__ __/ __ __/ __ __ __ __ ☐ No data
2.	☐ No data	10^9/L, Cells/µL	__ __/ __ __/ __ __ __ __ ☐ No data
3.	☐ No data	10^9/L, Cells/µL	__ __/ __ __/ __ __ __ __ ☐ No data
4.	☐ No data	10^9/L, Cells/µL	__ __/ __ __/ __ __ __ __ ☐ No data
5.	☐ No data	10^9/L, Cells/µL	__ __/ __ __/ __ __ __ __ ☐ No data

23) IgE Count

Please provide all available patient blood IgE test results within the last year

Number	IgE Counts	Unit of measurement (Please select)	Date of blood IgE count (DD/MM/YYYY or UNK/UNK/YYYY)
1.	☐ No data	IU/mL, kU/L	__ __/ __ __/ __ __ __ __ ☐ No data
2.	☐ No data	IU/mL, kU/L	__ __/ __ __/ __ __ __ __ ☐ No data
3.	☐ No data	IU/mL, kU/L	__ __/ __ __/ __ __ __ __ ☐ No data
4.	☐ No data	IU/mL, kU/L	__ __/ __ __/ __ __ __ __ ☐ No data
5.	☐ No data	IU/mL, kU/L	__ __/ __ __/ __ __ __ __ ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

DIAGNOSTIC TESTS

Please record the patient's diagnostic test details collected at the baseline visit

24) Was chest CT Scan performed within the last year?

- ○ Normal
- ○ Abnormal
- ○ Not Done ☐ No data

-Date of chest CT Scan within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

25) Was bone densitometry test (DEXA) performed within the last year?

- ○ Normal
- ○ Abnormal
- ○ Not Done ☐ No data

-Date of bone densitometry test (DEXA) within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

LUNG FUNCTION

Please record all available patient spirometry test results within the last year

Number	26) Pre-bronchodilator FVC (L)	27) Pre-bronchodilator FEV1 (L)	28) Post-bronchodilator FVC (L)	29) Post-bronchodilator FEV1 (L)	Date of spirometry test (DD/MM/YYYY or UNK/UNK/YYYY)
1.	☐ No data	☐ No data	☐ No data	☐ No data	__/__/____ ☐ No data
2.	☐ No data	☐ No data	☐ No data	☐ No data	__/__/____ ☐ No data
3.	☐ No data	☐ No data	☐ No data	☐ No data	__/__/____ ☐ No data
4.	☐ No data	☐ No data	☐ No data	☐ No data	__/__/____ ☐ No data
5.	☐ No data	☐ No data	☐ No data	☐ No data	__/__/____ ☐ No data

Predicted FVC (L)
(Auto-Calculated)

Predicted FEV1 (L)
(Auto-Calculated)

Pre-bronchodilator FVC (percentage predicted) (%)
(Auto-Calculated)

Post-bronchodilator FVC (percentage predicted) (%)
(Auto-Calculated)

Pre-bronchodilator FEV1 (percentage predicted) (%)
(Auto-Calculated)

Post-bronchodilator FEV1 (percentage predicted) (%)
(Auto-Calculated)

FEV1/FVC ratio pre-bronchodilator
(Auto-Calculated)

FEV1/FVC ratio post-bronchodilator
(Auto-Calculated)

30) Was the PC20 Methacholine/Histamine challenge test performed within the last year?

○ No ○ Yes ○ No Data

-Date of PC20 challenge test within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

-PC20 challenge test result: ☐.☐☐ mg/mL ☐ No data

31) Was the fractional exhaled nitric oxide (FeNO) Test performed within the last year?

○ No ○ Yes ○ No Data

-Date of fractional exhaled nitric oxide (FeNO) Test within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

- Fractional exhaled Nitric Oxide Test result:

☐☐.☐ ppb at flow rate of 50mL/s ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

ALLERGEN TESTS

Please record patient allergen test details collected at the baseline visit.

32) Was an environmental allergen test performed within the last year?
(Please select all that apply)

- ○ Serum Allergen test (ImmunoCAP®, ELISA, RAST)
- ○ Skin Prick Test
- ○ Not Done ☐ No data

Serum Allergen Test (ImmunoCAP, ELISA, RAST)

-Date of serum allergen test performed within the last year:
☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

- Positive allergens to serum allergen test?

○ No ○ Yes ○ No Data

+Please specify Serum Allergen Test (ImmunoCAP®, ELISA, RAST) positive allergens
(Select all that apply)

☐ Dust Mite (D.Pteronyssinus)
Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Grass Mix
Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Cat Hair
Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Mould Mix
Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Dog Hair

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Aspergillus

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Other

Please Specify: _____ ☐ No data

Result: ☐☐☐.☐☐ kU/L ☐ No data

Skin Prick Test (SPT)

-Date of SPT performed within the last year:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

- Positive Skin Prick Test to allergens?

○ No ○ Yes ○ No Data

+Please specify SPT positive allergens

(Select all that apply)

☐ Grass Mix

Result: ☐☐.☐ mm ☐ No data

☐ Trees

Result: ☐☐.☐ mm ☐ No data

☐ Weed Mix

Result: ☐☐.☐ mm ☐ No data

☐ Aspergillus

Result: ☐☐.☐ mm ☐ No data

☐ Mould Mix

Result: ☐☐.☐ mm ☐ No data

☐ Food Mix

Result: ☐☐.☐ mm ☐ No data

☐ Dust Mite

Result: ☐☐.☐ mm ☐ No data

☐ Animal Mix

Result: ☐☐.☐ mm ☐ No data

☐ Cat hair

Result: ☐☐.☐ mm ☐ No data

☐ Dog hair

Result: ☐☐.☐ mm ☐ No data

☐ Other

Please Specify: _____ ☐ No data

Result: ☐☐.☐ mm ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

ASTHMA CONTROL

Please record the patient's GINA Asthma Control Assessment results collected at the baseline visit

In the past 4 weeks, has the patient had:

33) Daytime symptoms more than twice per week?

- ○ No
- ○ Yes ☐ No data

34) Nocturnal awakening/symptoms due to asthma?

- ○ No
- ○ Yes ☐ No data

35) Requirement for reliever medication use more than twice per week?

- ○ No
- ○ Yes ☐ No data

36) Experienced any activity limitation due to asthma?

- ○ No
- ○ Yes ☐ No data

37) Lung function (PEF[6] or FEV1) <80% of predicted or personal best (if known)?

- ○ No
- ○ Yes ☐ No data

[6] PEF: Peak Expiratory Flow

Patient ID: _____ Date of Visit: _____ Centre ID: _____

ASTHMA MEDICATION

Please record all patient asthma medication details collected within the last year:

Maintenance Oral Steroids

38) Has the patient been prescribed Maintenance Oral Steroids within the last year? ○ No ○ Yes ○ No Data

- If "Maintenance Oral Steroid" prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Number	(a) Medication Name	(b) Label Dose	(c) Frequency per day	(d) Start & End date
1	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
2	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
3	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data

38 (b) Please input the label dose[7] for Maintenance Oral Corticosteroids (OCS).

38 (c) Please indicate the number of tablets/units prescribed for consumption per day

38 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date can be any time prior to the baseline visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

[7] Label Dose: Per unit dose as indicated on the medication label.
Formula: ∑ (((No. of tablets OR prescription doses OR pack sizes) / baseline time-period) x mg strength

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Inhaled Corticosteroids (ICS)

39) Has the patient been prescribed ICS within the last year? ○ No ○ Yes ○ No Data

- If "Inhaled Corticosteroid" prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Prescription Number	(a) Medication Name	(b) Label Dose	(c) Frequency per day	(d) Start & End date
1	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __ / __ __ / __ __ __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __ / __ __ / __ __ __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
3	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __ / __ __ / __ __ __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data

39 (b) Please input the label indicated dose of the Inhaled Corticosteroid administered.
39 (c) Please indicate the number of puffs prescribed for inhalation per day.
39 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date can be any time prior to the baseline visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Long-Acting β-adrenoreceptor agonist (LABA)

40) Has the patient been prescribed LABA within the last year?

○ No ○ Yes ○ No Data

Number	Please select LABA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Formoterol, Salmeterol, Indacaterol, Arformoterol, Olodaterol, Other: Please Specify

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Inhaled Corticosteroid +Long-Acting β-adrenoreceptor agonist (ICS+LABA) Combination

41) Has the patient been prescribed ICS+LABA combination therapy within the last year?

- If ICS+LABA prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Number	(e) Medication Name	(f) Label Dose	(g) Frequency per day	(h) Start & End date
1	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
3	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data

41 (b) Please input the label indicated dose of the ICS+LABA administered.
41 (c) Please indicate the number of puffs prescribed for inhalation per day.
41 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date can be any time prior to the baseline visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Long-Acting Muscarinic Antagonist (LAMA)

42) Has the patient been prescribed LAMA within the last year?

○ No ○ Yes ○ No Data

Number	Please select LAMA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Aclidinium, Tiotropium, Umeclidinium, Glycopyrronium, Other: Please Specify

Theophyllines

43) Has the patient been prescribed Theophyllines within the last year?

○ No ○ Yes ○ No Data

Number	Please select Theophyllines Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Theophylline, Aminophylline, Other: Please Specify

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Leukotriene Receptor Antagonist (LTRA)

44) Has the patient been prescribed LTRA within the last year?

○ No ○ Yes ○ No Data

Number	Please select LTRA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
2.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
3.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
4.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
5.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data

Options list: Zafirlukast, Monteleukast, Other: Please Specify

Anti-Immunoglobin E Treatment (Anti-IgE)

45) Has the patient been prescribed Anti-IgE treatment within the last year?
(Prescription for Omalizumab)

○ No ○ Yes ○ No Data

Number	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
2.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
3.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
4.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
5.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Anti-Interleukin 5 Treatment (Anti-IL5)

46) Has the patient been prescribed Anti-IL5 treatment within the last year?

○ No ○ Yes ○ No Data

Number	Please select Anti-IL5 Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
2.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
3.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
4.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
5.	☐ No data	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data

Options list: Reslizumab, Mepolizumab, Benralizumab, Other: Please Specify

Anti-Interleukin 4 Treatment (Anti-IL4)

45) Has the patient been prescribed Anti-IL4 treatment within the last year?
(Prescription for Dupilumab)

○ No ○ Yes ○ No Data

Number	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
2.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
3.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
4.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data
5.	__ __/__ __/__ __ __ __ ☐ No data	☐ Ongoing __ __/__ __/__ __ __ __ ☐ No data

- *If biologics (anti-IgE/anti-IL5 therapy) is indicated as "Yes" during ISAR Baseline Core data collection*

AND

  - *If patient was switched from any previous therapy to a biologic during baseline (last 12 months)*

  OR

  - *If a biologic prescription was stopped during baseline (last 12 months)*

**Note: If the patient's biologic prescription is ongoing for more than 12 months, this question will not apply*

- Please specify the reason for switch in patient's asthma medication/treatment.

- ☐ Lack of clinical efficacy
- ☐ Side effects
- ☐ Biologic access restriction
- ☐ Patient preference
- ☐ No Data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

Macrolide Antibiotic Treatment

47) Has the patient been prescribed Macrolide Antibiotic within the last year?

○ No ○ Yes ○ No Data

Number	Please select Macrolide Antibiotic Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Fidaxomicin, Telithromycin, Other: Please Specify

Steroid Sparing Agents

48) Has the patient been prescribed steroid sparing agents within the last year?

Please specify the steroid sparing agent prescribed.

☐ No data

(Please input any steroid sparing medications prescribed)

Adherence Evaluation

49) Is there evidence of poor adherence?

(Please select from list)

No
Yes: Clinical Impression
Yes: Prescription Records

☐ No data

Patient ID: _____ Date of Visit: _____ Centre ID: _____

SYSTEMATIC MANAGEMENT AND CLINICAL ASSESSMENT PLAN

External Factors

50) Are there any other factors contributing to severe asthma symptoms?

☐ No data

(Please comment on any other possible factors contributing to severe asthma symptoms)

Current Clinical Management Plan

51) What is the current clinical management plan?
(Select all that apply)

Discharge to local asthma service	○ No ○ Yes
Optimization of current treatment	○ No ○ Yes
Biologic therapy	○ No ○ Yes
Bronchial Thermoplasty	○ No ○ Yes
Maintenance oral corticosteroids	○ No ○ Yes
Steroid sparing agent	○ No ○ Yes
Enter into clinical trial	○ No ○ Yes
Other	○ No ○ Yes

Please specify:

☐ No data

Form Completed By: _____

Date: _____

Signature: _____

REFERENCES

1) Global Initiative for Asthma: (GINA), G. I. (2017). Global Strategy for Asthma Management and Prevention. Available from: www.ginasthma.org.
2) Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., . . . Djukanov, R. (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal, 343-373.
3) Fuhlbrigge, A., Peden, D., Apter, A. J., Boushey, H. A., Camargo, C., Gern, J., Blaisdell, C. (2012). Asthma Outcomes: Exacerbations. *The Journal of Allergy and Clinical Immunology*, *129*(3 Suppl), S34–S48. http://doi.org/10.1016/j.jaci.2011.12.983
4) Helen K. Reddel, D. R.-P. (2009). An official American thoracic society/European respiratory society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Americal Journal of Respiratory and Critical Care Medicine, Volume 180, No. 1, 59-99.
5) G., C., D., M., A., M., J.M., F., & S., L. (2006). Bronchial Thermoplasty for Asthma. American Journal of Respiratory Critical Care Medicine (173), 965 - 969.

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

INTERNATIONAL SEVERE ASTHMA REGISTRY

Follow-Up Questionnaire

Data Collection Form

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

GENERAL GUIDE TO COMPLETE THE CRF

Completing the CRF

- Use a ballpoint pen to fill in the CRF, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the CRF are consistent with the source documents.
- Do not leave questions unanswered. If data is not available for a field, check the “No Data” box and move to the next question.
- Sign and date the CRF each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the CRF

- Each correction in the CRF must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Indicator	Field
–	**This secondary branch question is probed when the primary trunk question is filled**
+	**This tertiary branch question is probed when the primary trunk and secondary branch questions are filled**
Greyed Out Text	**This greyed out question is auto-calculated and does not require data input.**

Form Completed By: _____

Date: _____

Signature: _____

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

PATIENT DETAILS

Please record the patient's demographic data collected at the follow-up visit

1) Date of Visit

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY)

2) Height: ☐.☐☐ m ☐ No data

3) Weight: ☐☐☐.☐ kg ☐ No data

Patient Body Mass Index (BMI) kg/m^2
(Auto-Calculated)

Patient Body Surface Area (BSA) m^2
(Auto-Calculated)

4) Has the patient had Bronchial Thermoplasty[1] since the last visit?

○ No ○ Yes ○ No Data

5) What is the current occupation of the patient?

☐ No data

(Please input job description)

[1] Bronchial Thermoplasty (Alair™ System): FDA approved treatment(2010) for severe asthma where controlled therapeutic radiofrequency energy is supplied to the airway wall, inducing heat and damaging smooth muscle tissue present in the airway wall to alleviate smooth muscle constriction during an asthma attack (5)

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

MEDICAL HISTORY

Please record the patient's medical history collected at the follow-up visit

Smoking History

6) What is the current smoking status of the patient?

- ○ Never smoked
- ○ Ex-Smoker
- ○ Current Smoker ☐ No data

-Number of cigarettes smoked per day? *(if indicated for Ex-Smoker, Current Smoker)*

☐☐☐ cigarettes/day ☐ No data

-Number of smoking years? *(if indicated for Ex-Smoker, Current Smoker)*

☐☐.☐ smoking years ☐ No data

-Pack Years[2]? (if indicated for Ex-Smoker, Current Smoker)
(Auto-Calculated)

-Date when the patient quit smoking *(if indicated for Ex-Smoker)*
(Please input at least the year if the exact date is not available)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

[2] Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked

ISAR Follow-up Questionnaire

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Exacerbation Status

7) Total number of exacerbations requiring rescue steroids since the last visit?

(Severe asthma exacerbations are defined as events that require urgent action (rescue steroids) on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma)(3)(4)

☐☐☐ exacerbations ☐ No data

- For each exacerbation since the last visit, please specify the date of exacerbation, starting from the most recent:

Number	(a) Date of Exacerbation	(b) Rescue Steroid Used	(c) Label Dose	(d) Frequency per day	(e) Start & End date
1	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
2	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
3	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Number	(a) Date of Exacerbation	(b) Rescue Steroid Used	(c) Label Dose	(d) Frequency per day	(e) Start & End date
4	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
5	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
6	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data
7	__/__/____ ☐ No Data	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____	_____	__/__/____ ☐ No Data ☐ Ongoing __/__/____ ☐ No Data

7 (c) Please input the label indicated dose of the rescue steroid administered.
7 (d) Please indicate the frequency of rescue steroid administered per day.
7 (a) and (e) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Exacerbation and Start/Diagnosis date should be since the last visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

8) Total number of episodes of invasive ventilation since the last visit?

☐☐☐ episodes ☐ No data

9) Total number of A&E attendances (Emergency room visits) for asthma since the last visit?

☐☐☐ attendances ☐ No data

10) Total number of hospital admissions for asthma since the last visit?

☐☐☐ admissions ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

RELEVANT COMORBIDITIES

Please record the patient's comorbidity details collected at the follow-up visit.

Does the patient have an indication of the following:

11) Allergic Rhinitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

12) Chronic Rhinosinusitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

13) Atopic Dermatitis

- ○ Never
- ○ Current
- ○ Past ☐ No data

14) Nasal Polyps

- ○ Never
- ○ Current
- ○ Past ☐ No data

Current Atopic Disease? (if indicated current for Eczema and/or Allergic Rhinitis)
(Auto-Populated)

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

BLOOD AND SPUTUM

Please record highest patient blood and sputum test details since the last visit.

15) What is the highest blood eosinophil count since the last visit?

☐☐☐.☐☐☐ (Unit: 10^9/L, µL) ☐ No data

-Date of highest blood eosinophil count since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

-Was the highest blood Eosinophil count during an exacerbation event since the last visit?

(This Question will only populate if Q20 is indicated)

○ No ◉ Yes ○ No Data

+What is the Highest Blood Eosinophil count?
(since the last visit AND NOT during exacerbation)

(This Question will only populate if Yes is indicated)

☐☐☐.☐☐☐ (Unit: 10^9/L, µL) ☐ No data

+Date of highest blood eosinophil count
(since the last visit AND NOT during exacerbation)

(This Question will only populate if Yes is indicated)

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

16) What is the highest sputum eosinophil count since the last visit?

☐☐.☐ % ☐ No data

-Date of highest sputum eosinophil count since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

BLOOD LOG

Please record all available patient blood test details since the last visit

17) Blood eosinophil count

Please provide all available patient blood eosinophil test results since the last visit

Number	Blood Eosinophil Counts	Unit of measurement (Please select)	Date of blood eosinophil count (DD/MM/YYYY or UNK/UNK/YYYY)
1.		10^9/L, Cells/µL	__ __ / __ __ / __ __ __ __ ☐ No data
2.		10^9/L, Cells/µL	__ __ / __ __ / __ __ __ __ ☐ No data
3.		10^9/L, Cells/µL	__ __ / __ __ / __ __ __ __ ☐ No data
4.		10^9/L, Cells/µL	__ __ / __ __ / __ __ __ __ ☐ No data
5.		10^9/L, Cells/µL	__ __ / __ __ / __ __ __ __ ☐ No data

18) IgE Count

Please provide all available patient blood IgE test results since the last visit

Number	IgE Counts	Unit of measurement (Please select)	Date of blood IgE count (DD/MM/YYYY or UNK/UNK/YYYY)
1.		IU/mL, kU/L	__ __ / __ __ / __ __ __ __ ☐ No data
2.		IU/mL, kU/L	__ __ / __ __ / __ __ __ __ ☐ No data
3.		IU/mL, kU/L	__ __ / __ __ / __ __ __ __ ☐ No data
4.		IU/mL, kU/L	__ __ / __ __ / __ __ __ __ ☐ No data
5.		IU/mL, kU/L	__ __ / __ __ / __ __ __ __ ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

DIAGNOSTIC TESTS

Please record the patient's diagnostic test details collected at the follow-up visit

19) Was chest CT Scan performed since the last visit?

- ○ Normal
- ○ Abnormal
- ○ Not Done ☐ No data

-Date of chest CT Scan since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

20) Was bone densitometry test (DEXA) performed since the last visit?

- ○ No
- ○ Yes ☐ No data

-Date of bone densitometry test (DEXA) since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

LUNG FUNCTION

Please record all available patient spirometry test results since the last visit

Number	21) Pre-bronchodilator FVC (L)	22) Pre-bronchodilator FEV1 (L)	23) Post-bronchodilator FVC (L)	24) Post-bronchodilator FEV1 (L)	Date of spirometry test (DD/MM/YYYY or UNK/UNK/YYYY)
1.					__/__/____ ☐ No data
2.					__/__/____ ☐ No data
3.					__/__/____ ☐ No data
4.					__/__/____ ☐ No data
5.					__/__/____ ☐ No data

Predicted FVC (L)
(Auto-Calculated)

Predicted FEV1 (L)
(Auto-Calculated)

Pre-bronchodilator FVC (percentage predicted) (%)
(Auto-Calculated)

Post-bronchodilator FVC (percentage predicted) (%)
(Auto-Calculated)

Pre-bronchodilator FEV1 (percentage predicted) (%)
(Auto-Calculated)

Post-bronchodilator FEV1 (percentage predicted) (%)
(Auto-Calculated)

FEV1/FVC ratio pre-bronchodilator
(Auto-Calculated)

FEV1/FVC ratio post-bronchodilator
(Auto-Calculated)

25) Was the PC20 Methacholine/Histamine challenge test performed since the last visit?

○ No ○ Yes ○ No Data

-Date of PC20 Challenge Test since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

-PC20 Challenge Test result: ☐.☐☐ mg/mL ☐ No data

26) Was the Fractional exhaled Nitric Oxide Test performed since the last visit?

○ No ○ Yes ○ No Data

-Date of Fractional exhaled Nitric Oxide Test since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

- Fractional exhaled Nitric Oxide Test result:

☐☐.☐ ppb at flow rate of 50mL/s ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

ALLERGEN TESTS

Please record patient allergen test details collected at the follow-up visit.

27) Was an environmental allergen test performed since the last visit?
(Please select all that apply)

- ○ Serum Allery test (ImmunoCAP®, ELISA, RAST)
- ○ Skin Prick Test
- ○ Not Done ☐ No data

Serum Allergen Test (ImmunoCAP®, ELISA, RAST)

-Date of serum allergen test performed since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

-Positive allergens to serum allergen test?

○ No ○ Yes ○ No Data

+Please specify Serum Allergen Test (ImmunoCAP®, ELISA, RAST) positive allergens
(Select all that apply)

☐ Dust Mite (D.Pteronyssinus)

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Grass Mix

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Cat Hair

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Mould Mix

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Dog Hair

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Aspergillus

Result: ☐☐☐.☐☐ kU/L ☐ No data

☐ Other

Please Specify: _____ ☐ No data

Result: ☐☐☐.☐☐ kU/L ☐ No data

Skin Prick Test (SPT)

-Date of SPT performed since the last visit:

☐☐ ☐☐ ☐☐☐☐ (DD/MM/YYYY or UNK/UNK/YYYY) ☐ No data

- Positive Skin Prick Test to allergens?

◯ No ◯ Yes ◯ No Data

+Please specify SPT positive allergens

(Select all that apply)

☐ Grass Mix

Result: ☐☐.☐ mm ☐ No data

☐ Trees

Result: ☐☐.☐ mm ☐ No data

☐ Weed Mix

Result: ☐☐.☐ mm ☐ No data

☐ Aspergillus

Result: ☐☐.☐ mm ☐ No data

☐ Mould Mix

Result: ☐☐.☐ mm ☐ No data

☐ Food Mix

Result: ☐☐.☐ mm ☐ No data

☐ Dust Mite

Result: ☐☐.☐ mm ☐ No data

☐ Animal Mix

Result: ☐☐.☐ mm ☐ No data

☐ Cat hair

Result: ☐☐.☐ mm ☐ No data

☐ Dog hair

Result: ☐☐.☐ mm ☐ No data

☐ Other

Please Specify: _____ ☐ No data

Result: ☐☐.☐ mm ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

ASTHMA CONTROL

Please record the patient's GINA Asthma Control Assessment results collected at the follow-up visit.

In the past 4 weeks, has the patient had:

28) Daytime symptoms more than twice per week?

- ○ No
- ○ Yes ☐ No data

29) Nocturnal awakening/symptoms due to asthma?

- ○ No
- ○ Yes ☐ No data

30) Requirement for reliever medication use more than twice per week?

- ○ No
- ○ Yes ☐ No data

31) Experienced any activity limitation due to asthma?

- ○ No
- ○ Yes ☐ No data

32) Lung function (PEF[3] or FEV1) <80% of predicted or personal best (if known)?

- ○ No
- ○ Yes ☐ No data

[3] PEF: Peak Expiratory Flow

ISAR Follow-up Questionnaire

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

ASTHMA MEDICATION

Please record all patient asthma medication details collected since the last visit:

Maintenance Oral Steroids

33) Has the patient been prescribed Maintenance Oral Steroids since the last visit? ○ No ○ Yes ○ No Data

- If "Maintenance Oral Steroid" prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Number	(a) Medication Name	(b) Label Dose	(c) Frequency per day	(d) Start & End date
1	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
2	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
3	☐ Betamethasone ☐ Deflazacort ☐ Dexamethasone ☐ Hydrocortisone ☐ Prednisone ☐ Prednisolone ☐ Methylprednisolone ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____tablets	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data

33 (b) Please input the label indicated dose of the OCS.

33 (c) Please indicate the number of tablets prescribed for consumption per day.

33 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date should be since the last visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Inhaled Corticosteroids (ICS)

34) Has the patient been prescribed ICS since the last visit? ○ No ○ Yes ○ No Data

- If "Inhaled Corticosteroid" prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Prescription Number	(a) Medication Name	(b) Label Dose	(c) Frequency per day	(d) Start & End date
1	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
2	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data
3	☐ Ciclesonide ☐ Flunisonide ☐ Budesonide ☐ Beclomethasone ☐ Fluticasone Furoate ☐ Fluticasone Propionate ☐ Mometosone Furoate ☐ Triamcinolone acetonide ☐ Other: _____	_____mg	_____puffs	__ __/__ __/__ __ __ __ ☐ No Data ☐ Ongoing __ __/__ __/__ __ __ __ ☐ No Data

34 (b) Please input the label indicated dose of the inhaled corticosteroid administered.
34 (c) Please indicate the number of puffs prescribed for inhalation per day.
34 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date should be since the last visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Long-Acting β-adrenoreceptor agonist (LABA)

35) Has the patient been prescribed LABA since the last visit?

◯ No ◯ Yes ◯ No Data

Number	Please select LABA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__ __ / __ __ / __ __ __ __ ☐ No data	☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No data
2.	☐ No data	__ __ / __ __ / __ __ __ __ ☐ No data	☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No data
3.	☐ No data	__ __ / __ __ / __ __ __ __ ☐ No data	☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No data
4.	☐ No data	__ __ / __ __ / __ __ __ __ ☐ No data	☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No data
5.	☐ No data	__ __ / __ __ / __ __ __ __ ☐ No data	☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No data

Options list: Formoterol, Salmeterol, Indacaterol, Arformoterol, Olodaterol, Other: Please Specify

ISAR Follow-up Questionnaire

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Inhaled Corticosteroid +Long-Acting β-adrenoreceptor agonist (ICS+LABA) Combination

36) Has the patient been prescribed ICS+LABA combination therapy since the last visit? ○ No ○ Yes ○ No Data

- If ICS+LABA prescription is indicated as "Yes", please provide the following details for each prescription starting from the most recent.

Number	(e) Medication Name	(f) Label Dose	(g) Frequency per day	(h) Start & End date
1	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data
3	☐ Budesonide + Formoterol ☐ Fluticasone Furoate + Vilanterol ☐ Fluticasone propionate + Salmeterol ☐ Fluticasone propionate + Formoterol ☐ Mometasone + Formoterol ☐ Beclomethasone + Formoterol ☐ Other: _____	ICS: _____mg LABA:_____mg	_____puffs	__ __ / __ __ / __ __ ☐ No Data ☐ Ongoing __ __ / __ __ / __ __ __ __ ☐ No Data

36 (b) Please input the label indicated dose of the ICS+LABA administered.

36 (c) Please indicate the number of puffs prescribed for inhalation per day.

36 (d) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start/Diagnosis date should be since the last visit. If the prescription is active, please indicate as "Ongoing". End date to be specified if the prescription has ceased.

ISAR Follow-up Questionnaire

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Long-Acting Muscarinic Antagonist (LAMA)

37) Has the patient been prescribed LAMA since the last visit?

○ No ○ Yes ○ No Data

Number	Please select LAMA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Aclidinium, Tiotropium, Umeclidinium, Glycopyrronium, Other: Please Specify

Theophyllines

38) Has the patient been prescribed Theophyllines since the last visit?

○ No ○ Yes ○ No Data

Number	Please select Theophyllines Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Theophylline, Aminophylline, Other: Please Specify

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Leukotriene Receptor Antagonist (LTRA)

39) Has the patient been prescribed LTRA since the last visit?

◯ No ◯ Yes ◯ No Data

Number	Please select LTRA Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Zafirlukast, Monteleukast, Other: Please Specify

Anti-Immunoglobin E Treatment (Anti-IgE)

40) Has the patient been prescribed Anti-IgE treatment since the last visit?
(Prescription for Omalizumab)

◯ No ◯ Yes ◯ No Data

Number	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Anti-Interleukin 5 Treatment (Anti-IL5)

41) Has the patient been prescribed Anti-IL5 treatment since the last visit?

○ No ○ Yes ○ No Data

Number	Please select Anti-IL5 Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Reslizumab, Mepolizumab, Benralizumab, Other: Please Specify

Anti- Interleukin 4 Treatment (Anti-IL4)

42) Has the patient been prescribed Anti-IL4 treatment since the last visit?

(Prescription for Dupilumab)

○ No ○ Yes ○ No Data

Number	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

- *If biologics is indicated as "Yes" during ISAR Follow-up Core data collection*

AND

  - *If patient was switched from any previous therapy to a biologic since the last visit*

  OR

  - *If a biologic prescription was stopped since the last visit*

**Note: If the patient's biologic prescription is ongoing since the last visit, this question will not apply*

- Please specify the reason for switch in patient's asthma medication/treatment.

☐ Lack of clinical efficacy

☐ Side effects

☐ Biologic access restriction

☐ Patient preference

☐ No Data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

Macrolide Antibiotic Treatment

43) Has the patient been prescribed Macrolide Antibiotic since the last visit?

○ No ○ Yes ○ No Data

Number	Please select Macrolide Antibiotic Therapy (Refer to the options list below)	Start Date (DD/MM/YYYY or UNK/UNK/YYYY)	End Date (DD/MM/YYYY or UNK/UNK/YYYY) (If prescription is active, please check "Ongoing". Otherwise, please provide the End Date.)
1.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
2.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
3.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
4.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data
5.	☐ No data	__/__/____ ☐ No data	☐ Ongoing __/__/____ ☐ No data

Options list: Azithromycin, Clarithromycin, Erythromycin, Roxithromycin, Fidaxomicin, Telithromycin, Other: Please Specify

Steroid Sparing Agents

44) Has the patient been prescribed steroid sparing agents since the last visit?

Please specify the steroid sparing agent prescribed.

☐ No data

(Please input any steroid sparing medications prescribed)

Adherence Evaluation

45) Is there evidence of poor adherence?

(Please select from list)

No
Yes: Clinical Impression
Yes: Prescription Records

☐ No data

Patient ID: _____ Centre ID: _____

Date of Previous visit: _____ Date of current Follow-up visit: _____

SYSTEMATIC MANAGEMENT AND CLINICAL ASSESSMENT PLAN

External Factors

46) Are there any other factors contributing to severe asthma symptoms?

☐ No data

(Please comment on any other possible factors contributing to severe asthma symptoms)

Current Clinical Management Plan

46) What is the current clinical management plan? ☐ No data

(Select all that apply)

Discharge to local asthma service	○ No ○ Yes
Optimization of current treatment	○ No ○ Yes
Biologic therapy	○ No ○ Yes
Bronchial Thermoplasty	○ No ○ Yes
Maintenance oral corticosteroids	○ No ○ Yes
Steroid sparing agent	○ No ○ Yes
Enter into clinical trial	○ No ○ Yes
Other	○ No ○ Yes

Please specify:

Form Completed By: _____

Date: _____

Signature: _____

REFERENCES

1) Global Initiative for Asthma: (GINA), G. I. (2017). Global Strategy for Asthma Management and Prevention. Available from: www.ginasthma.org.
2) Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., . . . Djukanov, R. (2014). International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal, 343-373.
3) Fuhlbrigge, A., Peden, D., Apter, A. J., Boushey, H. A., Camargo, C., Gern, J., Blaisdell, C. (2012). Asthma Outcomes: Exacerbations. *The Journal of Allergy and Clinical Immunology*, *129*(3 Suppl), S34–S48. http://doi.org/10.1016/j.jaci.2011.12.983
4) Helen K. Reddel, D. R.-P. (2009). An official American thoracic society/European respiratory society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Americal Journal of Respiratory and Critical Care Medicine, Volume 180, No. 1, 59-99.
5) G., C., D., M., A., M., J.M., F., & S., L. (2006). Bronchial Thermoplasty for Asthma. American Journal of Respiratory Critical Care Medicine (173), 965 - 969.

INTERNATIONAL SEVERE ASTHMA REGISTRY

Baseline Questionnaire

Safety Variables

Data Collection Form

General Guide to Complete the Questionnaire

Completing the Questionnaire

- Use a ballpoint pen to fill in the questionnaire, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the questionnaire are consistent with the source documents.
- Do not leave questions unanswered. If data is not available for a field, check the “No Data” box and move to the next question.
- Sign and date the questionnaire each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the Questionnaire

- Each correction in the questionnaire must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Form Completed By: _____

Date: _____

Signature: _____

Serious Infection

1) Number of serious infections *within* the last 12 months? ☐ serious infections *(If none, indicate "NIL".)* ☐ No data

Serious Infection Definition: Infection requiring hospitalization, IV antibiotics, or resulting in a fatal outcome.

If one or more serious infections within the last 12 months, please provide the following details for each event starting from the most recent:

	(a) Type	(b) Site	(c) Outcome	(d)Start/Diagnosis Date	(e) End Date
1	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
2	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
3	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
4	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
5	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data

1(c): *If the serious infection is still active, please indicate as ongoing.*

1(d) and 1(e): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).*

1(d): *Start/Diagnosis date of serious infection should be WITHIN the 12- month period prior to the first visit.*

1(e): *End Date to be specified if the outcome of serious infection is resolved.*

Cancer

2) Has the patient ever been diagnosed with cancer[1]? Yes ☐ No ☐ No Data ☐

(Please input cancer events starting from the most recent)

	(a) Status at Diagnosis	(b) Diagnosis Confirmation	(c) Cancer location/site	(d) Cancer cell type	(e) TNM Stage	(f) Number Stage	(g) Outcome	(h) Start/ Diagnosis Date	(i) End Date
1	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
2	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
3	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data

[1] informed by medical record and/or reported by patient

4	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M:_____ ☐ No data	Stage: _____ ☐ No data	☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
5	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M:_____ ☐ No data	Stage: _____ ☐ No data	☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data

2(a): *Please clarify if this cancer is a recurrence (relapse or metastasis) of a previous cancer or a new onset cancer.*

2(b): *Cancer diagnosis confirmation (yes) can be given via reviewing medical records from test results of: Biopsy, Mammography, Colonoscopy, MRI, Bronchoscopy, PET-CT, etc. Please confirm if the cancer diagnosis is confirmed by medical records.*

2(c): *Cancer location/site examples: Multiple sites, Hematic, Stomach, Lungs, Breast, Bladder, Ovary, etc.*

2(d): *Cancer cell type examples: Carcinoma, Sarcoma, Leukemia, Lymphoma etc.*

2(e): *Staging at the time of diagnosis, TNM staging guide: T=Value from **0 to 4 or X** and **a or b or c**, N=Value from **0 to 3 or X** and **a or b or c**, M=Value of **0 or 1 or X***

2(f): *Staging at the time of diagnosis, Number staging guide: Value from **0 to 4** and **A or B or C***

2(g): *Please indicate the outcome of cancer at the time of the baseline visit. If the cancer is still active, please indicate as ongoing.*

2(h) & 2(i): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)*

2(h): *Start/Diagnosis date of new onset cancer should be any time prior to the first visit.*

2(i): End date to be specified if the outcome of cancer is remission.

Anaphylaxis

3) Number of anaphylactic episodes† *within* the last 12 months? ☐ anaphylactic episodes *(If none, indicate "NIL".)* ☐ No data

If one or more anaphylactic episodes within the last 12 months, please provide the following detail for each event:

	(a) Exposure suspected to cause the anaphylactic reaction	(b)Time to reaction	(c) Outcome	(d) Date of event
1	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ No data ☐ >2-4 hrs ☐ >24hrs	☐ Resolved ☐ No Data	Date: _____ ☐ No data
2	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ No data ☐ >2-4 hrs ☐ >24hrs	☐ Resolved ☐ No Data	Date: _____ ☐ No data
3	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ No data ☐ >2-4 hrs ☐ >24hrs	☐ Resolved ☐ No Data	Date: _____ ☐ No data
4	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ No data ☐ >2-4 hrs ☐ >24hrs	☐ Resolved ☐ No Data	Date: _____ ☐ No data
5	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ No data ☐ >2-4 hrs ☐ >24hrs	☐ Resolved ☐ No Data	Date: _____ ☐ No data

†Definition of an anaphylactic episode: Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND at least 1 of the following:

1)Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
2)Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

3(a): *Suspected exposure examples: Biologics (Mepolizumab, Omalizumab, Benralizumab, Reslizumab), Macrolide Antibiotics, Steroid sparing agents, etc.*
*Steroid Sparing Agent examples are: Methotrexate, Azathioprine, Cyclophosphamide, Mycophenolate Mofetil and Cyclosporine.

3(b): *Time to reaction is defined as the time period between the administration of medication and the onset of the anaphylactic reaction.*

3(d): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)*

3(d): *Date of anaphylaxis event should be <u>WITHIN the 12-month period prior to the first visit.</u>*

INTERNATIONAL SEVERE ASTHMA REGISTRY

Follow-up Questionnaire

Safety Variables

Data Collection Form

General Guide to Complete the Questionnaire

Completing the Questionnaire

- Use a ballpoint pen to fill in the questionnaire, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the questionnaire are consistent with the source documents.
- Do not leave questions unanswered. If data is not available for a field check the “No Data” box and move to the next question.
- Sign and date the questionnaire each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the Questionnaire

- Each correction in the questionnaire must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Form Completed By: _____

Date: _____

Signature: _____

Serious Infection

1) Number of serious infections *since* the last visit? ☐ serious infections *(If none, indicate "NIL".)* ☐ No data

Serious Infection Definition: Infection requiring hospitalization, IV antibiotics, or resulting in a fatal outcome.

If one or more serious infections since the last visit, please provide the following details for each event starting from the most recent:

	(a) Type	(b) Site	(c) Outcome	(d)Start/Diagnosis Date	(e) End Date
1	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
2	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
3	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
4	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
5	☐ Bacterial ☐ Parasitic ☐ Viral ☐ Other: _____ ☐ Fungal ☐ No Data	Site: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Resolved ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data

1(c): *If the severe infection is still active, please indicate as ongoing.*

1(d) and 1(e): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).*

1(d): *Start/Diagnosis date of severe infection should be WITHIN the time-period between the current visit and the previous visit.*

1(e): *End Date to be specified if the outcome of severe infection is death or resolved.*

Cancer

2) Does the patient have a previous[2] or new diagnosis[3] of cancer? ☐ Previous Diagnosis ☐ New Diagnosis ☐ No Cancer Diagnosis ☐ No Data

2.1) For an ongoing cancer diagnosis ("Previous Diagnosis") reported at a previous visit:

	(a) Diagnosis Confirmation	(b) Cancer location/site	(c) Cancer cell type	(d) TNM Stage	(e) Number Stage	(f) Outcome/Status	(g) End Date
1	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M:_____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data
2	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M:_____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data
3	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M:_____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data

[2] Ongoing cancer diagnosis reported during the previous visit
[3] New diagnosis of cancer informed by medical record and/or reported by patient

(a): *Cancer diagnosis confirmation can be shown by medical records from test results of: Biopsy, Mammography, Colonoscopy, MRI, Bronchoscopy, PET-CT, etc. Please confirm if the cancer diagnosis is confirmed by medical records.*

(b): *Cancer location/site examples: Multiple sites, Hematic, Stomach, Lungs, Breast, Bladder, Ovary, etc. (This should match report from the previous visit)*

(c): *Cancer cell type examples: Carcinoma, Sarcoma, Leukemia, Lymphoma etc. (This should match report from the previous visit)*

(d): *Staging at the most recent visit, TNM staging guide: T=Value from **0 to 4 or X** and **a or b or c**, N=Value from **0 to 3 or X** and **a or b or c**, M=Value of **0 or 1 or X***

(e): *Staging at the most recent visit, Number staging guide: Value from **0 to 4** and **A or B or C***

(f): *Please indicate the outcome of cancer at the most recent visit. If the cancer is still active, please indicate as ongoing.*

(g): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)*

(g): *End Date to be specified if the outcome of cancer is death or remission.*

Cancer

2.2. *For a diagnosis of a new onset cancer*[4] *("New Diagnosis") since the last visit:*

	(a) Status at Diagnosis	(b) Diagnosis Confirmation	(c) Cancer location/site	(d) Cancer cell type	(e) TNM Stage	(f) Number Stage	(g) Outcome	(h) Start/ Diagnosis Date	(i) End Date
1	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
2	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data
3	☐ Recurrent ☐ New Onset ☐ No data	☐ Yes ☐ No ☐ No data	Site: _____ ☐ No data	Type: _____ ☐ No data	T: _____ N: _____ M: _____ ☐ No data	Stage: _____ ☐ No data	☐ Death ☐ Ongoing ☐ Remission ☐ No Data	Date: _____ ☐ No data	Date: _____ ☐ No data

[4] New diagnosis of cancer informed by medical record and/or reported by patient

(a): *Please clarify if this cancer is a recurrence (relapse or metastasis) of a previous cancer or a new onset cancer.*

(b): *Cancer diagnosis confirmation (yes) can be given via reviewing medical records from tests such as: Biopsy, Mammography, Colonoscopy, MRI, Bronchoscopy, PET-CT, etc. Please confirm if the cancer diagnosis is confirmed by medical records.*

(c): *Cancer location/site examples: Multiple sites, Hematic, Stomach, Lungs, Breast, Bladder, Ovary, etc.*

(d): *Cancer cell type examples: Carcinoma, Sarcoma, Leukemia, Lymphoma etc.*

(e): *Staging at the time of diagnosis, TNM staging guide: T=Value from* ***0 to 4 or X*** *and* ***a or b or c****, N=Value from* ***0 to 3 or X*** *and* ***a or b or c****, M=Value of* ***0 or 1 or X***

(f): *Staging at the time of diagnosis, Number staging guide: Value from* ***0 to 4*** *and* ***A or B or C***

(g): *Please indicate the outcome of cancer at the most recent visit. If the cancer is still active, please indicate as ongoing.*

(h) and (i): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)*

(h): *Start/Diagnosis date of new onset cancer should be WITHIN the time-period between the current visit and the previous visit.*

(i): *End Date to be specified if the outcome of cancer is death or remission.*

Anaphylaxis

3) Number of anaphylactic episodes† *since* the last visit? ☐ anaphylactic episodes *(If none, indicate "NIL".)* ☐ No data

If one or more anaphylactic episodes since the last visit, please provide the following details for each event:

	(a) Exposure suspected to cause the anaphylactic reaction	(b)Time to reaction	(c) Outcome	(d) Date of event
1	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ >2-4 hrs ☐ >24hrs ☐ No data	☐ Death ☐ Resolved ☐ No Data	Date: _____ ☐ No data
2	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ >2-4 hrs ☐ >24hrs ☐ No data	☐ Death ☐ Resolved ☐ No Data	Date: _____ ☐ No data
3	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ >2-4 hrs ☐ >24hrs ☐ No data	☐ Death ☐ Resolved ☐ No Data	Date: _____ ☐ No data
4	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ >2-4 hrs ☐ >24hrs ☐ No data	☐ Death ☐ Resolved ☐ No Data	Date: _____ ☐ No data
5	Exposure: _____ ☐ No data	☐ 0-2 hrs ☐ >4-24hrs ☐ >2-4 hrs ☐ >24hrs ☐ No data	☐ Death ☐ Resolved ☐ No Data	Date: _____ ☐ No data

†Definition of an anaphylactic episode: acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND at least 1 of the following:

1)Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
2)Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)

3(a): *Suspected exposure examples: Biologics (Mepolizumab, Omalizumab, Benralizumab, Reslizumab), Macrolide Antibiotics, Steroid sparing agents, etc.*
*Steroid Sparing Agent examples are: Methotrexate, Azathioprine, Cyclophosphamide, Mycophenolate Mofetil and Cyclosporine.

3(b): *Time to reaction is defined as the time period between the administration of medication and the onset of the anaphylactic reaction.*

3(d): *Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)*

3(d): *Date of anaphylaxis event should be <u>WITHIN the time period between the current visit and the previous visit.</u>*

PAREXEL International

Mock Case Report Form

Sponsor Name: AstraZeneca

Protocol Number: D3250R00023

Protocol Title

THE CHRONICLE Study: A Longitudinal Prospective Observational Study of the Characteristics, Treatment Patterns and Health Outcomes of Individuals with Severe Asthma in the United States

Mock Case Report Form

PAREXEL Project Number: 234262

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

Chris Ambrose Date
Franchise Head, US Medical Affairs, Respiratory
AstraZeneca

PAREXEL SIGNATURE PAGE

This document has been approved and signed electronically on the final page by the following:

Author	Signatory
	Ramona Bosley Project Role: Data Management Lead

Reviewer	Signatory
	Mahendra Konda Project Role: Primary Clinical Database Programmer

Forms

Time and Event Structure:

Matrix: PRIMARY	Pre-Enrollment	Common	Baseline	6-Monthly *(every 6mth interval Visit)*	Discontinuation
Subject ID [SUBJID]	X				
Pre-Enrollment [PRENROL]	X				
Respiratory Comorbidities [AE_R]		X			
Non-Respiratory Comorbidities [AE_N]		X			
Relevant Medical Events & Procedures [AE_OTH]		X			
Diagnosed Malignancy Log [MALIG]		X			
Serious Infection Event Log [SI_LOG]		X			
Anaphylaxix Event Log [ANPHY_LOG]		X			
Asthma Treatments [CM_AC]		X			
Relevant Non-Asthma Treatments [CM_NA]		X			
Asthma Exacerbation Log [EXAC]		X			
Hospitalization Log [HOSP]		X			
Laboratory Assessment: CBCs with Differentials [CBCLB]		X			
Laboratory Assessment: BAL and Sputum Sample [LBBALSP]		X			
Eligiblity Crtieria [CRIT]			X		
Demography and Asthma History [DEMG]			X		
Social, Environmental, and Smoking Status (SOCSTATB)			X	X	
Vital Signs & Physical Exam [VSPE]			X	X	
Imaging and FENO [TEST]			X	X	

Matrix: PRIMARY	**Pre-Enrollment**	**Common**	**Baseline**	**6-Monthly *(every 6mth interval Visit)***	**Discontinuation**
Spirometry [SPIRO]			X	X	
Complete Pulmonary Function Test [CMPFT]			X	X	
Laboratory Testing [LABTST]			X	X	
Specific Events of Interest [SEI]			X	X	
Patient and Treatment Assessment [ASSMT]			X	X	
End of Study [DS]					X

SUBJECT ID (SUBJID)			
1	Enrollment code	SUBJECT	Char 8.

PRE-ENROLLMENT (PRENROL)			
1	Does the patient meet all study inclusion criterion (see protocol)?	CRITCOMP	(0) No (1) Yes * Radio button
2	Age in Years	AGE	Num. 3 Years (hard-coded)
3	Sex	SEX	C20197 Male C16576 Female * Radio Button
4	Primary Insurance Status	INSURA	1) Commercial: No PCP referral required for specialist (e.g. PPO) 2) Commercial: PCP referral required for specialist (e.g. HMO) 3) Medicaid 4) Medicare 5) Uninsured 6) Other Government Insurance (e.g. Tricare, VA, etc.) 7) Other *Drop Down List
4.5	If Other , specify	INSUROT	Free Text
5	Age in Years at Time of First Asthma diagnosis	AGEASTH	Num. 2 (Years)
6	Number of Asthma Exacerbations in the past 12 months	ASTEXAC	(1) None (2) 1 (3) 2 (4) 3 (5) 4 (6) 5 (7) 6 (8) 7 (9) 8 (10) 9 (11) 10+ *Drop Down list
7	Asthma Treatment Classification(s) (Check all that apply)	ASTHCLAS	☐ Uncontrolled on High-Dose ICS/LABA (Class01)

			☐ Monoclonal Antibody Agent (Class02) ☐ Systemic Corticosteroids or Immunosuppressant (Class03) *Check Box
8	For patients with Class01 only, did this patient meet the every 3rd patient selection scheme as detailed in section 3.7 of the protocol? *Note: For patients with Class02 or Class 03, select Does Not Apply.*	PTSELECT	(0) No (1) Yes (2) Not Applicable * Radio button
9	Was the patient approached for enrollment?	APPROYN	(0) No (1) Yes * Radio button
10	If Yes, date patient was approached for enrollment	APPRDAT	DD -MMM-YYYY Char 10
11	Is this patient consented and enrolling?	PTENROL	(0) No (1) Yes * Radio button
Note	*If Yes, proceed to Eligibility page*		
12	Reason for Not enrolling?	NOENROL	Free Text $80

RESPIRATORY COMORBIDITIES (AE_R)

Record diagnosed respiratory comorbidities ***present at the time of entry into the study or occurring during the study period.*** *Enter a stop date if the comorbidity resolves (no longer symptomatic) for any reason. If the severity of comorbidity changes during the study period, please enter a stop date for the prior entry and create a new record of the comorbidity at the new severity level.*
Note: will display list to assess sites with noting conditions of interest

1.2	Comorbidity Term	COTERM1	(1) Allergy to perennial aeroallergen, confirmed by testing (skin prick or specific IgE) (2) Allergy to seasonal aeroallergen, confirmed by testing (skin prick or specific IgE) (3) Chronic Bronchitis (4) Nasal / Sinus Polyps (5) Recurrent/chronic non-allergic Rhinosinusitis (6) Allergic Rhinitis (7) Allergic Conjunctivitis (8) Bronchiectasis (9) Interstitial lung disease (10) Sarcoidosis (11) Cystic Fibrosis (12) Obstructive Sleep Apnea (13) Pulmonary Tuberculosis (14) Vocal Cord Dysfunction (15) COPD (16) Alpha-1 Anti-Trypsin Deficiency (17) Eosinophilic Granulomatosis with Polyangiitis [EGPA] (Churg-Strauss syndrome) (18) Granulomatosis with Polyangiitis (formerly Wegener's Granulomatosis) (19) Airway Stenosis (20) Allergic Bronchopulmonary Aspergillosis (ABPA) (21) Chronic Eosinophilic Pneumonia (22) Atelectasis (23) Pulmonary Hypertension (24) Aspirin Sensitivity

			(25) Hyperventilation Syndrome (26) Other *Drop Down List
1.3	More specific diagnosis, if available	OTHSPC1	Free Text Field $200
1.4	Influencing asthma control?	ASTCTRL	(1) No (2) Yes *Drop down list
1.5	Severity	SEVER	(1) Mild (2) Moderate (3) Severe *Drop down list
1.7	Start Date	RESTDT	MMM-YYYY Char 10
1.8	Ongoing	ONGON1	Ongoing
1.9	Stop Date	REENDT	MMM-YYYY Char 10

NON-RESPIRATORY COMORBIDITIES (AE_NR)

*Record any diagnosed non-respiratory comorbidities **present at the time of entry into the study or occurring during the study period**. Enter a stop date if the comorbidity resolves (no longer symptomatic) for any reason. If the severity of a comorbidity changes during the study period, please enter a stop date for the prior entry and create a new record of the comorbidity at the new severity level.*

Note: will display list to assess sites with noting conditions of interest

1.2	Comorbidity Term	COTERM2	(1) Type I Diabetes (2) Type II Diabetes (3) Retinopathy related to Diabetes (4) Nephropathy related to Diabetes (5) Neuropathy related to Diabetes (6) Hypercholesterolemia (7) Thyroid disease (8) Osteopenia/Osteoporosis (9) Peripheral Vascular Disease (10) Coronary Artery Disease (11) Hypertension (12) Congestive Heart failure (13) Valvular Heart Disease (14) Cardiac Arrhythmia (15) Cerebrovascular disease (16) Chronic Kidney Disease (17) Osteoarthritis or unspecified arthritis (18) Rheumatoid Arthritis (19) Other Connective tissue/Autoimmune disease (20) Neuromuscular disease (21) Gastro-esophageal Reflux Disease (22) Inflammatory Bowel Disease (23) HIV/AIDS (24) Immunodeficiency (not AIDS) (25) Anxiety (26) Panic disorder (27) Depression (28) Alcohol Abuse (29) Drug abuse (30) Other Psychiatric Disorders (31) Contact Dermatitis

			(32) Atopic Dermatitis/Eczema (33) Chronic Urticaria (34) Angioedema (35) Hip or Spinal Fracture (36) Avascular Necrosis (37) Cataract (38) Glaucoma (39) Cushing Syndrome/Hypercortisolism (40) Adrenal Insufficiency (41) Peptic Ulcer Disease (42) Myopathy (43) Pseudotumor Cerebri (44) Insomnia or Sleep Disturbance (45) Other *Drop Down List
1.3	More specific diagnosis, if available	OTHSPC2	Free Text Field $200
1.4	Influencing asthma control?	ASTCTRL	(1) No (2) Yes *Drop down list
1.4	Start Date	NRSTDT	MMM-YYYY (Char 10)
1.5	Ongoing	ONGON2	Ongoing
1.6	Stop Date	NRENDT	MMM-YYYY (Char 10) Allow designation of ongoing

RELEVANT MEDICAL EVENTS & PROCEDURES (AE_OTH)

*Record Relevant Medical Events and Procedures experienced by the patient **at any point prior to study entry and during the study period**.*

Note: will display list to assess sites with noting conditions of interest

1.0	Event/Procedure	EVENT1	(1) Pneumonia (2) Pulmonary Embolism (3) Pulmonary Tuberculosis (4) Pneumothorax (5) Pleural effusion (6) Pulmonary Rehabilitation (7) Airway Clearance (Chest percussion) Therapy (8) Outpatient supplemental oxygen therapy (9) Allergy immunotherapy (any route) (10) Bariatric Surgery (11) Sleep Apnea Surgery (12) Surgery for GERD (e.g fundoplication) (13) Nasal Polypectomy (14) Sinus Surgery (15) Pulmonary Lobectomy (16) Bronchial Thermoplasty (17) Thoracentesis (18) Video-assisted Thoracoscopic lung biopsy (19) Bronchoscopy without transbronchial biopsy (20) Bronchoscopy with transbronchial biopsy (21) Airway stents (22) Spinal/vertebral fracture (23) Hip fracture (24) Hip Replacement (25) Stroke (26) Myocardial Infarction (27) Coronary Artery bypass, angioplasty, or cardiac stent placement (28) Menopause

			(29) Influenza vaccination for 2016-17 season and later (report each one) (30) Pneumococcal vaccination (ever) *Drop Down List
2.0	More specific description, if available	DESCRIP	Free text
3.0	Influenced asthma control?	ASTCTRL	0) No 1) Yes *Drop down list
4.0	Start Date	ORSTDT	MMM-YYYY Char 10
5.0	Ongoing	ONGON	Ongoing
6.0	Stop Date (can be same as start date)	ORENDT	MMM-YYYY Char 10 Allow designation of ongoing

DIAGNOSED MALIGNANCY LOG (MALIG)			
*Record all malignancies that were diagnosed **at any point prior to study entry as well as any diagnosed during the study enrollment.***			
1.0	Date of diagnosis	DIAGDT	(1) DD-MM-YYYY
2.0	Was/is this malignancy a recurrence of a previous malignancy (relapse or metastasis) or a new onset malignancy?	STATUS	(1) Recurrence (relapse or metastasis) (2) New onset (3) Unknown *Dropdown list
3.0	Location/Site	LOCTN	Free Text
4.0	Cell Type	TYPE	Free Text
5.0	TNM Staging at Diagnosis	TNMSTG	(1) Unknown
6.0	T (Primary Tumor)	TSCALE	1) X 2) 0 3) 1 4) 2 5) 3 6) 4 *Drop Down List
7.0	T (Primary Tumor Substage)	TDIAG	1) a 2) b 3) c 4) Unknown *Drop Down List
8.0	N (Lymph Nodes)	NSCALE	1) X 2) 0 3) 1 4) 2 5) 3 *Drop Down List
9.0	N (Lymph Nodes Substage)	NDIAG	1) a 2) b 3) c

			4) Unknown *Drop Down List
10.0	M (Distant Metastasis)	MSCAL	1) X 2) 0 3) 1 *Drop Down List
11.0	Number Staging at Diagnosis	STDT	1) Stage 0 2) Stage I 3) Stage II 4) Stage III 5) Stage IV 6) Unknown *Drop Down List
12.0	Stage Details	STGABC	1) A 2) B 3) C 4) Unknown *Drop Down List
13.0	Outcome	OUTCM	1) Ongoing 2) Remission 3) Death 4) Unknown Status (not death) *DropDown List

SERIOUS INFECTION EVENT LOG (SI_LOG)			
Record all serious infections that **occurred 12 months prior to Baseline as well as any that occur during study enrollment**.			
1.0	Why was the infection considered serious?	PATS14	1) Required hospitalization *2)* Required intravenous antibiotics/medication *3)* Fatal *Select all that apply*
2.0	Location/Site	LOCTN	Free Text
3.0	Specific pathogen(s) if known	PATHG	Free Text
4.0	Type of Infection	INFTYP	1) Bacterial 2) Viral 3) Fungal 4) Parasitic (helminth, protozoa, etc.) 5) Unknown 6) Other (with free text) *Drop Down List
5.0	Other, specify	OTHSPY	Free Text
6.0	Infection Start Date	STRTDT	DD-MMM-YYYY
7.0	Outcome	OUTCM	1) Resolved 2) Ongoing 3) Death 4) Unknown *DropDown List
8.0	Infection End Date	ENDDT	DD-MMM-YYYY

ANAPHYLAXIS EVENT LOG (ANPHY_LOG)

Record all anaphylaxis events* that **occurred 12 months prior to Baseline as well as any that occur during study enrollment**.

***Note:** Any acute onset of illness (minutes to several hours) involving skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips/tongue/uvula) AND at least 1 of the following:

1) Respiratory compromise *(e.g dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)*
2) Reduced BP or associated symptoms of end-organ dysfunction *(e.g. Hypotonia [collapse], syncope, incontinence)*

1.0	Exposure(s) suspected of causing anaphylaxis	SUSCAU	Free text
2.0	Time from exposure to reaction (hours)	LOCTN	1) 0 to 2 hrs 2) > 2 to 4 hrs 3) > 4 to 24 hrs 4) >24 hrs 5) Unknown *Dropdown
3.0	Reaction Start Date	STRTDT	DD-MMM-YYYY
4.0	Outcome	OUTCM	1) Resolved 2) Death 3) Unknown *DropDown List

ASTHMA TREATMENTS (CM_AC)

Record all acute or chronic medications taken for asthma ***in the 12 months prior to Baseline visit and any new medications or change to existing medications after Baseline visit.***
Note: Include any changes to Type of Medication, Frequency or Dose as a new entry.Each Medication category entry should be used to record the details of only one Medication. For entry of Mulitple medication categories, a new record/line should be added to record those details

T	Asthma Medication Category	Asthma Medication	
	Therapy Reason	Dose	Dose Unit
	Frequency	Route	Start Date
	End Date	Ongoing	
2.1	Medication Number	CMSPID	Num.3
2.2	Asthma Treatment Details (not required for Other Asthma-specific medication - for those, please record in Specific Medication for "Other" responses field	CMTRT	(1) Rescue Medication (Inhalers & Nebulized) (2) Inhaled Corticosteroids (ICS) (3) Combination Inhaled Products with ICS (ICS/LABA, ICS/LABA/LAMA) (4) Inhaled Long acting bronchodilators (LABA, LAMA, LABA/LAMA) (5) Leukotriene Antagonists & Cromolyns (6) Systemic Bronchodilators (7) Oral Corticosteriods (8) Injectable Corticosteriods (9) Macrolide Antibiotics (Chronic) (10) Biologics & Monoclonal Antibody Therapies (11) Other Systemic Immunomodulators (12) Other Asthma-specific Medication *Drop Down list
2.3 a	Rescue Medications (Inhalers & Nebulized)	MEDOSP1	(1) Albuterol (e.g. *ProAir, Proventil, Ventolin, AccuNeb*) (2) Levalbuterol (*Xopenex*)

			(3) Ipratropium bromide (*Atrovent*) (4) Ipratropium/albuterol (*Combivent, DuoNeb*) (5) Ephedrin/Guaifenesin (*Primatene, Bronkaid*) (6) Other
2.3 b	Inhaled Corticosteroids (ICS)	MEDOSP2	(1) Beclomethasone (*QVAR*) (2) Budesonide (*budesonide nebulized, Pulmicort Flexhaler/Respules*) (3) Ciclesonide (*Alvesco*) (4) Flunisolide (*Aerobid, Aerospan*) (5) Fluticasone furoate (*Arnuity Ellipta*) (6) Fluticasone propionate (*Flovent Diskus/HFA*) (7) Mometasone (*Asmanex*) (8) Other
2.3 c	Combination Inhaled Products with ICS (ICS/LABA, ICS/LABA/LAMA)	MEDOSP3	(1) Budesonide/formoterol (*Symbicort*) (2) Fluticasone furoate/Vilanterol (*Breo*) (3) Fluticasone propionate/Salmeterol (*Advair HFA/Diskus, AirDuo RespiClick*) (4) Mometasone/Formoterol (*Dulera*) (5) Fluticasone furoate/Umeclidium/Vilanterol *(Trelegy)* (6) *Other*
2.3 d	Inhaled Long acting bronchodilators (LABA, LAMA, LABA/LAMA)	MEDOSP4	(1) Aclidinium (*Tudorza Pressair*) (2) Arformoterol (*Brovana*)

			(3) Formoterol (*Foradil inhaler, Performomist nebulized*) (4) Glycopyrrolate/formoterol (*Bevespi Aerosphere*) (5) Glycopyrrolate (*Seebri Neohaler)* (6) Indacaterol (*Arcapta*) (7) Indacaterol/glycopyrrolate (*Utibron Neohaler*) (8) Olodaterol (*Striverdi Respimat*) (9) Salmeterol (*Serevent*) (10) Tiotropium (*Spiriva Respimat/Handihaler*) (11) Tiotropium/olodaterol (*Stiolto Respimat*) (12) Umeclidinium (*Incruse Ellipta*) (13) Umeclidium/Vilanterol (*Anoro*) (14) Other
2.3 e	Leukotriene Antagonists & Cromolyns	MEDOSP5	(2) Montelukast (*Singulair*) (3) Zafirlukast (*Accolate*) (4) Zileuton (*Zyflo*) (5) Cromolyn (*Intal*) (6) Other
2.3 f	Systemic Bronchodilators	MEDOSP6	(4) Theophylline (e.g. Theo-24, Uniphyl, Elixophyllin, Theodur) (5) Aminophylline (6) Roflumilast (7) Oral Albuterol (*VoSpire ER*) (8) Metaproterenol (9) Terbutaline (10) Magnesium

			(11) Other
2.3 g	Oral Corticosteriods	MEDOSP7	(1) Prednisone (2) Prednisolone (3) Dexamethasone (4) Methylprednisolone (5) Hydrocortisone (6) Other
2.3 h	Injectable Corticosteriods	MEDOSP8	(1) Dexamethasone (2) Methylprednisolone (3) Hydrocortisone (4) Triamcinolone (5) Other
2.3 i	Macrolide Antibiotics (Chronic)	MEDOSP9	(2) Azithromycin (*Zithromax*) (3) Clarithromycin (*Biaxin*) (4) Erythromycin (*Erythrocin, Ery-Tab*) (5) Other
2.3 j	Biologics & Monoclonal Antibody Therapies	MEDOSP10	(1) Benralizumab (*Fasenra)* (2) Mepolizumab (*Nucala*) (3) Omalizumab (*Xolair*) (4) Reslizumab (*Cinqair*) (5) Dupilumab (*Dupixent)* (6) *Other*
2.3 k	Other Systemic Immunomodulators	MEDOSP11	(1) Methotrexate (2) Cyclophosphamide (3) Cyclosporine (4) Azathioprine (5) Mycophenylate (6) Gold Salts (7) Intravenous gammaglobulin (IVIG) (8) Other

2.3 l	Other Asthma-specific Medication, Including Any Alternative, Complementary, or Integrative Therapies for Asthma (Use only if medication is not on one of the preceding lists)	MEDOSP12	Free text field $200
To be updated once programmers update the Log			
2.3	Asthma Medication	MEDOSP	Reference Appendix I. Note: Associating Asthma medication/therapy Dropdown List
2.4	Specific medication for "Other" responses	OTHSPY	Free text
	Dictionary Coding fields to be included in eCRF		
2.5	Therapy Reason	CMTREAS	Asthma [Default]
2.6	Dose	CMDSTXT	6.1 (Numeric)
2.7	Dose Unit	CMDOSU	C48155 = g C28253 = mg C48152 = ug C67402 = ug/m2 C48579 = IU C70492 = kIU C48542 = Tablet C48480 = Capsule C65060 = Puff C69442 = gtt 97 = Unknown 99 = Other *Drop Down List
2.8	Unit Other, Specify	UNITOTH	Free Text
2.9	Frequency	CMDOSFRQ	C25473 = Daily C64496 = Twice per day C64527 = 3 times per day C64530 = 4 times per day C64525 = Every other day XXXX = 3 times per week C67069 = Every Week XXXX = Every 2 weeks C64535 = Every 3 Weeks C64529 = Every 4 Weeks/Monthly XXXX = Every 8 weeks

			C64499 = As needed C17998 = Unknown 99 = Other *Drop Down List
2.10	Frequency Other, Specify	FRQOTH	Free Text
new	Route	ROUTE	C42946 = Injection C38216 = Respiratory (Inhalation) C38288 = Oral 99 = Other
new	Route Other,Specify	ROUTEOT	Free Text
2.11	Start Date	CMSTDAT	DD-MMM-YYYY Char 10 (Allow incomplete date)
2.12	Ongoing	CMONGO	☐ Checkbox
2.13	End Date	CMENDAT	DD-MMM-YYYY Char 10 (Allow incomplete date)

RELEVANT NON-ASTHMA TREATMENTS (CM_NA)

Do not record medications taken for Asthma; instead those must be recorded on the Asthma treatments form.

*Record any medications in the categories below taken for conditions other than asthma **in the 12 months prior to Baseline visit or during study enrollment.***

L	• NSAIDs or aspirin • Beta blockers • Antihistamine medication • Acid reducers (proton pump inhibitors or H2 antagonists) • Hormone replacement therapy (e.g. estrogen) • Intranasal corticosteroids	• Systemic corticosteroids • Biologics (monoclonal antibody therapy) • Other systemic anti-inflammatory medication • Chemotherapy • Other systemic immunosuppressive medication • Other immunomodulatory medication

T	Medication or Therapy	Therapy Reason		
	Pre-Enrollment	Start Date	Ongoing	Stop Date

1.0	Medication category	MEDCAT	1) NSAIDs or aspirin 2) Beta blockers 3) Antihistamine medication 4) Acid reducers (proton pump inhibitors or H2 antagonists) 5) Hormone replacement therapy (e.g. estrogen) 6) Intranasal corticosteroids 7) Systemic corticosteroids 8) Biologics (monoclonal antibody therapy) 9) Other systemic anti-inflammatory medication 10) Chemotherapy 11) Other systemic immunosuppressive medication 12) Other immunomodulatory medication *Drop Down List
2.0	Medication or Therapy	CMTRT	Free Text Field

			$200
	Dictionary Coding fields to be included in eCRF		
3.0	Start Date	CMSTDT	DD -MMM-YYYY
4.0	Ongoing	CMONGO	☐ Checkbox
5.0	Stop Date	CMENDT	DD -MMM-YYYY
6.0	Therapy Reason	CMREAS	Free Text Field
7.0	Route		C38288 = Oral C38291 = Parenteral C38276 = Intravenous C38299 = Subcutaneous C28161 = Intramuscular C38223 = Intra-articular C38222 = Intra-arterial C38675 = Cutaneous C38216 = Respiratory (Inhalation) C38295 = Rectal C38284 = Nasal C38287 = Ophthalmic C38197 = Dental C38209 = Enteral C38300 = Sublingual C38271 = Urethral C38313 = Vaginal C38192 = Auricular (OTIC) C38267 = Intrathecal C38258 = Intraperitoneal C64906 = Oromucosal C38304 = Topical C38210 = Epidural C38193 = Buccal C38229 = Intracaudal C38263 = Intraspinal C38305 = Transdermal C38207 = Intrathoracic C38238 = Intradermal 99 = Other C38311 = Unknown C48623 = Not Applicable
8.0	Route, other specify		Free text

ASTHMA EXACERBATION LOG (EXAC)

Record all asthma exacerbations that occurred ***during the 12 months prior to Baseline or that occur during study enrollment.***

1.0	Start date of exacerbation	STRDT	DD -MMM-YYYY
1.1	End date of exacerbation	ENDDT	DD -MMM-YYYY
2.0	# days of oral corticosteroids burst (or days of extra if receiving chronic systemic corticosteroids?)	DAYCS	NUM 2 Note: Enter zero if no oral corticosteroids were taken
3.0	# corticosteroid injections	NUINJ	NUM 2 Note: Enter zero if no corticosteroid injections were taken
4.0	Antibiotic course	ANBIOYN	(0) No (1) Yes (2) Unknown * Radio Button
5.0	Unscheduled Health Care Provider (HCP) visit	ANEYN	(0) No (1) Yes (2) Unknown * Radio Button
6.0	Emergency Department (ED) visit	UNSNONYN	(0) No (1) Yes (2) Unknown * Radio Button
7.0	Suspected exacerbation trigger (select primary):	EXACTRIG	(1) Allergen (2) Tobacco smoke (3) Other airborne irritant (4) Cold air (5) Exercise (6) Gastroesophageal reflux (7) Medication (8) Viral respiratory infection, no lab confirmation (9) Laboratory-confirmed influenza

			(10) Other lab-confirmed viral illness (not influenza) (11) Bacterial respiratory infection (12) Respiratory infection of unknown etiology (13) Unknown (14) Other
8.0	Other, Specify	TRIGOTH	Free Text

HOSPITALIZATIONS LOG (HOSP)

1. *For asthma hospitalizations, record all hospitalizations that have ever occurred or occur during study enrollment.*
2. *For all other hospitalizations (non-asthma), record all hospitalizations during the 12 months prior to Baseline or that occur during study enrollment.*

2.0	Admission Date	ADMDAT	DD -MMM-YYYY
3.0	Discharge Date	DISCDAT	DD -MMM-YYYY
4.0	Related to asthma exacerbation (primary or secondary cause)?	ASTHYN	(0) No (1) Yes * Radio Button
5.0	Days in Intensive Care?	INTSCAR	NUM 2 Note: Enter "0" if none.
6.0	Required invasive mechanical ventilation (i.e. intubation)?	VENTIL	(0) No (1) Yes * Radio Button
7.0	Required non-invasive mechanical ventilation?	NONVENT	(0) No (1) Yes * Radio Button
8.0	Primary Diagnosis ICD10 code	DIAGPR	Free text field $200
9.0	Secondary Diagnoses ICD10 codes	DIAGSD	10 free text fields. Note: *No responses required as the number of secondary diagnoses varies*

LABORATORY ASSESSMENT: CBC WITH DIFFERENTIAL (LBCBC)			
Please enter all complete blood count (CBC) results conducted during the 12 months prior to Baseline or that occur during study enrollment.			
T	Assessment Date	Red blood cell count	White blood cell count
	Platelet count	Hematocrit (%)	Neutrophil (%)
	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)
	Basophil (%)		
1	Assessment Date	CBCDT	DD-MMM-YYYY Char 10
2	Red blood cell count (K/mcL)	RBCRSLT	NUM 5.2
3	White blood cell count (M/mcL)	WBCRSLT	NUM 5.2
4	Platelet count (K/mcL)	PLTRSLT	NUM 5.2
5	Hematocrit (%)	HEMRSLT	NUM 5.2
6	Neutrophil (%)	NEURSLT	NUM 5.2
7	Lymphocyte (%)	LYMRSLT	NUM 5.2
8	Monocyte (%)	MONRSLT	NUM 5.2
9	Eosinophil (%)	EOSIRSLT	NUM 5.2
10	Basophil (%)	BASORSLT	NUM 5.2
11	Calculated Absolute Eosinophil Count (K/mcL)	EOSIABS	NUM 5.2

LABORATORY ASSESSMENT: BAL AND SPUTUM (LBBALSP)

Please enter all Bronchoalveolar lavage (BAL) and Sputum sample testing completed for this patient.

T	Type of Assessment	Fungal Culture Result	Bacterial Culture Result	AFB Culture Result	Cytology Results
	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)
	Mast Cell (%)	RBC (%)	Epithelial Cell (%)		
2	Assessment date	ASSESDT		DD-MMM-YYYY Char 10	
3	Type of Assessment	ASSESTYP		1) BAL 2) Sputum Sample * Drop Down List	
4	Fungal Culture Result	FUNGRSLT		1) Negative 2) Positive * Drop Down List	
5	Fungal Result Details	FUNGDTL		Free Text	
6	Bacterial Culture Result	BACRSLT		1) Negative 2) Positive * Drop Down List	
7	Bacterial Result Details	BACDTL		Free Text	
8	AFB culture Result	AFBRSLT		1) Negative 2) Positive * Drop Down List	
9	AFB Result Details	AFBDTL		Free Text	
10	Cytology Results	CYTORSLT		1) Normal 2) Abnormal * Drop Down List	
11	Cytology Result Details	CYTODTL		Free Text	
8	Neutrophils (%)	NEURSLT		NUM 3.2	
9	Lymphocytes (%)	LYMRSLT		NUM 3.2	
10	Monocytes (%)	MONRSLT		NUM 3.2	
11	Eosinophils (%)	EOSIRSLT		NUM 3.2	
12	Macrophages (%)	MACOPRSLT		NUM 3.2	
13	Basophils (%)	BASORSLT		NUM 3.2	
14	Mast Cell (%)	MASTRSLT		NUM 3.2	
15	Red Blood Cell (%)	RBCRSLT		NUM 3.2	
16	Epithelial Cell (%)	EPITRSLT		NUM 3.2	

ELIGIBILITY CRITERIA (CRIT)			
T	**Informed Consent**		
0.0	Date Informed Consent Signed	MCONSDAT	DD -MMM-YYYY Char 10
T	**Inclusion Criteria** ***(Edit check: Must have Yes to each major criterion – see protocol)***		
1.0	INC01 part 1: Diagnosis of severe asthma for at least 12 months prior to enrollment	INC01	(0) No (1) Yes * Radio button
2.0	INC01 part 2: Asthma symptoms confirmed by the specialist not to be due to alternative diagnoses	INC01a	(0) No (1) Yes * Radio button
3.0	INC02: Currently receiving care from specialist physicians at the study site	INC02	(0) No (1) Yes – Allergist (2) Yes – Pulmonologist (3) Yes – Allergist and Pulmonologist * Radio button
4.0	INC04a: Uncontrolled on asthma treatment consistent with GINA Step 4 or 5 receiving high-dose ICS with additional controllers	INC04a	(0) No (1) Yes * Radio button
4.0.1	- i1: Poor symptom control: Asthma Control Questionnaire consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)	INC4i1	(0) No (1) Yes (2) Unknown * Radio button
4.0.2	- i2: Frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous 12 months.	INC4i2	(0) No (1) Yes * Radio button

4.0.3	- i3: Serious exacerbations: at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous 12 months.	INC4i3	(0) No (1) Yes * Radio button
4.0.4	- i4: Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal).	INC4i4	(0) No (1) Yes (2) Unknown * Radio button
4.0.5	- ii1: Prescribed ICS at a cumulative dose of >500 µg fluticasone propionate equivalents daily (see protocol appendix for conversion chart)	INC4ii1	(0) No (1) Yes * Radio button
4.0.6	- ii2: Prescribed highest labeled dose of a combination of ICS/LABA	INC4ii2	(0) No (1) Yes * Radio button
5.0	INC04b: Current use of a FDA-approved monoclonal antibody agent for treatment of severe asthma	INC04b	(0) No (1) Yes * Radio button
6.0	INC04c: 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	INC04b	(0) No (1) Yes * Radio button
T	**Exclusion Criteria** ***(Edit check: Must have Yes, Yes, Yes – see protocol)***		
7.0	EXC02: Fluent in English or Spanish	EXC02	(0) No (1) Yes * Radio button

8.0	EXC03: Able to complete study follow-up and web-based PROs	EXC03	(0) No (1) Yes * Radio button
9.0	EXC04: Did not receive an investigational therapy for asthma, allergy, atopic disease, or eosinophilic disease as part of a clinical trial during the 6 months prior to enrollment.	EXC04	(0) No (1) Yes * Radio button

DEMOGRAPHY and ASTHMA HISTORY (DEMG)				
L	**Demography**			
1	Birth Date	BRTHDAT	DD -MMM-YYYY (Char 10)	
2	Age (auto calculated)	AGE	Num. 3 Years (hard-coded)	
4	Ethnicity	ETHNIC	C17459 Hispanic or Latino C41222 Not Hispanic or Latino * Radio Button	
5	Race	RACE	(1) White (2) Black (3) Asian (4) American Indian or Alaska Native	(5) Native Hawaiian or Other Pacific Islander (6) Not Reported (7) Other * Radio Button
6	If Other, specify	RACEOTH	Free text $200	
L	**Asthma & Treatment History**			
1	Does the patient have a first-degree relative with asthma?	RELATIV	(1) No (2) Yes (3) Unknown *Radio Button	
2	Year of first visit with any asthma specialist (allergist or pulmonologist)	INTASDT	YYYY ☐ Unknown	
3	Date of first visit with current Specialist	CURASDT	MMM-YYYY* (*Note: Allow Month and Year only entry)	
4	Best estimated date of first prescribed treatment with High-Dose Inhaled Corticosteriod (ICS) with additional controller medications. High-dose ICS is defined as a cumulative dose of >500 μg fluticasone propionate	ICSDT	MMM-YYYY* (*Note: Allow Month and Year only entry)	

	equivalents daily as defined in Appendix A of the protocol or The highest labelled dose of a combination of ICS/LABA.		
5	Has the patient ever received the following systemic therapies for severe asthma (select all that apply)	ADDCTLR	☐ Monoclonal Antibody Therapy ☐ Chronic systemic corticosteroid (regular use daily or every other day, not for acute exacerbation treatment) ☐ Other systemic immunosuppressant (e.g. cyclosporine, cyclophosphamide, azathioprine, mycophenylate, etc.) *Check Box
Edit Check Note	*If Chronic systemic selected. should answer Q6-7 (and 8 if discontinued)* *If Other systemic selected. Trigger Q9-11 (and 12 if discontinued)* *If Monoclonal selected. Trigger Q13-15 (and 16 if discontinued)*		
6	Best estimated date of first use of chronic systemic corticosteroid therapy for severe asthma (regular use on a daily or every other day basis; not acute use for exacerbation treatment)	CSCDT	MMM-YYYY* (*Note: Allow Year only entry)
7	Is chronic systemic corticosteroid therapy ongoing or discontinued?	CSYSTM	☐ Ongoing ☐ Discontinued (provide date of discontinuation)
8	If discontinued, chronic systemic corticosteroid discontinuation date	CSDISDT	MMM-YYYY* (*Note: Allow Year only entry)
9	Best estimated date of first use of other systemic immunosuppressant for severe asthma	SIMDT	MMM-YYYY* (*Note: Allow Year only entry)

10	Please select name of first other systemic immunosuppressant	OTHIMMU	(0) Methotrexate (1) Cyclophosphamide (2) Cyclosporine (3) Azathioprine (4) Mycophenylate (5) Gold Salts (6) Intravenous gammaglobulin (IVIG) (7) Other Drop down list
10.5	If Other , specify	OTHIMOT	Free Text
11	Is other systemic immunosuppressant therapy ongoing or discontinued?	IMMUTH	☐ Ongoing ☐ Discontinued (provide date of discontinuation)
12	If discontinued, other systemic immunosuppressant discontinuation date	MDISDT	MMM-YYYY* (*Note: Allow Year only entry)
13	Best estimated date of first use of monoclonal antibody therapy for severe asthma	MONDT	MMM-YYYY* (*Note: Allow Year only entry)
14	Please enter name of first monoclonal antibody therapy	MTHERP	(0) Benralizumab (Fasenra) (1) Mepolizumab (Nucala) (2) Omalizumab (Xolair) (3) Reslizumab (Cinqair) (4) Dupilumab (Dupixent) (5) Other Drop down list
14.5	If Other , specify	MTHEROT	Free Text
15	Is first monoclonal antibody therapy ongoing or discontinued?	TPYSTAT	☐ Ongoing ☐ Discontinued (provide date of discontinuation)
16	If discontinued, monoclonal antibody discontinuation date	MDISDT1	MMM-YYYY* (*Note: Allow Year only entry)

SOCIAL, ENVIRONMENTAL, AND SMOKING STATUS (SOCSTATB)

Programming note: Same page to be used at baseline and every 6 months. Post-baseline, original results will be displayed so sites can confirm or update.

1	Current Marital Status	MARITST	(1) Married (Living as married) (2) Married (Separated) (3) Not Married, Living with partner (4) Single, Never Married (5) Single, Divorced/ Separated (6) Single, Widowed *Drop Down List
2	Education level	SOCEDUY	(1) Never attended or only attended Kindergarten (2) Elementary/middle school (grade 1-8) (3) Some high school (grade 9-11) (4) Graduated high school (grade 12 or GED) (5) College (including 1-3 year college or technical school) (6) Graduate school(e.g., Masters, Doctorate, or professional degree) *Drop Down List
3	Employment Status (select best option)	EMPLOYN	(1) Employed full-time (2) Employed part-time (3) Self-employed (4) Homemaker (5) Full-time Student (6) Retired (7) Disabled due to asthma (8) Disabled due to non-asthma condition (9) Unemployed (not retired or disabled or homemaker) * Drop Down List
4	Occupation (current or predominant previous	OCCUP	(1) Management, Business, and Financial Occupations

	occupation if not currently working)		(2) Computer, Engineering, and Science Occupations (3) Education, Legal, Community Service, Arts, and Media Occupations (4) Healthcare Practitioners and Technical Occupations (5) Service Occupations (6) Sales and Related Occupations (7) Office and Administrative Support Occupations (8) Farming, Fishing, and Forestry Occupations (9) Construction and Extraction Occupations (10) Installation, Maintenance, and Repair Occupations (11) Production Occupations (12) Transportation and Material Moving Occupations (13) Military Specific Occupations (14) Other *Drop Down List
	If Other, specify	OCCUPOT	Free text$200
5	Estimated Annual Household Income	INCOME	(1) 0-20,000 (2) 20,000-40,000 (3) 40,000-65,000 (4) 65,000-100,000 (5) 100,000-200,000 (6) >200,000 (7) Prefer not to Answer *Drop Down List
6	Number of adults living in the household	ADULT	Num 2
7	Number of children living in the household	CHILD	Num 2
8	Residential Area	RESIDAR	1) Urban 2) Rural 3) Suburban *Drop Down List
9	Zip Code	ZIPCOD	5 Numeric digits

10	Type of Residence	RESIDTYP	(0) Single family detached house (1) Single family attached house (townhouse, row house) (2) Multiple family detached house (3) Apartment or condominium (4) Mobile home (5) Other *Drop Down List
	If Other, specify	RESIDOT	Free text $200
11	Does the patient live within 150 meters (500 feet) of a major road (e.g. highway)?	LIVE150M	(0) No (1) Yes (2) Unknown * Radio Button
Text	Are any of the following used as a primary source for heating and/or cooking in the patient's household?: (Select maximum of two items, if applicable)		
12	Gas	HEAT	(0) Gas
12.1	Coal	HEATCL	(1) Coal
12.2	Wood	HEATWD	(2) Wood
12.3	None of above	NONE	(3) None of above
13	How often is there visible air pollution or a poor air quality index in the area where the patient currently lives? Please provide your best estimate.	AIRPOL	(0) Never (1) Less than 25% of days (2) 25% to 50% of days (3) 51% to 75% of days (4) More than 75% of days * Radio Button
14	Is the patient regularly exposed to any allergens (Cat, Dog, House dust mite, Mold, Cockroach, Rodent, or Other) to which they have a diagnosed, clinically-relevant allergy and which are known to exacerbate their asthma symptoms?	EXPALLE	(0) No (1) Yes (2) Unknown * Radio Button

15	Is the patient exposed to significant second-hand smoke in the home or workplace?	FSMOKR	(0) No (1) Yes * Radio Button
16	Is the patient regularly exposed to dust or fumes in a job or other setting (e.g. hobby)?	JOBDUFU	(0) No (1) Yes (2) Unknown * Radio Button
17	Does the patient routinely use smokeless tobacco (e.g. chewing tobacco or snuff)?	SMOKLES	(0) No (1) Yes * Radio Button
L	Smoking Assessments		
18	Current or Former Smoker (including vaping or marijuana) and/or Tobacco User?	SMSTAT	(0) Never (1) Former (2) Current *Dropdown List
18.5	If former smoker, provide year the patient last smoked	FORMER	YYYY (4 digits)
19	Type of Smoke or Tobacco exposure (Check all that apply)	SUTRT	☐ Cigarettes ☐ Cigarillos ☐ Cigars ☐ Pipe Tobacco ☐ Other tobacco for smoking ☐ Nicotine Inhalator ☐ e-Cigarette ☐ Marijuana smoking Other *Check Box
Complete the following questions for each smoke exposure selected. Provide responses for the patient's lifetime.			
20	Cigarettes: Number smoked per day	SUCIG1D	Num.2 (per day)
21	Cigarettes: Number of years smoked	SUCIG1Y	Num.2 (years)
22	Cigarillos: Number smoked per day	SUCIG2D	Num.2 (per day)
23	Cigarillos: Number of years smoked	SUCIG2Y	Num.2 (years)
24	Cigars: Number smoked per day	SUCIG3D	Num.2 (per day)

25	Cigars: Number of years smoked	SUCIG3Y	Num.2 (years)
26	Pipe Tobacco: Number smoked per day	SUPIPED	Num.2 (per day)
27	Pipe Tobacco: Number of years smoked	SUPIPEY	Num.2 (years)
28	Tobacco for Smoking: Amount smoked per week (25 grams = 1 ounce)	SUTOBAW	Num.2 (per week)
29	Tobacco for Smoking: Number of years smoked	SUTOBAY	Num.2 (years)
30	Marijuana smoking: Number smoked per week	MARIJW	Num.2 (per week)
31	Marijuana smoking: Number of years	MARIJY	Num.2 (years)
32	E-cigarette use: Number of sessions per week	ECIGRW	Num.2 (per week)
33	E-cigarette use: Number of years	ECIGRY	Num.2 (years)
34	Nicotine inhalator use: Number of sessions per week	INHALW	Num.2 (per week)
35	Nicotine inhalator use: number of years	INHALY	Num.2 (years)
36	If Other, specify		Free text $ 200

VITAL SIGNS & PHYSICAL EXAM (VSPE)

Please provide responses for vital signs and physicial exam conducted since the last study assessment. For the baseline visit, report the most recent assessment. For 6-month follow-up periods, report the most recent assessment done since the prior Follow-up period.

1	Were vital signs conducted?		(0) No (1) Yes *Drop Down List
2	Most Recent Date Vital Signs were Collected	VIT_DAT	DD -MMM-YYYY Char 10

3	Height in inches	HEIGHT	Num. 3
4	☐ Not Done Height	HEIGHTND	
5	Weight in lb.	WEIGHT	Num. 3
6	☐ Not Done Weight	WEIGHTND	
7	Body Mass Index (auto calculated)	BMI	Num. 3
8	Systolic blood pressure (mmhg)	VSSBP	Num. 3
9	Diastolic blood pressure (mmhg)	VSDBP	Num. 3
10	☐ Not Done Bp	BPND	
11	Heart rate (beats/min))	HRATE	Num. 3
12	☐ Not Done Heart Rate	HRND	
13	Respiratory rate (resp/min)	VSRR	Num. 3
14	☐ Not Done RR	RRND	
15	Resting oxygen saturation on room air	SPOXY	Num. 3
16	☐ Not Done SpO2	SPOND	
17	Peak expiratory flow (L/min)	PEFR	Num. 3
18	☐ Not Done PE Flow	PEFND	
19	Waist circumference (inches)	WAISTC	Num.3
20	☐ Not done Waist circumference	WAISTCND	
21	Hip circumference (inches)	HIPC	Num.3
22	☐ Not Done Hip circumference	HIPCND	

L	**PHYSICAL EXAM**		
22.5	Was a physical examination performed?	PHEX	(0) No (1) Yes *Drop Down List
23	Are there any abnormal physical examination findings that have not been reported elsewhere that are relevant to the patient's severe asthma or overall health status?	PEYN	(0) No (1) Yes *Drop Down List

Note	Note: Must save form before adding any additional entries.			
T	Body System	If Other, specify the Body System	Results	Abnormality
25	Body system		PECAT	(1) HEENT (2) Respiratory (3) Cardiovascular (4) Gastrointestinal (5) Urogenital (6) Breasts

			(7) Musculoskeletal (8)Dermatologic (9)Hematopoietic/Lymphatic (10) Endocrine/Metabolic (11) Neurological (12) Allergic/Immunologic (13) Psychiatric (14) Reproductive (15) Rectal (16) Vascular (17) Other *Drop Down List
26	If Other, specify the Body System	PECATO	$60
27	Abnormality	PETERM	$200

IMAGING and FENO

Please provide responses for any testing completed conducted since the last study assessment. For the baseline visit, report any testing ever done previously. For 6-month follow-up periods, report any testing done since the prior Follow-up period.

1	Are any lung CT imaging results available?	ASMPERFC	(0) No (1) Yes – not high resolution (2) Yes – high resolution * Radio Button
Edit Note	*If Yes, Q2-Q4 Triggered*		
2	Date of most recent assessment	ASM_DATC	DD -MMM- YYYY Char 10
3	Description of Findings (select all that apply)	RDEXABN	☐ Normal ☐ Air trapping ☐ Increased airway thickness (bronchial wall thickening) ☐ Reduced airway luminal area ☐ Hyperinflation ☐ Bronchiectasis ☐ Atelectasis ☐ Mild emphysema ☐ Upper lobe predominant moderate-to-severe emphysema ☐ Diffuse moderate-to-severe emphysema ☐ Paraseptal emphysema ☐ Bullae ☐ Bronchiectasis ☐ Mucoid impaction ☐ Tracheobronchomalacia ☐ Pneumothorax ☐ Mosaic attenuation ☐ Cavitation ☐ Pulmonary nodules ☐ Mediastinal or hilar adenopathy ☐ Other *Check Box
4	Abnormal Other, specify	ABNOTH	Free Text $100

5	Are any Chest X-Ray results available?	XIPERF	(0) No (1) Yes * Radio Button
Edit Note	*If Yes, Q6-Q8 Triggered*		
6	Date of most recent assessment	XIDT	DD -MMM- YYYY Char 10
7	Response Result	XIORRES	(1) Within normal limits (2) Abnormal, not clinically significant (3) Abnormal, clinically significant * Drop Down List
8	Comment on Findings	XICOMM	Free Text Field $200
9	Has a Fractional exhaled nitric oxide (FENO) been performed?	ASMPERF	(0) No (1) Yes *Drop Down list
Edit Note	*If Yes selected, Q10 –Q11 triggered*		
10	Date of most recent Assessment	ASM_DAT	DD -MMM-YYYY Char 10
11	Mean FENO result (ppb)	FENO	Num. 4

SPIROMETRY

Please provide responses for any testing completed conducted since the last study assessment. For the baseline visit, report any testing ever done previously. For 6-month follow-up periods, report any testing done since the prior Follow-up period.

12	Has spirometry been performed?	PFTPERF	(0) No (1) Yes *Radio Button
13	Date of most recent Assessment	ASM_DAT	DD -MMM-YYYY Char 10
14	Time of Assessment (00:00-23:59)	ASM_TIM	HH:MM (Char 5)
15	Did patient withhold short-acting rescue inhaler (SABA such as albuterol or SAMA such as ipratropium) within 6 hours and long-acting twice daily bronchodilators (LABAs or LAMAs) within 12 hours or 24 hours (for once daily LABAs or LAMAs) prior to spirometry?	WHOLDS	(0) No (1) Yes (2) Unknown *Drop Down List
L	**BASELINE SPIROMETRY**		
16	Forced Vital Capacity (FVC (L))	FVC	Num. 3.2
17	FVC (% Predicted)	FVCP	Num. 5.2
18	Forced Expiratory Volume in the first second (FEV1 (L))	FEV1	Num. 3.2
19	FEV1 (% Predicted)	FEV1P	Num. 5.2
20	FEV1/FVC Ratio (%)	FEV1FVC	Num. 3
21	FEV1/FVC Ratio (% Predicted)	FEV1FVCP	Num. 5.2
22	Peak Expiratory Flow (PEF (L/min))	PEF	Num. 3.2
23	Forced Expiratory Flow (FEF 25-75% (L/sec))	FEF25_75	Num. 3.2
24	Inspiratory Capacity (IC (L))	IC	Num. 4.2
25	Was Post-Bronchodilator Testing performed for this spirometry assessment?	BRONCH	(0) No (1) Yes *Drop Down List
Edit Note	*If Yes, Q26-38 should be triggered* *[Requested Details should pertain to the Most Recent Assessment]*		

L	**POST-BRONCHODILATOR SPIROMETRY RESULTS**		
26	Forced Vital Capacity (FVC (L))	FVC	Num. 3.2
27	FVC (% Predicted)	FVCP	Num. 5.2
28	Forced Expiratory Volume in the first second (FEV1 (L))	FEV1	Num. 3.2
29	FEV1 (% Predicted)	FEV1P	Num. 5.2
30	FEV1/FVC Ratio (%)	FEV1FVC	Num. 3
31	FEV1/FVC Ratio (% Predicted)	FEV1FVCP	Num. 5.2
32	Peak Expiratory Flow (PEF (L/min))	PEF	Num. 3.2
33	Forced Expiratory Flow (FEF 25-75% (L/sec))	FEF25_75	Num. 3.2
34	Inspiratory Capacity (IC (L))	IC	Num. 4.2
L	Reversibility Results		
35	FEV1 Reversibility (%)	FEV1REVP	Num. 5.2
36	FEV1 Reversibility (mL)	FEV1REV	Num. 6.2
37	FEF 25-75% Reversibility (%)	FEFREVP	Num. 3
38	FEF 25-75% Reversibility (mL)	FEFREV	Num. 6.2

COMPLETE PULMONARY FUNCTION TEST (CMPFT)

Please provide responses for any testing completed conducted since the last study assessment. For the baseline visit, report any testing ever done previously. For 6-month follow-up periods, report any testing done since the prior Follow-up period.

Complete Pulmonary Function Test			
1	Has complete pulmonary function testing been performed?	CMPFT_YN	(0) No (1) Yes *Drop Down List
Note	*If Yes, please answer the questions below*		
2	Date of Most Recent Assessment	ASM_DAT	DD -MMM-YYYY Char 10
3	Time of Assessment (00:00 – 23:59)	ASM_TIM	HH:MM (Char 5)
4	Did patient withhold short-acting rescue inhaler (SABA such as albuterol or SAMA such as ipratropium) within 6 hours and long-acting twice daily bronchodilators (LABAs or LAMAs) within 12 hours or 24 hours (for once daily LABAs or LAMAs) prior to spirometry?	WHOLDS	(0) No (1) Yes (2) Unknown *Drop Down List
L	Baseline Complete PFT Results		
5	Forced Vital Capacity (FVC (L))	FVC	Num. 3.2
6	FVC (% Predicted)	FVCP	Num. 5.2
7	Forced Expiratory Volume in the first second (FEV1 (L))	FEV1	Num. 3.2
8	FEV1 (% Predicted)	FEV1P	Num. 5.2
9	FEV1/FVC Ratio (%)	FEV1FVC	Num. 3
10	FEV1/FVC Ratio (% Predicted)	FEV1FVCP	Num. 5.2
11	Peak Expiratory Flow (PEF (L/min))	PEF	Num. 3.2
12	Forced Expiratory Flow (FEF 25-75% (L/sec))	FEF25_75	Num. 3.2
13	Inspiratory Capacity (IC (L))	IC	Num. 4.2
L	Lung Volume Results		
14	Lung Volume Estimation Methods	LVMETH	(1) Plethysmography/Body Box (2) Nitrogen (N_2) wash-out (3) Unknown *Drop Down List

15	Expiratory Reserve Volume (ERV (L))	ERV	Num. 3.2
16	Inspiratory Reserve Volume (IRV (L))	IRV	Num. 3.2
17	Residual Volume (RV (L))	RV	Num. 3.2
18	Vital Capacity (VC (L))	VC	Num. 4.2
19	Functional Residual Capacity (FRC (L))	FRC	Num. 4.2
20	Total Lung capacity (TLC (L))	TLC	Num. 4.2
21	Was Post-Bronchodilator Testing performed?	BRONCH	(0) No (1) Yes *Drop Down List
Note	*If Yes, please answer the questions below*		
L	Post-Bronchodilator Complete PFT Results		
23	Forced Vital Capacity (FVC (L))	FVC	Num. 3.2
24	FVC (% Predicted)	FVCP	Num. 5.2
25	Forced Expiratory Volume in the first second (FEV1 (L))	FEV1	Num. 3.2
26	FEV1 (% Predicted)	FEV1P	Num. 5.2
27	FEV1/FVC Ratio (%)	FEV1FVC	Num. 3
28	FEV1/FVC Ratio (% Predicted)	FEV1FVCP	Num. 5.2
29	Peak Expiratory Flow (PEF (L/min))	PEF	Num. 3.2
30	Forced Expiratory Flow (FEF 25-75% (L/sec))	FEF25_75	Num. 3.2
31	Inspiratory Capacity (IC (L))	IC	Num. 4.2
	Reversibility Results		
32	FEV1 Reversibility (%)	FEV1REVP	Num. 5.2
33	FEV1 Reversibility (mL)	FEV1REV	Num. 6.2
34	FEF 25-75% Reversibility (%)	FEFREVP	Num. 3
35	FEF 25-75% Reversibility (mL)	FEFREV	Num. 6.2
36	Was DLCO evaluated?	DLCOND	0) No 1) Yes *DropDown List
Note	*If Yes, please answer the questions below*		
37	DLCO result (mL/mmHg/min). Provide adjusted result if available.	DLCO	Num. 3.2
38	DLCO % predicted (provide adjusted result if available)	DLCOP	Num. 3
39	DLCO/VA (ml/mmHg/min/L). Provide adjusted result if available.	DLCOVA	Num. 3.2
40	DLCO/VA % predicted (provide adjusted result if available)	DLCVAP	Num. 3

LABORATORY TESTING (LABTST)

Please provide responses for any testing completed conducted since the last study assessment. For the baseline visit, report any testing ever done previously. For 6-month follow-up periods, report any testing done since the prior Follow-up period

1	Are any Bronchial hyper-responsiveness (BHR) (including methacholine challenge) results available?	TESTYP	(1) No (2) Methacholine Challenge (3) Histamine Challenge (4) Exercise Challenge, (5) Eucapneic Hyperventilation Test (6) Cold Air Challenge (7) Antigen-Specific Challenge *Drop Down list
Edit check Note	*If Any field but No answered, Q2-3 Triggered*		
2	Date of most recent assessment	BHRDT	DD -MMM- YYYY Char 10
3	Bronchial hyper-responsiveness (BHR) results	BHRRSLT	(0) Negative (1) Borderline (2) Positive *Drop Down list
8	Please indicate which clinical chemistry tests results are available (Check all that apply)	ASMPERF	☐ Bone densitometry ☐ Eosinophil Count (not part of CBC) ☐ Vitamin D levels ☐ Total Immunoglobulin E(IgE) ☐ Hemoglobin A1C ☐ C-reactive protein ☐ Alpha-1 antitrypsin testing *Check Box
5	Date of most recent Bone densitometry assessment	BDENDT	DD -MMM- YYYY Char 10
6	T-Score	TSCORE	NUM 3.2
7	Z-Score	ZSCORE	NUM 3.2
9	Date of most recent Eosinophil Test *(not part of CBC)*	EOSINDT	DD-MMM-YYYY (Char 10)
10	Eosinophil Count (K/mcL)	EOSRSLT	NUM 5.2

11	Date of most recent collection of Vitamin D levels	VITDDT	DD-MMM-YYYY (Char 10)
12	Vitamin D Results (ng/ml)	VITRST	NUM 5.2
13	Date of most recent Total Immunoglobulin E (IgE) assessment	ASIGEDAT	DD-MMM-YYYY (Char 10)
14	Most recent Total Immunoglobulin E result	LBORIGE	NUM 5.2
15	Total Immunoglobulin E units	LBORIGEU	(1) kU/L (2) IU/mL * Radio Button
16	Date of most recent HbA1C test	HBADAT	DD-MMM-YYYY (Char 10)
17	HbA1C (%) result	HBA1CR	NUM 5.2
18	Date of most recent C-Reactive Protein test	CRPDAT	DD-MMM-YYYY (Char 10)
19	C-Reactive Protein Result (mg/L)	CRPRSL	NUM 4.2
20	Date of most recent alpha-1 antitrypsin test	ALP1ADT	DD-MMM-YYYY (Char 10)
21	Alpha-1 antitrypsin level (mg/dL)	ALP1AT	Num. 4.2
22	Alpha-1 antitrypsin Phenotype	ALP1PHE	(1) Pi MM (2) Pi ZZ (3) Pi MZ (4) Pi MS (5) Pi SZ (6) Pi Null Null (7) Pi SS (8) Other *Drop Down List
23	Phenotype Other, specification	ALPHENO	Free Text $50
24	Are any results of CBC with Differential available?	CBCDIFF	(0) No (1) Yes * Radio Button
Edit Note	*If Yes, an edit Notification will trigger to remind the site to make the necessary updates to the CBC with Differential Lab Log*		
25	Are any results of Sputum testing available?	SPUTCEL	(0) No (1) Yes * Radio Button

Edit Note	*If Yes, an edit Notification will trigger to remind the site to make the necessary updates to the BAL and Sputum Lab Log*		
26	Are any results of bronchoalveolar lavage (BAL) available?	BALPERF	(0) No (1) Yes * Radio Button
Edit Note	*If Yes, an edit Notification will trigger to remind the site to make the necessary updates to the BAL and Sputum Lab Log*		

SPECIFIC EVENTS OF INTEREST (SEI)

Programming note: Same form completed at baseline and 6-month follow-up. We should not show the prior responses – they need to newly complete it every time.

L	Participation in Respiratory Interventional Trials		
1	Since the last visit, has the patient participated in an investigational trial for asthma or allergic diseases? (Should be No for baseline visit)	TRIALPRT	(0) No (1) Yes *Radio Button
Note	*If No, skip to Specific Events of Interest questions below*		
2	Investigational Trial Type	INVTYPE	(1) Blinded (2) Unblinded/Open label *Drop Down list
3	What is the study ct.gov NCT number?		Free text
4	If the trial is unblinded/open-label, what investigational treatment is the patient receiving (include name of treatment)?	INVTRT	Free text
5	Participation: Start Date	TRISTDAT	DD-MMM-YYYY (Char 10)
6	Has patient completed trial?	CMPTRL	(0) No (1) Yes *Radio Button
7	If Yes, Participation: End Date	TRIENDAT	DD-MMM-YYYY (Char 10)
Note	Specific Events of Interest *(Details of any events should be recorded on the relevant log pages.)*		
8	Did the patient experience any of these 3 specific types of events in the relevant follow-up period (in the past 12 months if at baseline visit or since the prior follow-up period if at a 6-month	MECAT	☐ Diagnosed malignancy ☐ Serious Infection (requiring hospitalization, intravenous medication, or with fatal outcome) ☐ Anaphylaxis reaction ☐ No events in these 3 categories *Check Box

PATIENT AND TREATMENT STATUS (ASSMT)

Programming note: Same form completed at baseline and 6-month follow-up. We should not show the prior responses – they need to newly complete it every time.

1	Date Data collection Completed for this Study Assessment	VIS_DAT	DD -MMM- YYYY Char 10
2	Number of specialist visits for asthma in the past 6 months.	SPECILST	NUM 3
3	Date of most recent visit to study specialist	SPECLDT	DD-MMM-YYYY
4	How does the specialist physician categorize the patient's asthma at present?	ASTHSEV	(0) Severe uncontrolled (1) Severe controlled (2) No longer severe but uncontrolled (3) No longer severe and controlled *Drop Down List
5	How did the specialist assess control to inform his/her current view?	CONTROL	☐ Clinical impression (not patient report) ☐ Patient report – no standardized survey ☐ Patient report – ACT ☐ Patient report – other survey ☐ Recent exacerbations (e.g. OCS bursts) ☐ Lung function ☐ Other (free text) **Select all that apply*
6	If Other, specify	CONTROTH	Free text $ 200
7	In the specialist physician's current view, how effective has the patient's treatment been in controlling the patient's severe asthma in the last 6 months?	TRTEFFV	(0) Complete control of asthma (1) Marked improvement of asthma (2) Discernible, but limited improvement in asthma (3) No appreciable change in asthma (4) Worsening of asthma *Drop Down List

L	As of the patient's most recent visit to the study specialist:		
8	Does the patient have daytime asthma symptoms more than twice per week?	DAYTIME	(0) No (1) Yes (2) Don't know *Drop Down List
9	Does the patient have any nocturnal awakening/symptoms due to asthma?	NOCTURN	(0) No (1) Yes (2) Don't know *Drop Down List
10	Does the patient require asthma reliever medication use more than twice per week?	RELIEVE	(0) No (1) Yes (2) Don't know *Drop Down List
11	Does the patient have any activity limitation due to asthma?	LIMITAT	(0) No (1) Yes (2) Don't know *Drop Down List
L	Treatment Status		
12	Please describe the rationale for any significant changes to the patient's asthma treatment in the past 6 months	TREATCHG	☐ No significant changes ☐ Change due to side effects ☐ Change due to worsening of asthma control, increase in symptoms ☐ Change due to new asthma symptoms ☐ Change due to medication being ineffective (never was effective) ☐ Change due to medication being ineffective (was effective but waned over time) ☐ Switched to cheaper medication or medication with better insurance coverage ☐ Change as medication no longer necessary for asthma control ☐ Change due to preference for different device ☐ Other reasons not listed above *Select all that apply

	If Other, specify	TREATCH OT	Free text $200
13	If there was a significant change, whose concerns primarily led to the change?	CONCER N	☐ No significant change ☐ Patient ☐ Family member ☐ Physician/NP/PA ☐ Nurse or other staff ☐ Pharmacist ☐ Other *Select all that apply
14	If Other, specify	CONCER OT	Free text $ 200
15	Is there evidence of poor asthma treatment adherence?	ADHRYN	(0) No (1) Yes: Based on Clinical Impression (including patient report) but no objective measures (2) Yes: Based on Objective Measures (but not review of prescription records) (3) Yes: Based on Review of Prescription Records *Drop Down List
16	Are there any other external factors not described elsewhere contributing to the patient's severe asthma?	CONTRI	(0) No (1) Yes *Drop Down List
17	If Yes, please describe the external factor	EXTFACT	Free Text
L	Future Management Plan		
18	What is the specialist's Clinical Management Plan for Next 6 Months? (Select All that apply):	CMPLAN	☐ Continue current management – no changes ☐ Additional inhaled therapy ☐ Reduce inhaled therapy ☐ Change to different inhaled therapy ☐ Start biologic therapy ☐ Stop biologic therapy ☐ Change to different biologic therapy

			☐ Recommend Bronchial Thermoplasty ☐ Start Chronic Systemic Corticosteroids or Other Systemic Immunosuppressant ☐ Stop Chronic Systemic Corticosteroids or Other Systemic Immunosuppressant ☐ Change to different chronic Systemic Corticosteriods or Other Systemic Immunosuppressant ☐ Recommend entry into clinical trial of investigational therapy ☐ Other *Check Boxes
19	Management Other, specify	CMPLNO	Free text field ($ 200)
20	As outlined in the study protocol, were medical records collected from the patient's primary care provider(s) and used as an additional resource to characterize the patient's health status and healthcare utilization?	PCPRES	(0) No (1) Yes *Radio Button
21	Given that patients have access to multiple healthcare sites (primary care, hospitals, etc.) and multiple healthcare providers (PCP, specialist, pharmacist, etc.), how likely is it that your answers to the questions about healthcare utilization represent a complete view of the patient's treatment over the previous months, using a 0-100% scale?	ACCPER	NUM.3
22	Did you update the following Logs where necessary: Comorbidities, Relevant Medical Events/Procedures, Treatment	LOGUPD	0) No 1) Yes *Radio Button

	Logs (Asthma & Non Asthma), Lab Assessment Logs (CBC, BAL/ Sputum), Asthma Exacerbations, and Hospitalizations.		
23	The patient is continuing in the study.	PTCONTU	0) No 1) Yes *Radio Button
Note	If Yes, Trigger next Visit Folder (Next Visit is accessible) If No, Trigger End of Study Folder		

END OF STUDY (DS)			
1	Completion/Discontinuation Date	DSSTDAT	DD -MMM-YYYY Char 10
2	Main reason for withdrawal	DSDECOD	(C28554) Death (C48227) Lost to Follow-Up (C49632) Study Terminated by Sponsor (C49634) Withdrawal by Patient (1) Change of address (99) Other *Radio Button
	If Other, Specify	DSOTH	Free text $ 200
3	If Status is Death, please select the Primary cause of death	DSCAUSE	(1) Asthma (2) Non-asthma respiratory disease (3) Heart failure (4) Cardiovascular disease (other than heart failure) (5) Lung Cancer/Malignancy (6) Other Cancer/Malignancy (7) Anaphylaxis (8) Infection (9) Sudden and unexplained death (10) Injury or Trauma or Accident (11) Suicide (12) Unknown (13) Other * Radio Button *Note: if select "cancer" or "infection" or "anaphylaxis" need to display message that any newly diagnosed malignancies or serious (requiring hospitalization, intravenous medication, or with fatal outcome) infections during study period need to be reported in greater detail (refer them to appropriate CRF page)*

	If Other, specify	DSCOTH	Free text $ 200
4	If Status is Death, please provide the investigator's 2-3 sentence narrative of the causes of death		Free text (prompt long response with large text box)

APPENDIX I

234262 Asthma Medication List for US sites by category
All "Other" responses must trigger free text field

I. Rescue Medications (Inhalers & Nebulized)

1) Albuterol (e.g. *ProAir, Proventil, Ventolin, AccuNeb*)
2) Levalbuterol (*Xopenex*)
3) Ipratropium bromide (*Atrovent*)
4) Ipratropium/albuterol (*Combivent, DuoNeb*)
5) Ephedrin/Guaifenesin (*Primatene, Bronkaid*)
6) Other

II. Inhaled Corticosteroids (ICS)

1) Beclomethasone (*QVAR*)
2) Budesonide (*budesonide nebulized, Pulmicort Flexhaler/Respules*)
3) Ciclesonide (*Alvesco*)
4) Flunisolide (*Aerobid, Aerospan*)
5) Fluticasone furoate (*Arnuity Ellipta*)
6) Fluticasone propionate (*Flovent Diskus/HFA*)
7) Mometasone (*Asmanex*)
8) Other

III. Combination Inhaled Products with ICS (ICS/LABA, ICS/LABA/LAMA)

1) Budesonide/formoterol (*Symbicort*)
2) Fluticasone furoate/Vilanterol (*Breo*)
3) Fluticasone propionate/Salmeterol (*Advair HFA/Diskus, AirDuo RespiClick*)
4) Mometasone/Formoterol (*Dulera*)
5) Fluticasone furoate/Umeclidium/Vilanterol *(Trelegy)*
6) *Other*

IV. Inhaled Long acting bronchodilators (LABA, LAMA, LABA/LAMA)

1) Aclidinium (*Tudorza Pressair*)
2) Arformoterol (*Brovana*)
3) Formoterol (*Foradil inhaler, Performomist nebulized*)
4) Glycopyrrolate/formoterol (*Bevespi Aerosphere*)
5) Glycopyrrolate (*Seebri Neohaler)*
6) Indacaterol (*Arcapta*)
7) Indacaterol/glycopyrrolate (*Utibron Neohaler*)
8) Olodaterol (*Striverdi Respimat*)
9) Salmeterol (*Serevent*)

10) Tiotropium (*Spiriva Respimat/Handihaler*)
11) Tiotropium/olodaterol (*Stiolto Respimat*)
12) Umeclidinium (*Incruse Ellipta*)
13) Umeclidium/Vilanterol (*Anoro*)
14) Other

V. Leukotriene Antagonists & Cromolyns

1) Montelukast (*Singulair*)
2) Zafirlukast (*Accolate*)
3) Zileuton (*Zyflo*)
4) Cromolyn (*Intal*)
5) Other

VI. Systemic bronchodilators

1) Theophylline (e.g. Theo-24, Uniphyl, Elixophyllin, Theodur)
2) Aminophylline
3) Roflumilast
4) Oral Albuterol (*VoSpire ER*)
5) Metaproterenol
6) Terbutaline
7) Magnesium
8) Other

VII. Oral Corticosteroids

1) Prednisone
2) Prednisolone
3) Dexamethasone
4) Methylprednisolone
5) Hydrocortisone
6) Other

VIII. Injectable Corticosteroids

1) Dexamethasone
2) Methylprednisolone
3) Hydrocortisone
4) Triamcinolone
5) Other

IX. Macrolide Antibiotics (Chronic)

1) Azithromycin (*Zithromax*)
2) Clarithromycin (*Biaxin*)
3) Erythromycin (*Erythrocin, Ery-Tab*)

4) Other

X. Biologics/Monoclonal Antibody Therapies

1) Benralizumab (*Fasenra)*
2) Mepolizumab (*Nucala*)
3) Omalizumab (*Xolair*)
4) Reslizumab (*Cinqair*)
5) Dupilumab (*Dupixent)*
6) *Other*

XI. Other Systemic Immunomodulators

1) Methotrexate
2) Cyclophosphamide
3) Cyclosporine
4) Azathioprine
5) Mycophenylate
6) Gold Salts
7) Intravenous gammaglobulin (IVIG)
8) Other

XII. Other Asthma-specific Medication, Including Any Alternative, Complementary, or Integrative Therapies for Asthma (Use only if medication is not on one of the preceding lists): *Triggers free text field*

Version Number	Effective Date	Author	Summary of Changes Made
1.0	Signature Date	Ramona Bosley	Initial Document
1.1	Signature Date	Ramona Bosley	- **Pre-Enrollment form:** o Re-ordered the question Patient meet all study inclusion criterion to top of the page o Q4: Added "Primary" to the Insurance Status field o Re-ordered the "Number of Asthma Excerbation" field after the "Age in Years at time of first Asthma" o Q7: Added (Check all that applies) to "Asthma Treatment Classifications" field o Q8: Reworded question of "For patients with Class01 only, did this patient meet the every 3rd patient selection scheme as detailed in section 3.7 of the protocol? *Note: For patients with Class02 or Class 03, select Does Not Apply.*" Also added an additional option of "Does not apply" - **Eligibility Criteria form:** o (page split)->Eligibility Criteria and Demography/Asthma History o Removed Note of "Check all the applicable criteria among i1 to i4 if INC04a is answered as Yes" - **Social, Environment and Smoking Status form:** o Q17 [Re-ordered: question "Does the patient routinely use smokeless tobacco (e.g chewing tobacco or snuff?" is located after "IS the patient regularly

Version Number	Effective Date	Author	Summary of Changes Made
			exposed to dust or fumes in a job or other setting (e.g hobby)?" - **Relevant Medical Events & Procedures form:** o Updated Event/Procedure drop down list: ▪ added "22-Spinal/Vertebral Fracture" and"23-Hip fracture" ▪ updated 29-Influeza vaccination for 2016-2017 to include "(report each one)" - **Asthma Treatment form:** o Added Route and Route other Specify for coding purposes - **Non-Asthma Treatment form:** o Added Route and Route Other specify - **Asthma Exacerbation Log:** o **Q2:** Question of "# days of oral corticosteroids burst (or days of extra if receiving chronic systemic corticosteroids?). ▪ "Added "burst" and removed "Taken in addition to their regular medication" - **Hospitalizations Log:** *3.* Updated the page instruction to read as follows: *For asthma hospitalizations, record all hospitalizations that have ever occurred or occur during study enrollment.* *4. For all other hospitalizations (non-asthma), record all hospitalizations during the 12 months prior to Baseline or that occur during study enrollment.*

Version Number	Effective Date	Author	Summary of Changes Made
			- **Vital Signs & Physical Exam form:** o Page Level instructions added in the header o **Q1:** Change lead question to "Were Vital signs conducted?" o **Q22.5:** Added question of "Was physical Examination performed?" o **Q23:** Added "abnormal" to question of "Are there any abnormal physical examination findings that have not been reported elsewhere that are relevant to the patient's severe asthma or overall health status?" o Since site are instructed to capture System with abnormal findings "Results" field removed. - **Testing Assessment form (page split):** o Imaging/ FENO o Spirometry - **Spirometry Form (new form):** o Removed Section title of Spirometry Results - **Specific Events of interest Form (new form):** o Created a Section header "Specific Events of Interest questions below" o **Q3:** Added "If the Trial is unblinded/open-label," to question of "If the trial is unblinded/open-label, what investigational treatment is the patient receiving (include name of treatment and ct.gov NCT number if known)?"

Version Number	Effective Date	Author	Summary of Changes Made
			o **Q9 & Q9.5:** Added new question of "If yes, date of biopsy" and "Biopsy Not Done" - **Patient and Treatment Status Form:** o (page split)-> Specific Events of interest and Patient and Treatment Status o Q**17:** Updated to read "If yes, please describe the external factor" - **End of Study form:** o **Q4:** Replaced "comprehensive" with "2-3 sentence" to question of "If Status is Death, please provide the investigator's 2-3 sentence narrative of the causes of death" - **General:** o Removed all Page level dynamic with exception to the Asthma Treatment page. o Removed Line # field for all Log pages.
1.2	Signature date	Ramona Bosley	- **Specific Events of interest Form:** o Created Q2.5: "What is the study ct. gov NCT number?" o **Q3:** Removed "ct.gov NCT number if known" created as a separate question. "If the Trial is unblinded/open-label," to question of "If the trial is unblinded/open-label, what investigational treatment is the patient receiving (include name of treatment ~~and ct.gov NCT number if known~~)?"
2.0	Signature	Ramona Bosley	Final Sign off

Version Number	Effective Date	Author	Summary of Changes Made
2.1	Signature	Ramona Bosley	• **Pre-Enrollment Form:** o Added two new options to Q4 "Other" and "Other Government Insurance (e.g. Tricare, VA, etc.)" o Added an 'Other specify' field • **Visit Matrix:** o Re-Order the Common Folder (prior) to the Pre-Enrollment o Moved all of the log pages to display after the Pre-Enrollment page • **General update Log Forms:** o Re-Order "Ongoing" field to after the start date. • **Asthma Treatment Form:** o Q2.2: Updated text to now read "Asthma Treatment Details (not required for Other Asthma-specific medication - for those, please record in Specific Medication for "Other" responses field" • **Asthma Exacerbation Form:** o Q3: Correct text to now read "Enter zero if no corticosteroid injections were taken" • **Laboratory Assessment: BAL & Sputum Form:** o Negative/Positive options added for following fields: ▪ Fungal Culture Result ▪ Bacterial Culture Result ▪ AFB Culture Result o Normal/Abnormal option added to "Cytology Result" o Added new field for Positve and Abnormal result details: ▪ Fungal Result Details ▪ Bacterial Result Details

Version Number	Effective Date	Author	Summary of Changes Made
			▪ AFB Result Details ▪ Cytology Results Details • **Eligibility Criteria Form:** o Revise text for INC04a: changed 5^2 to 5. • **Demog and Asthma History:** o **Demography Section:** Revise text for INC04a: changed 5^2 to 5. o **Asthma Treatment History section:** ▪ Q3: Date of First visit w/ Specialist updated to only capture Month and Year ▪ Q4: Best estimated Date of 1st prescribe treatment HD-ICS..etc updated to only capture Month and Year ▪ Q10: Changed from Free Text field to Drop down list (list of value associated with the option for "Other Systemic Immunomodulators" found in Appendix I. Since "Other" is a option an "If Other, specify" field has also been added. ▪ Q14: Changed from Free Text field to Drop down list (list of value associated with the option for "Biologic/Monoclonal Antibody Therapies" found in Appendix I. Since "Other" is a option an "If Other, specify" field has also been added. • **Vital Signs & Physical Exam Form:**

Version Number	Effective Date	Author	Summary of Changes Made
			Vital Sign Section: o Q17 (PEF): Added units of (L/min) **Physical Section:** o Q24: Date Identified Removed • **Spirometry Form:** o Q14 (Time of Assessment): (00:00 -23:59) added to signify millitary time. o Q15 (Did patient withhold SABA or SAMA..etc): add option of "Unknown" • **Complete PFT Form:** o Q3 (Time of Assessment): (00:00 -23:59) added to signify millitary time. o Q4 (Did patient withhold SABA or SAMA..etc): add option of "Unknown" o Q14 (Lung Volume Method): Updated Option to "Plethysmography/Body Box" o Q22: Removed Broncodilator Dose field • **Specific Events of Interest Form:** o Q11 (Staging/Grading): Added option of "Unknown" • **Patient &Treatment Status Form:** o Q18 (What is specialist Clinical management Plan next 6mths): Added option "Change to different inhaled therapy"
3.0	Signature	R.Bosley	Final Sign document
3.1		R.Bosley	• **Asthma Exacerbation Form:** o Added new Question (Q7) - Suspected exacerbation trigger (select primary): o Associated Drop down list value:

Version Number	Effective Date	Author	Summary of Changes Made
			(1) Allergen (2) Tobacco smoke (3) Other airborne irritant (4) Cold air (5) Gastroesophageal reflux (6) Medication (7) Viral respiratory infection, no lab confirmation (8) Laboratory-confirmed influenza (9) Other lab-confirmed viral illness (not influenza) (10) Bacterial respiratory infection (11) Respiratory infection of unknown etiology (12) Unknown (13) Other o Other Specify field • **Laboratory Assessment: CBC with Differential Form:** o Updated Mock to include the following field has it was already present in the database (inadvertantly omitted in Mock in error): Absolute Eosinophil Count ▪ Changed the associated Unit reference from (/mcL) to (K/mcL) • **Social, Environment and Smoking Status form:** o Revised Q12: Added the following text "(Select maximum of two item, if applicable)" o Field to be updated capture multiple selections • **Vital Signs & Physical Exam Form:** **Physical Section:**

Version Number	Effective Date	Author	Summary of Changes Made
			○ Added the following note: "Note: Save before adding any additional records, if applicable." • **Laboratory Testing Form:** ○ Q10 Eosinophil Count: Added unit reference of "(K/mcL)" ○ Q17 HbA1C (%) result: Update the Numeric length • **Patient &Treatment Status Form:** ○ Revised Options for Q18 (What is specialist Clinical management Plan next 6mths): ○ Re-ordered option: "Change to different inhaled therapy" moved to become the 4th option. ○ Added two new options: ○ Change to different biologic therapy ○ Change to different chronic Systemic Corticosteriods or Other Systemic Immunosuppressant ○ Revised two options: ○ ~~Recommend~~ Start biologic therapy ○ ~~Recommend~~ Start Chronic Systemic Corticosteriods or Other Systemic Immunosuppressant
3.2		R.Bosley	• **Asthma Exacerbation Form:** Added option of "Exercise" to the new question ->Suspected exacerbation trigger (select primary): • **Laboratory Assessment: CBC with Differential Form:**

Version Number	Effective Date	Author	Summary of Changes Made
			o Updated 'Absolute Eosinophil Count' to 'Calculated Absolute Eosinophil Count' • **Social, Environment and Smoking Status form:** o Changed the format for question of the "Are any of the following used as a primary source for heating and/or cooking in the patient's household?" ▪ Added the following text "(Select maximum of two item, if applicable)" ▪ allow selections of multiple options o Add new question. "If former smoker, provide year the patient last smoked • **Vital Signs & Physical Exam Form:** **Physical Section:** o Revised new text for newly added note: New text now read "Note: Must save form before adding any additional entries." • **Specific Events of Interest (SEI) form:** o Remove following questions: ▪ If Yes, date of biopsy ▪ Biopsy Not Done o Add following new questions and all relevant fields: ▪ TNM Staging ▪ Staging
3.3		R.Bosley	• **Respiratory Comorbidities Form:** o Remove "Lung Cancer" from the list of Comorbidity Terms • **Non-Respiratory Comorbidities Form:**

Version Number	Effective Date	Author	Summary of Changes Made
			○ Remove both "Malignancy in complete remission" and "Active Malignancy" from the list of Comorbidity Terms • **Created 3 new log Form:** ○ Diagnosed Malignancy Log ○ Serious infection Event Log ○ Anaphylaxis Event Log • **Specific Events of Interest (SEI) form:** ○ Changes special events of interest lead question **from** "Did the patient experience any of these 3 specific types of events in the past 6 months?" **to** "Did the patient experience any of these 3 specific types of events in the relevant follow-up period (in the past 12 months if at baseline visit or since the prior follow-up period if at a 6-month follow-up)?" ○ Updated the 2 of the response options for the lead questions: ▪ Revised "New Onset malignancy" to "Diagnosed malignancy" ▪ Revised "Severe Infection" to "Serious Infection" ○ Removed the following sections and converted to individual log forms: Remove following questions: ▪ New Onset Malignancy (which was changed to Diagnosed Malignancy) ▪ Serious infections ▪ Anaphylaxis ▪ **Summary of Changes:** The summary table was moved from the

Version Number	Effective Date	Author	Summary of Changes Made
			front of the document to the back/ end of the document.

INTERNATIONAL SEVERE ASTHMA REGISTRY

Effectiveness Bolt-on Module

Case Report Form

Baseline Visit

General Guide to Complete the Bolt-on

Completing the Bolt-on

- Use a ballpoint pen to fill in the Bolt-on, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the Bolt-on are consistent with the source documents.
- Do not leave questions unanswered. If data is not available check the “No Data” Box and move to the next question.
- Sign and date the Bolt-on each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the Questionnaire

- Each correction in the Bolt-on must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Form Completed By: _____

Date: _____

Signature: _____

Comorbidity Section

Please indicate all current comorbidities at the baseline visit

(Onset of comorbidity may be any time prior to the baseline visit.)

1) Diagnosis of osteoporosis?

☐ No

☐ Yes

If osteoporosis is indicated as "Yes";

(a) Please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

Comorbidity Section

2) Diagnosis of circulatory system disease?

☐ No ☐ Yes

If circulatory system disease is indicated as "Yes", please provide the following details for each type starting from the most recent:

Event Number	(a) Type of circulatory system disease	(b) Start/diagnosis date
1	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
3	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
4	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
5	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data

2(b) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year). Start date can be any time prior to the baseline visit.

Comorbidity Section

3) Diagnosis of cataract or glaucoma disease?

☐ No ☐ Yes

If cataract or glaucoma is indicated as "Yes", please provide the following details for each type starting from the most recent:

Event Number	(a) Type of ocular disease	(b) Start/diagnosis date
1	☐ Glaucoma ☐ Others: _____ ☐ Cataract	__ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Glaucoma ☐ Others: _____ ☐ Cataract	__ __ / __ __ / __ __ __ __ ☐ No Data

3(b) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).
Start date can be any time prior to the baseline visit.

4) Diagnosis of obstructive sleep apnoea?

☐ No

☐ Yes

If obstructive sleep apnoea is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).
Start date can be any time prior to the baseline visit.

Comorbidity Section

5) Diagnosis of renal failure?

☐ No

☐ Yes

If renal failure is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

6) Diagnosis of depression?

☐ No

☐ Yes

If depression indicated as "Yes", please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).
Start date can be any time prior to the baseline visit.

Comorbidity Section

7)Diagnosis of anxiety?

☐ No

☐ Yes

If anxiety is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

8)Diagnosis of type II diabetes?

☐ No

☐ Yes

If type II diabetes is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

Comorbidity Section

9) Diagnosis of peptic ulcer?

☐ No ☐ Yes

If peptic ulcer is indicated as "Yes," please provide the following details for each event starting from the most recent:

Event Number	(a) Start/diagnosis date
1	__ __ / __ __ / __ __ __ __ ☐ No Data
2	__ __ / __ __ / __ __ __ __ ☐ No Data
3	__ __ / __ __ / __ __ __ __ ☐ No Data
4	__ __ / __ __ / __ __ __ __ ☐ No Data
5	__ __ / __ __ / __ __ __ __ ☐ No Data

9(a) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

Comorbidity Section

10) Diagnosis of pneumonia?

☐ No ☐ Yes

If pneumonia is indicated as "Yes," *please provide the following details for each event of pneumonia starting from the most recent:*

Event Number	(a) Start/diagnosis date
1	__ __ / __ __ / __ __ __ __ ☐ No Data
2	__ __ / __ __ / __ __ __ __ ☐ No Data
3	__ __ / __ __ / __ __ __ __ ☐ No Data
4	__ __ / __ __ / __ __ __ __ ☐ No Data
5	__ __ / __ __ / __ __ __ __ ☐ No Data

10(a) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date can be any time prior to the baseline visit.

INTERNATIONAL SEVERE ASTHMA REGISTRY

Effectiveness Bolt-on Module

Case Report Form

Follow-up Visit

General Guide to Complete the Bolt-on

Completing the Bolt-on

- Use a ballpoint pen to fill in the Bolt-on, refrain from using pencil.
- All entries should be in CAPITAL LETTERS.
- Only enter results in the fields provided.
- Make sure the data collected in the Bolt-on are consistent with the source documents.
- Do not leave questions unanswered. If data is not available check the “No Data” Box and move to the next question.
- Sign and date the Bolt-on each time a visit is completed. By doing so, you take responsibility for the correctness and accuracy of the data.

Correcting the Questionnaire

- Each correction in the Bolt-on must be dated and initialled (or signed).
- The original entry should remain legible. Do not use any correction fluid or pen to erase the entry you wish to modify. Draw a single line through the error, initialize, and write the correct answer next to the original entry.
- Depending on the study progress or study, amendments to these instructions or other instructions might be added.

Form Completed By: _____

Date: _____

Signature: _____

Comorbidity Section

Please indicate all new comorbidities diagnosed since the last visit

(Onset of comorbidity should be after the last visit)

1) New diagnosis of osteoporosis since the last visit?

☐ No

☐ Yes

If osteoporosis is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

Comorbidity Section

2) New diagnosis of circulatory system disease since the last visit?

☐ No ☐ Yes

If circulatory system disease is indicated as "Yes", please provide the following details for each event starting from the most recent:

Event Number	(a) Type of circulatory system disease	(b) Start/diagnosis date
1	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
3	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
4	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data
5	☐ Heart Failure ☐ Pulmonary Embolism/Venous Thromboembolism ☐ Myocardial Infarction ☐ Others: _____ ☐ Stroke	__ __ / __ __ / __ __ __ __ ☐ No Data

2(b) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year) Start date should occur after the last visit.

Comorbidity Section

3) New diagnosis of cataract or glaucoma since the last visit?

☐ No ☐ Yes

If cataract or glaucoma is indicated as "Yes", please provide the following details for each event starting from the most recent:

Event Number	(a) Type of ocular disease	(b) Start/diagnosis date
1	☐ Glaucoma ☐ Others: _____ ☐ Cataract	__ __ / __ __ / __ __ __ __ ☐ No Data
2	☐ Glaucoma ☐ Others: _____ ☐ Cataract	__ __ / __ __ / __ __ __ __ ☐ No Data

3(b) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

4) New diagnosis of obstructive sleep apnoea since the last visit?

☐ No

☐ Yes

If obstructive sleep apnoea is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

Comorbidity Section

5) New diagnosis of renal failure since the last visit?

☐ No

☐ Yes

If renal failure is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

6) New diagnosis of depression since the last visit?

☐ No

☐ Yes

If depression indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

Comorbidity Section

7)New diagnosis of anxiety since the last visit?

☐ No

☐ Yes

If anxiety is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

8)New diagnosis of type II diabetes since the last visit?

☐ No

☐ Yes

If type II diabetes is indicated as "Yes," please specify the start/diagnosis date.

Start/Diagnosis date: ☐☐ ☐☐ ☐☐☐☐ ☐ No Data

Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year)
Start date should occur after the last visit.

Comorbidity Section

9) New diagnosis of peptic ulcer since the last visit?

☐ No ☐ Yes

If peptic ulcer is indicated as "Yes*", please provide the following details for each event starting from the most recent:*

Event Number	(a) Start/diagnosis date
1	__ __ / __ __ / __ __ __ __ ☐ No Data
2	__ __ / __ __ / __ __ __ __ ☐ No Data
3	__ __ / __ __ / __ __ __ __ ☐ No Data
4	__ __ / __ __ / __ __ __ __ ☐ No Data
5	__ __ / __ __ / __ __ __ __ ☐ No Data

9(a) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).
Start date should occur after the last visit.

Comorbidity Section

10) New diagnosis of pneumonia since the last visit?

☐ No ☐ Yes

If pneumonia is indicated as "Yes," *please provide the following details for each event starting from the most recent:*

Event Number	(a) Start/diagnosis date
1	__ __ / __ __ / __ __ __ __ ☐ No Data
2	__ __ / __ __ / __ __ __ __ ☐ No Data
3	__ __ / __ __ / __ __ __ __ ☐ No Data
4	__ __ / __ __ / __ __ __ __ ☐ No Data
5	__ __ / __ __ / __ __ __ __ ☐ No Data

10(a) Date format is DD/MM/YYYY. If the exact date is unknown, please enter any known part of the date (e.g. year).
Start date should occur after the last visit.

Appendix 6. ISAR and CHRONICLE List of Variables

Demographic variables

Variable Name[a]	Description
Age Gender Height Weight	Patient age in years, height measurement in metres (m), and weight measurement in kilograms (kg)
Race/Ethnicity	Patient race/ethnicity
Occupation	Patient occupation
Body Mass Index (BMI)	Defined as the ratio of weight (kg) to squared height (m^2). • Categorised as underweight (< 18.5 kg/m^2), normal weight (≥18.5 kg/m^2 and <25 kg/m^2), overweight (≥ 25 kg/m^2 and <30 kg/m^2), and obese (≥ 30 kg/m^2)
Smoking status	Categorised as non-smoker, current smoker, or ex-smoker
Pack years	Defined as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked

[a]All variables are measured at baseline, which will refer to the first patient visit at which data are collected.

Clinical variables

Variable Name[a]	Description
Severe Asthma Criteria	
Inclusion (GINA guidelines [b])	Patient on GINA Step 5 treatment OR Patient on GINA Step 4 treatment with • Poor symptom control • Frequent severe exacerbations • Serious exacerbations • Airflow limitation
Medical History and Healthcare Utilization	
Age of asthma onset	Patient age in whole years or months (if less than 1 year) at which asthma symptoms began
Number of exacerbations	Count of exacerbations requiring rescue steroids in the past 1 year • For analysis: continuous and categorical values (1, 2, 3, 4, or more)
Number of invasive ventilations	Count of episodes of invasive ventilation ever prior to baseline.
Number of hospital admissions	Count of hospital admissions for asthma in the past 1 year
Number of emergency department admissions	Count of emergency department admissions for asthma in the past 1 year
Maintenance oral corticosteroids	Prescription for maintenance oral corticosteroids
Adherence	Poor adherence to prescribed therapy: Yes or No. Yes is derived from one or more of the following: subjective clinical impression, objective measure, or prescription records
Asthma control	Categorised as controlled, partly controlled, or uncontrolled according to the GINA Asthma Control Criteria
Blood and Sputum Tests (as conducted as a part of routine care)	
Immunoglobulin E level	Counts of immunoglobulin E, measured in kilounits per litre (kU/L) or international units per litre (IU/mL)
Blood eosinophil level	Counts of blood eosinophils, measured in cells per litre (10^9/L)

Highest blood eosinophil level	Highest count of blood eosinophils, measured in cells per litre (10^9/L) in the past 1 year
Fractional exhaled nitric oxide (FE_{NO}) test	Measurements of fractional nitric oxide concentration in exhaled breath, measured in parts per billion (ppb) at a flow rate of 50mL/s • Categorised as low FE_{NO} (<25ppb) and high FE_{NO} (>45ppb)
Allergy Testing (as conducted as a part of routine care)	
Skin Prick Test	House dust mite (HDM), animal dander (cat, dog), pollen (tree, grass), and moulds (Aspergillus). • Categorised as positive reaction if >3 mm is wheal diameter
Allergen-specific serum immunoglobulin E tests (ImmunoCAP, Enzyme-linked immunosorbent assay (ELISA), Radioallergosorbent test (RAST)) (ISAR only)	IgE mediated allergy test • Categorised[1] as Undetectable (<0.10kU/L), low (0.10-0.69kU/L), moderate (0.70-3.49kU/L), high (3.50-17.40kU/L), very high (17.40-49.0kU/L)
Spirometry (as conducted as a part of routine care)	
Predicted FEV1	Predicted normal Forced Expiratory Volume in the first second value for indicated age, gender, ethnicity, and height
Predicted FVC	Predicted normal Forced Vital Capacity value for indicated age, gender, ethnicity, and height
Pre-bronchodilator FEV1	Forced expiratory volume in the first second, measured in litres (L), before administering bronchodilator
Post-bronchodilator FEV1	Forced expiratory volume in the first second, measured in litres (L), after administering bronchodilator
Pre-Bronchodilator FVC	Forced vital capacity, measured in litres (L), before administering bronchodilator
Post-Bronchodilator FVC	Forced vital capacity, measured in litres (L), after administering bronchodilator
Pre-bronchodilator FEV1 (percentage of predicted)	Measured pre-bronchodilator FEV1 as a percentage (%) of predicted FEV1
Post-bronchodilator FEV1 (percentage of predicted)	Measured post-bronchodilator FEV1 as a percentage (%) of predicted FEV1
Pre-bronchodilator FVC (percentage of predicted)	Measured pre-bronchodilator FVC as a percentage (%) of predicted FVC
Post-bronchodilator FVC (percentage of predicted)	Measured post-bronchodilator FVC as a percentage (%) of predicted FVC
FEV1/FVC ratio pre-bronchodilator	Measured pre-bronchodilator FEV1 as a ratio of measured pre-bronchodilator FVC
FEV1/FVC ratio post-bronchodilator	Measured post-bronchodilator FEV1 as a ratio of measured post-bronchodilator FVC
Comorbidity	
Allergic rhinitis	Allergic rhinitis diagnosis
Chronic rhinosinusitis	Chronic rhinosinusitis diagnosis
Eczema	Eczema diagnosis
Nasal polyps	Nasal polyp diagnosis
Atopic disease	Eczema or allergic rhinitis diagnosis

[1] Categorization based on review article: Interpretation of IgE-Mediated Allergy Tests (RAST)

OCS related comorbidities	Osteoporosis, circulatory system disease (heart failure, myocardial infarction, stroke, pulmonary embloism/benous thromboembolism), cataract or glaucoma disease, obstrcutive sleep apnoea, renal failure, depression, anxiety, type II diabetes, peptic ulcer, pneumonia
Medication	
ICS	Prescription for inhaled corticosteroid (ICS)
LABA	Prescription for long-acting β-adrenoreceptor agonist (LABA)
ICS+LABA	Prescription for inhaled corticosteroids and long-acting β-adrenoreceptor agonist (ICS+LABA)
LAMA	Prescription for long-acting muscarinic antagonist (LAMA)
Theophylline	Prescription for theophylline
LTRA	Prescription for leukotriene receptor antagonist (LTRA)
Anti-IgE	Prescription for Anti-Immunoglobulin E (Anti-IgE)
Anti-IL5	Prescription for Anti-Interleukin 5 (Anti-IL5) or anti-eosinophil (benralizumab)
Other Biologics	Prescription for Other Biologic Treatments
Macrolide Antibiotic	Prescription for Macrolide Antibiotic
Other Steroid Sparing Agent	Prescription for Other Steroid Sparing Agent
Anaphylaxis	
Anaphylaxis	Occurrence of anaphylaxis
Serious Infection	
Serious Infection	Occurrence of serious infection
Malignancy	
New onset malignancy	Yes or no
Date of diagnosis	Malignancy date of diagnosis
Type of malignancy	Cell type
Location (site) of malignancy	Location/site of malignancy
Stage of malignancy	Staging at diagnosis
Outcome of malignancy	Ongoing, remission, death, or unknown status (not death)

[a]All variables are measured at baseline, which will refer to the first patient visit at which data are collected.
[b]Global Initiative for asthma 2017: GINA Stepwise approach for asthma control
[c]Categorisation based on review article: Interpretation of IgE-Mediated Allergy Tests (RAST)