“imPROve asthma”

Change in measured Patient-Reported Outcomes in severe eosinophilic asthma patients treated with benralizumab under real-life conditions in Germany

A prospective, 12-month, observational, multi-centre study to investigate the change in patient-reported outcomes in severe eosinophilic asthma patients treated with benralizumab biologic therapy under real-life conditions in Germany

Sponsor: AstraZeneca

Author:
TABLE OF CONTENTS

TABLE OF CONTENTS ...........................................................................................................2
RESPONSIBLE PARTIES ........................................................................................................6
PROTOCOL SYNOPSIS ...........................................................................................................7
AMENDMENT HISTORY .....................................................................................................15
MILESTONES .........................................................................................................................16
1. BACKGROUND AND RATIONALE ........................................................................17
   1.1 Background ...........................................................................................................17
   1.2 Rationale ...............................................................................................................18
2. OBJECTIVES AND HYPOTHESES ........................................................................19
3. METHODOLOGY .....................................................................................................22
   3.1 Study Design – General Aspects .................................................................22
   3.2 Study Population .................................................................................................24
   3.3 Inclusion Criteria .................................................................................................24
   3.4 Exclusion Criteria .................................................................................................25
   3.5 Participant Follow-up ............................................................................................25
4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS ................................25
   4.1 Exposures ..............................................................................................................25
   4.2 Data collection .......................................................................................................26
   4.2.1 Primary data collection .........................................................................................26
   4.2.2 Secondary data collection .....................................................................................26
   4.3 Outcomes ..............................................................................................................27
   4.3.1 Asthma control .....................................................................................................27
   4.3.1.1 Asthma Control Test (ACT) ..............................................................................27
   4.3.1.2 Asthma Control Questionnaire (ACQ-6) ...............................................................27
   4.3.2 Health-related quality of life (HRQL) ..................................................................28
   4.3.2.1 St George’s Respiratory Questionnaire ...............................................................28
   4.3.3 Investigator-reported reasons for change in therapy ..........................................28
   4.3.4 Patient-reported satisfaction and symptoms .........................................................28
   4.3.5 Nasal polyposis symptoms and sense of smell ....................................................29
   4.3.6 Administration of ePRO questionnaires .............................................................29
   4.3.7 Global evaluation of treatment effectiveness (GETE) ...........................................30
   4.3.8 Treatment adherence ..........................................................................................30
   4.3.9 Physical activity .................................................................................................30
4.3.10 Asthma exacerbations .................................................................34
4.4 Other Variables and Covariates ................................................35
5. STATISTICAL ANALYSIS PLAN ..................................................35
5.1 Statistical Methods – General Aspects .......................................35
5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability) ........36
5.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability) .............................................36
5.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability) .............................................37
5.2 Bias .............................................................................................39
5.2.1 Methods to Minimize Bias .......................................................39
5.2.2 Adjustment for Multiple Comparisons ....................................39
5.2.3 Strengths and Limitations .......................................................39
5.3 Interim Analyses ..........................................................................40
5.4 Sample Size and Power Calculations .........................................40
6. STUDY CONDUCT AND REGULATORY DETAILS ..............41
6.1 Study Conduct ...........................................................................41
6.1.1 Study Plan ..............................................................................42
6.1.2 Procedures ............................................................................45
6.1.2.1 Procedures for voluntary withdrawal/discontinuation ...........45
6.1.2.2 Early termination of study ..................................................45
6.1.3 Quality Control ......................................................................45
6.1.3.1 Data management .............................................................45
6.1.3.2 Monitoring activities .........................................................46
6.1.4 Storage and retention .............................................................47
6.2 Protection of Human Subjects ..................................................47
6.2.1 Subject Informed Consent (Primary Data Collection Only) .........48
6.2.2 Confidentiality of Study/Subject Data (Primary Data Collection Only) 48
6.3 Management and Report of Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Drug Reactions (ADRs) ........................................................................48
6.3.1 Definition of Adverse Events (AE) .........................................49
6.3.2 Definition of Serious Adverse Events (SAE) ............................49
6.3.3 Definition of Adverse Drug Reactions (ADR) .........................49
6.3.5 Reporting of serious adverse events, adverse events and adverse drug reactions 50
6.3.6 Pregnancy .............................................................................51
6.3.7 Overdose ..............................................................................52
7. LIST OF REFERENCES .................................................................53
8. APPENDICES ..............................................................................55
9. SIGNATURES ..............................................................................64
### LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<table>
<thead>
<tr>
<th>Abbreviation or special term</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Asthma Control Test</td>
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<tr>
<td>ACQ-6</td>
<td>Asthma Control Questionnaire-6</td>
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<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<td>AZ</td>
<td>AstraZeneca</td>
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<td>CRO</td>
<td>Contract Research Organization</td>
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<tr>
<td>DMP</td>
<td>Data Management Plan</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<tr>
<td>EOS</td>
<td>Eosinophil</td>
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<tr>
<td>ePRO</td>
<td>Electronic Patient-reported outcome</td>
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<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>Forced expiratory volume in 1 sec</td>
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<tr>
<td>FeNO</td>
<td>Fraction of exhaled nitric oxide</td>
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<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>GETE</td>
<td>Global evaluation of treatment effectiveness</td>
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<tr>
<td>HRQL</td>
<td>Health-related quality of life</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<td>ICS</td>
<td>Inhaled corticosteroid</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<td>IgE</td>
<td>Immunoglobulin E</td>
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<td>IL5</td>
<td>Interleukin-5</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>ITT</td>
<td>Intent-to-treat</td>
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<tr>
<td>LABA</td>
<td>Long-acting beta-agonist</td>
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<tr>
<td>MCID</td>
<td>Minimum clinically important difference</td>
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<td>MC</td>
<td>Marketing Company</td>
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<tr>
<td>Abbreviation or special term</td>
<td>Explanation</td>
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<td>------------------------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>NIS</td>
<td>Non-interventional study</td>
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<td>OCS</td>
<td>Oral corticosteroid</td>
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<td>PES</td>
<td>Primary Endpoint Set</td>
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<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<tr>
<td>SGRQ</td>
<td>St George’s Respiratory Questionnaire</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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# RESPONSIBLE PARTIES

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<thead>
<tr>
<th>Name</th>
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A Prospective, 12-month, Observational, Multi-centre Study to Investigate the Change in Patient-reported Outcomes in Severe Eosinophilic Asthma Patients Treated with Benralizumab Biologic Therapy under Real-life Conditions in Germany

Background/Rationale:

Asthma is a heterogeneous, chronic disease that is characterized by airway inflammation and recurrent symptoms [1,2]. Most asthma patients have mild to moderate disease that can be controlled by low- to medium-dose inhaled corticosteroids (ICS), with or without additional controllers such as long-acting bronchodilators, leukotriene modifiers or theophylline. However, approximately 5 to 10% of asthma patients have severe asthma characterized by a requirement for high-dose ICS plus a second controller (most commonly long-acting beta agonists [LABA]) to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy [1,2,3]. For those whose severe asthma remains uncontrolled, treatment options currently include the addition of another controller therapy (tiotropium, leukotriene receptor antagonist or theophylline), maintenance use of systemic corticosteroids, treatment with monoclonal antibody therapies that block Type 2 immune responses, and treatment with bronchial thermoplasty [1]. The population with severe, difficult to treat asthma, make up the majority of economic costs of asthma [4,5,6]. In 30% of severe adult asthma patients, oral corticosteroids (OCS) are required in addition to ICS to maintain some degree of asthma control [3], and OCS-related adverse events are common in severe asthma including type II diabetes, osteopenia/osteoporosis, dyspeptic disorders, obesity, hypertension, cataracts and obstructive sleep apnoea [7].

Furthermore, recent accelerometer data indicate that patients with severe asthma are highly physically inactive in daily life [8]. Interestingly, the level of physical inactivity in patients with severe asthma is comparable to that of patients with moderate to severe COPD [9], where physical inactivity has been identified to be major contributing factor of poor health outcomes [10].

Over the last decade, a shift towards evaluating specific phenotypes of asthma has led to the creation of targeted therapies to fit patient specific disease [11,12,13,14,15]. Through a better understanding of the inflammatory modulators involved in asthma, a number of monoclonal antibodies have emerged with the aim of providing patient-tailored asthma treatment and have demonstrated that in asthma patients with frequent exacerbations, the addition of a biologic agent targeting the Interleukin-5 (IL5) or
immunoglobulin E (IgE) pathway can significantly reduce exacerbations and improve asthma control [16]. Approved biologic therapies for severe asthma include omalizumab, an anti-IgE monoclonal antibody for treating patients with severe allergic asthma, and three anti-IL5/IL5R therapies, for treating patients with severe asthma with an eosinophilic phenotype, including mepolizumab, reslizumab, and benralizumab [16,17,18]. Benralizumab is a humanized afucosylated monoclonal antibody that binds with high affinity to the a-subunit of the IL-5 receptor, thus inhibiting the proliferation and activation of eosinophils (EOS), while simultaneously binding to the Fc receptor FcγRIIIa on natural killer cells, efficiently depleting existing EOS by inducing apoptosis through antibody-dependent cell-mediated cytotoxicity [17]. Benralizumab is administered subcutaneously every 8 weeks (after first three doses every 4 weeks) [17], approved for use in Europe and has been available in Germany since February 2018.

The clinical predictors of utility of specific agents overlap with one another, highlighting the importance of clinical judgment in the overall management of this complex disease [16]. Factors which physicians consider when deciding to initiate or switch biologic treatment include a combination of atopic history, biomarker presence, prior treatment response (e.g. prior biologic failure), specific goals and preferences of the patient or clinician (e.g. reduce exacerbations, improve lung function, reduce medication burden), and which side effect profile is most tolerable to the patient [1,17]. Assessment of the response to treatment is recommended after 3-6 months to review symptom control (symptom frequency, reliever use, night time awakenings, activity limitation), exacerbations since previous visit, medication side effects, inhaler technique and adherence, lung function, and patient satisfaction and concerns [19].

Identifying the characteristics of patients who are suitable for biologic treatment by generating real-life data of severe asthma patients in primary and secondary care settings across Europe was the main scientific approach in another non-interventional study (NIS), currently ongoing (RECOGNISE study (NCT03629782), started in April 2018). However, data on the therapeutic effects of biologic therapies for severe asthma in real world settings are scarce. The collection of data for benralizumab in a real-life setting in Europe is important and will aid physicians’ decisions about drug management in this asthma population.

The main aim of this study is to investigate the change in asthma control after 6 months of therapy in patients treated with benralizumab biologic therapy for severe eosinophilic asthma under real-life conditions in a pulmonary care setting in Germany. The study also aims to investigate QoL, the early treatment response, treatment effectiveness and the change in asthma control over time, following anti-IL5/IL5R therapy. This study will also describe the physician-chosen reasons for starting, switching and benralizumab therapy.

**Objectives and outcome measures**

All study analyses will be done separately for the anti-IL5/IL5R naïve and biologic experienced patients, as defined for the purpose of this study:
Anti-IL5/IL5R naïve patients:

- Severe eosinophilic asthma patients who have never received anti IL-5/anti IL-5R biologic treatment for severe eosinophilic asthma, for whom the investigator had decided to initiate benralizumab biologic treatment. Patients with previous omalizumab treatment will be analysed in this group if last dose was received > 6 months prior to study inclusion. These patients will be stratified as:
  - Biologic naïve: patients who never received any biologic treatment
  - Anti-IL5/ILR5 naïve, with former omalizumab experience: anti-IL5/ILR5 naïve patients who received their last dose of omalizumab > 6 months prior to study inclusion

Biologic experienced patients:

- Patients that previously received a biologic treatment for severe asthma (at least one dose). Patients in this group will be stratified for statistical analysis according to the time since the last biologic dose:
  - Direct switcher: last biologic dose received within last 12 weeks prior to benralizumab treatment (≤ 12 weeks)
  - Recent biologic experienced: last biologic dose received between 12 weeks to 6 months prior to benralizumab treatment (> 12 weeks and ≤ 6 months)
  - Former biologic experienced: last biologic dose received > 6 months prior to benralizumab treatment (NB patients who received omalizumab previously with the last dose received > 6 months ago that are also ‘anti-IL5/IL5R naïve patients’ will be analyzed in both groups.)
### Primary objective

| To describe the change in asthma control after 6 months of treatment vs baseline in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment | Change from baseline in Asthma Control Test (ACT) score after 6 months treatment in anti-IL5/IL5R naïve patients
| Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months

**Supported by:**

| Change from baseline in Asthma Control Questionnaire (ACQ)-6 score after 6 months treatment in anti-IL5/IL5R naïve patients
| Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (reduction of at least 0.5 units) in ACQ-6 after 6 months |

### Secondary objectives

| To describe the investigator reported treatment effectiveness after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment | Percentage of anti-IL5/IL5R naïve patients within each category of the global evaluation of treatment effectiveness (GETE) after 6 months of treatment |

| To describe the change in health-related quality of life (HRQL) after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment | Change from baseline in St George’s Respiratory Questionnaire (SGRQ) total score and domain scores (symptoms, activity and impact score) after 6 months treatment in anti-IL5/IL5R naïve patients
| Supported by:
| Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (decrease of at least 4 units) in SGRQ after 6 months |

<p>| To describe the early treatment response in anti-IL5/IL5R naïve patients initiated with benralizumab treatment | Change from baseline in ACQ-6 score after 7 and 14 days of treatment in anti-IL5/IL5R naïve patients |</p>
<table>
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<tr>
<th>Study protocol D3250R00053</th>
<th>AstraZeneca 03 May 2019</th>
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| And Change from baseline in patient satisfaction and patient symptoms (i.e. how bothersome) including cough severity (for patients with cough being a bothersome symptom at baseline), measured on visual analogue scales (VAS), after 7 and 14 days of treatment in anti-IL5/IL5R naïve patients | And % of the maximal response* achieved at Day 7 and Day 14 for ACQ-6 and patient satisfaction/symptoms VAS, in anti-IL5/IL5R naïve patients.  
*Maximal response as measured at any time point during the first 6 months |
| To describe the change of asthma control over time and the maintained response after initiation of benralizumab treatment, in anti-IL5/IL5R naïve patients | Change from baseline in asthma control at each visit during the study period, using ACQ-6/ACT in anti-IL5/IL5R naïve patients |
| | Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months that is maintained as such after 12 months |
| | Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (reduction of at least 0.5 points) in ACQ-6 after 6 months that is maintained as such after 12 months |
| To assess the reasons for biologic treatment change, as reported by the investigator | Investigator-chosen reasons (selected from pre-determined list), for |
- Initiation of/switching** to benralizumab at enrolment
- discontinuation of benralizumab during the treatment period

**The term 'Switch' is used generally to describe treatment change from one biologic to another, regardless of the time since the last dose of the previous biologic. Direct switchers are defined in Section 5.1, page 31

<table>
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<tr>
<th>Exploratory objective</th>
<th>Outcome measure</th>
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<tr>
<td>To describe the change in asthma control, HRQL, symptoms, patient satisfaction and treatment effectiveness at early timepoint and after 6 and 12 months Benralizumab treatment in biologic experienced patients (patients treated with any EU approved biologic treatment for severe asthma in the past)</td>
<td>Change from baseline in ACT, ACQ-6, SGRQ scores at the end of 6 and 12 months treatment; in ACQ-6 and patient satisfaction/patient symptoms (VAS) at 7 and 14 days; and GETE score after 6 months of benralizumab treatment in biologic experienced patients.</td>
</tr>
<tr>
<td>Percentage of biologic experienced patients initiated with benralizumab treatment, with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months, and out of those: Percentage of patients that maintained this improvement after 12 months</td>
<td>Percentage of biologic experienced patients initiated with benralizumab treatment, with a clinically meaningful improvement (reduction of at least 0.5 points) in ACQ-6 after 6 months, and out of those: Percentage of patients that maintained this improvement after 12 months</td>
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<tr>
<th>Exploratory objective</th>
<th>Outcome measure</th>
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<tbody>
<tr>
<td>To describe the change of physical activity over time in severe eosinophilic asthma patients treated with benralizumab, in anti-IL5/IL5R naïve patients</td>
<td>Change from baseline in steps per day over 12 months of treatment in anti-IL5/IL5R naïve patients</td>
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Methods:
**Study design:**

This is a prospective, observational, multi-centre, single-country study with a screening/baseline visit plus 5 study visits over 6 months, and 1 follow-up visit after 12 months. Due to the real-life setting of this study, assessments will be captured during routine scheduled clinical visits. To allow assessment of early response in the days after the first treatment dose, data will be captured using electronic patient-reported outcomes (PROs) at home (details in Table 1, study plan, Section 6.1.1). The study will be conducted under real-life conditions in the pulmonary care setting in Germany.

Approximately 250 anti-IL5/IL5R treatment naïve (refer to definition in Objectives and outcome measures on page 9) severe eosinophilic asthma patients that meet the eligibility criteria will be enrolled in special care centres and by suitable pulmonologists in Germany in order to achieve the study objectives. During the recruitment period, up to 250 biologic experienced (refer to definition in Objectives and outcome measures on page 9) patients will also be enrolled if they meet the eligibility criteria (minimum of 100 patients should be recruited to this group). The decision to initiate benralizumab treatment or switch to benralizumab treatment will be taken by the investigator, independent of the study.

**Data Source(s):**

Site staff will collect all necessary information from the patient’s medical record to determine eligibility for enrolment. Consecutively, adult patients with a diagnosis of severe asthma according to the American Thoracic Society/European Respiratory Society (ATS/ERS) and local German guidelines will be screened and those who meet all inclusion criteria and none of the exclusion criteria will be invited to participate, consented and enrolled.

The investigator will collect data from medical records, examination results or conducting interviews at every study visit. All data will be collected and documented in an electronic Case Report Form (eCRF). In addition, the patient will be asked to provide PRO data on HRQL (SGRQ), and asthma control (ACT, ACQ-6) questionnaires. In addition, treatment satisfaction level and symptoms (how bothersome) will be captured on day 7, 14 (home-recorded) and throughout the study. For those patients with cough being a bothersome symptom at baseline, severity of cough will be also recorded. Patient physical activity levels will be measured as steps per day, recorded on a dedicated armband device.

**Study Population:**

**Inclusion criteria:**

- Male or female patients aged 18 years or older with confirmed diagnosis of severe asthma according to the ATS/ERS and local German guidelines [2,3].
Decision was made by the investigator (regardless of this NIS) to start treating the patient with benralizumab according to severe eosinophilic asthma indication (NB: can include patients that are switched from another EU approved biologic treatment if required for a medical reason).

Patients must be able and willing to read and comprehend written instructions and comprehend and complete the questionnaires required by the protocol.

After full explanation, patients must have signed an informed consent document indicating that they understand the purpose of and the procedures required for the study and are willing to participate in the study.

Exclusion criteria

- Concomitant treatment with any other biologic for any indication
- Patients already treated with benralizumab
- Clinically important pulmonary disease other than asthma including: chronic obstructive pulmonary disease (as main diagnosis), bronchiectasis, idiopathic pulmonary fibrosis, pulmonary hypertension, alpha-1-antitrypsin-deficiency, and malignancy of any kind (NB: the following conditions are permitted: nasal polyposis, allergic rhinitis, atopic dermatitis, non-idiopathic pulmonary fibrosis).
- An acute or chronic condition that, in the investigator’s opinion, would limit the patient’s ability to complete questionnaires or participate in this study or impact the interpretations of results.
- Concurrent biologics for asthma are not allowed except for stable allergen immunotherapy (defined as a stable dose and regimen at the time of enrolment). Acceptable wash-out periods for other asthma biologics:
  - \( \geq 30 \) days from last dose of previous biologic
- Pregnancy or lactation period.
- Participation in an observational trial that might, in the investigator’s opinion, influence the assessment for the current study, or participation in a randomized clinical trial in the last 3 months.

Exposure(s):

Exposure data collected in this study will be on benralizumab biologic treatment indicated for severe eosinophilic asthma as part of routine medical care; the decision start benralizumab treatment will be made by the investigator according to the subject’s medical need and a positive benefit/risk balance.

Sample Size Estimations:

With no formal a priori hypotheses, this study uses a hypothesis-free approach focused on descriptive analyses. Thus, power calculation for any specific outcome is not strictly relevant. It is planned to enrol approximately 500 patients, 250 anti-IL5/IL5R treatment naïve patients with diagnosis of severe
eosinophilic asthma, with investigators decision to start benralizumab treatment for severe eosinophilic asthma in Germany, and up to 250 biologic experienced (refer to definition in Objectives and outcome measures on page 9) (minimum of 100 patients should be recruited to this group). The sample size of approximately 250 patients is driven by the need to enrol an adequate number of patients to address the mentioned objectives, also across various subgroups of interest with sufficient precision. The sample size will ensure that the descriptive data mandated by the primary and secondary endpoints are sufficiently precise and meaningful at a subgroup level.

**Statistical Analysis:**

The analyses will be of purely descriptive character since no hypotheses have been pre-specified. Variables will be analyzed with appropriate statistical methods; categorical variables by frequency tables and continuous variables by sample statistics (i.e. n, mean, standard deviation, minimum, median, maximum). For the primary endpoint, for the mean change in asthma control from baseline to month 6, the 95% confidence interval will be provided. Details of the planned analyses will be given in the statistical analysis plan (SAP).

**AMENDMENT HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Section of study protocol</th>
<th>Amendment or update</th>
<th>Reason</th>
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## Milestones

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<th>Planned date</th>
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<tr>
<td>Study Concept Document</td>
<td>March 2019</td>
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<tr>
<td>Final protocol</td>
<td>May 2019</td>
</tr>
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<td>First subject in</td>
<td>Q4 2019</td>
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<td>Last subject in</td>
<td>Q4 2020</td>
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<td>Interim analysis</td>
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<td>Last subject last visit</td>
<td>Q4 2021</td>
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<td>Database extraction</td>
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<td>Final results tables</td>
<td>Q4 2021</td>
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<td>Final report</td>
<td>Q4 2021</td>
</tr>
<tr>
<td>First main manuscript</td>
<td>Q2 2022</td>
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1. BACKGROUND AND RATIONALE

1.1 Background

Asthma is a heterogeneous, chronic disease that is characterized by airway inflammation and recurrent symptoms [1,2]. Most asthma patients have mild to moderate disease that can be controlled by low- to medium-dose inhaled corticosteroids (ICS), with or without additional controllers such as long-acting bronchodilators, leukotriene modifiers or theophylline. However, approximately 5 to 10% of asthma patients have severe asthma characterized by a requirement for high-dose ICS plus a second controller (most commonly long-acting beta agonists [LABA]) to prevent it from becoming ‘uncontrolled’ or that remains ‘uncontrolled’ despite this therapy [1,2,3]. For those whose severe asthma remains uncontrolled, treatment options currently include the addition of another controller therapy (tiotropium, leukotriene receptor antagonist or theophylline), maintenance use of systemic corticosteroids, treatment with monoclonal antibody therapies that block Type 2 immune responses, and treatment with bronchial thermoplasty [1]. The population with severe, difficult to treat asthma, make up the majority of economic costs of asthma [4,5,6]. In 30% of severe adult asthma patients, oral corticosteroids (OCS) are required in addition to ICS to maintain some degree of asthma control [3], and OCS-related adverse events are common in severe asthma including type II diabetes, osteopenia/osteoporosis, dyspeptic disorders, obesity, hypertension, cataracts and obstructive sleep apnoea [7]. Furthermore, recent accelerometer data indicate that patients with severe asthma are highly physically inactive in daily life [8]. Interestingly, the level of physical inactivity in patients with severe asthma is comparable to that of patients with moderate to severe COPD [9], where physical inactivity has been identified to be major contributing factor of poor health outcomes [10].

Over the last decade, a shift towards evaluating specific phenotypes of asthma has led to the creation of targeted therapies to fit patient specific disease [11,12,13,14,15]. Through a better understanding of the inflammatory modulators involved in asthma, a number of monoclonal antibodies have emerged with the aim of providing patient-tailored asthma treatment and have demonstrated that in asthma patients with frequent exacerbations, the addition of a biologic agent targeting the Interleukin-5 (IL5) or immunoglobulin E (IgE) pathway can significantly reduce exacerbations and improve asthma control [16]. Approved biologic therapies for severe asthma include omalizumab, an anti-IgE monoclonal antibody for treating patients with severe allergic asthma, and three anti-IL5/IL5R therapies, for treating patients with severe asthma with an eosinophilic phenotype, including mepolizumab, reslizumab, and benralizumab [16,17,18]. Benralizumab is a humanized afucosylated monoclonal antibody that binds with high affinity to the α-subunit of the IL5 receptor, thus inhibiting the proliferation and activation of eosinophils (EOS), while simultaneously binding to the Fc receptor Fcg RIIIA on natural killer cells, efficiently depleting existing EOS by inducing apoptosis through antibody-dependent cell-mediated cytotoxicity [17]. Benralizumab is administered subcutaneously every 8 weeks (after first three doses every 4 weeks) [17], approved for use in Europe and has been available in Germany since February 2018.
1.2  Rationale

The clinical predictors of utility of specific agents overlap with one another, highlighting the importance of clinical judgment in the overall management of this complex disease [16]. Factors which physicians consider when deciding to initiate or switch biologic treatment include a combination of atopic history, biomarker presence, prior treatment response (e.g. prior biologic failure), specific goals and preferences of the patient or clinician (e.g. reduce exacerbations, improve lung function, reduce medication burden), and which side effect profile is most tolerable to the patient [1,17]. Assessment of the response to treatment is recommended after 3-6 months to review symptom control (symptom frequency, reliever use, night time awakenings, activity limitation), exacerbations since previous visit, medication side effects, inhaler technique and adherence, lung function, and patient satisfaction and concerns [19].

Identifying the characteristics of patients who are suitable for biologic treatment by generating real-life data of severe asthma patients in primary and secondary care settings across Europe was the main scientific approach in another non-interventional study (NIS), currently ongoing (RECOGNISE study (NCT03629782)), started in April 2018. However, data on the therapeutic effects of biologic therapies for severe asthma in real world settings are lacking. The collection of data for benralizumab in a real-life setting in Europe is important and aid physicians’ decisions about drug management in this asthma population.

Patient-reported outcomes (PROs) are becoming more commonly assessed as outcome measures in both observational and randomised control trials in asthma, in addition to more traditional endpoints as lung function and asthma exacerbations. PROs can improve the quality of patient care by creating a holistic approach to clinical decision-making and are of increasing interest to policy makers, including informing reimbursement decisions. In this study, data will be collected from patients through validated PRO questionnaires (Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), St George’s Respiratory Questionnaire (SGRQ)) and exploratory Visual Analogue Scale (VAS) assessments (patient satisfaction with treatment and symptoms. Although the use of VAS in this population is not yet validated, its use for assessing the burden of symptoms in allergic rhinitis has already been successfully demonstrated [20], and widely used in Germany. Additionally cough severity will be assess by means of a VAS [21] for patient who reports cough as a bothersome symptom at baseline.

The main aim of this study is to investigate the change in asthma control after 6 months of treatment in patients treated with benralizumab biologic therapy for severe eosinophilic asthma under real-life conditions in a pulmonary care setting in Germany. The study also aims to investigate health-related quality of life (HRQL), the early treatment response, the change in asthma control over time (up to 12 months), as well as patient physical activity over 12 months, following benralizumab treatment. The rationale for including the follow-up of patients to 12 months is to mitigate the effects of seasonality. This study will also describe the physician-chosen reasons for starting, switching and discontinuing benralizumab treatment. The main objectives/endpoints will be assessed after the 6 month time-point, consistent with guideline recommendations and clinical practice to assess a treatment response after 4-6 months. The follow up at 12 months is to observe the long term effect/consistency of effect over time.
2. OBJECTIVES AND HYPOTHESES

All study analyses will be done separately for the anti-IL5/IL5R naïve and biologic experienced patients, as defined for the purpose of this study:

**Anti-IL5/IL5R naïve patients:**

- Severe eosinophilic asthma patients who have never received anti IL-5/anti IL-5R biologic treatment for severe eosinophilic asthma, for whom the investigator had decided to initiate benralizumab biologic treatment. Patients with previous omalizumab treatment will be analysed in this group if last dose was received > 6 months prior to study inclusion. These patients will be stratified as:
  - Biologic naïve: patients who never received any biologic treatment
  - Anti-IL5/IL5R naïve, with former omalizumab experience: anti-IL5/ILR5 naïve patients who received their last dose of omalizumab > 6 months prior to study inclusion

**Biologic experienced patients:**

- Patients that previously received a biologic treatment for severe asthma (at least one dose). Patients in this group will be stratified for statistical analysis according to the time since the last biologic dose:
  - Direct switcher: last biologic dose received within last 12 weeks prior to benralizumab treatment (≤ 12 weeks)
  - Recent biologic experienced: last biologic dose received between 12 weeks to 6 months prior to benralizumab treatment (> 12 weeks and ≤ 6 months)
  - Former biologic experienced: last biologic dose received > 6 months prior to benralizumab treatment (NB patients who received omalizumab previously with the last dose received > 6 months ago that are also ‘anti-IL5/IL5R naïve patients’ will be analyzed in both groups.)

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Outcome measure</th>
</tr>
</thead>
</table>
| To describe the change in asthma control after 6 months of treatment vs baseline in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment | Change from baseline in ACT score after 6 months treatment in anti-IL5/IL5R naïve patients
Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months |
<p>| Supported by: |</p>
<table>
<thead>
<tr>
<th>Secondary objectives</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>To describe the investigator reported treatment effectiveness after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment</td>
<td>Percentage of anti-IL5/IL5R naïve patients within each category of the global evaluation of treatment effectiveness (GETE) after 6 months of treatment.</td>
</tr>
<tr>
<td>To describe the change in health-related quality of life (HRQL) after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment</td>
<td>Change from baseline in SGRQ total score and domain scores (symptoms, activity and impact score) after 6 months treatment in anti-IL5/IL5R naïve patients. Supported by: Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (decrease of at least 4 units) in SGRQ after 6 months.</td>
</tr>
<tr>
<td>To describe the early treatment response in anti-IL5/IL5R naïve patients initiated with benralizumab treatment</td>
<td>Change from baseline in ACQ-6 score after 7 and 14 days of treatment in anti-IL5/IL5R naïve patients. And Change from baseline in patient satisfaction and patient symptoms (i.e. how bothersome) including cough severity (for patients with cough being a bothersome symptom at baseline), measured on VAS, after 7 and 14 days of treatment in anti-IL5/IL5R naïve patients. And</td>
</tr>
<tr>
<td>Study protocol</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>D3250R00053</td>
<td>03 May 2019</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study objective</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of the maximal response* achieved at Day 7 and Day 14 for ACQ-6 and patient satisfaction/symptoms VAS, in anti-IL5/IL5R naïve patients.</td>
<td>Change from baseline in asthma control at each visit during the study period, using ACQ-6/ACT in anti-IL5/IL5R naïve patients</td>
</tr>
<tr>
<td>*Maximal response as measured at any time point during the first 6 months</td>
<td>Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months that is maintained as such after 12 months</td>
</tr>
<tr>
<td></td>
<td>Percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (reduction of at least 0.5 points) in ACQ-6 after 6 months that is maintained as such after 12 months</td>
</tr>
</tbody>
</table>
| To describe the change of asthma control over time and the maintained response after initiation of benralizumab treatment, in anti-IL5/IL5R naïve patients | Investigator-chosen reasons (selected from predetermined list), for:  
|                                                                             | • Initiation of/switching** to benralizumab at enrolment  
|                                                                             | • discontinuation of benralizumab during the treatment period |
| **The term 'Switch' is used generally to describe treatment change from one biologic to another, regardless of the time since the last dose of the previous biologic. Direct switchers are defined in Section 5.1, page 31 |

**Exploratory objective**

To describe the change in asthma control, HRQL, symptoms, patient satisfaction and treatment effectiveness at early timepoint and after 6 and 12 months Benralizumab treatment in biologic

Change from baseline in ACT, ACQ-6, SGRQ scores at the end of 6 and 12 months treatment; in ACQ-6 and patient satisfaction/patient symptoms (VAS) at 7 and 14 days; and GETE score after 6
Study protocol
D3250R00053

3. METHODOLOGY

3.1 Study Design – General Aspects

This is a prospective, observational, multi-centre, single-country study with a screening/baseline visit plus 5 study visits over 6 months, and 1 follow-up visit at 12 months (Figure 1). The study will be conducted under real-life conditions in the pulmonary care setting in Germany.

Approximately 250 anti-IL5/IL5R treatment naïve (see definition in Section 2), severe eosinophilic asthma patients that meet the eligibility criteria will be enrolled in special care centres and by suitable pulmonologists in Germany in order to achieve the study objectives. During the recruitment period, up to 250 biologic experienced patients (see definition in Section 2) will also be enrolled if they meet the eligibility criteria (minimum of 100 patients should be recruited to this group). The decision to initiate benralizumab treatment or switch to benralizumab treatment will be taken by the investigator, independent of the study.
The study team will identify suitable pulmonology sites. Patients will be identified consecutively over a period of 12 months. For each single subject completing the study, the duration for the whole course will be 12 months including one baseline visit, 5 clinic study visits (over 6-month period), and 1 follow-up visit at 12 months (See Section 6.1.1 for Study Plan). Due to the real-life setting of this study, the study visits will be the regular scheduled clinical visits, and data captured outside of the regular clinical visits of treatment will be collected using a patient electronic PRO (ePRO) and smart phone, at home. No exact schedule of the study visits will be defined within the observational plan, but all patients will complete the study over 12 months and study visits should occur approximately every month (visits 1-3), then every 2 months (visits 4 and 5), then at 12 months (follow-up visit). Exact timing of study visits depends only on the decision made by the investigator.

Patients are assigned to benralizumab within current best practice and not according to a randomized trial protocol. Every medical decision and course of treatment will reflect exclusively the decision of the investigator in a routine clinical situation according to the Summary of Product Characteristics of the corresponding medicinal products. There are no dose regimens or diagnostic procedures pre-defined within this study plan. The concept of this observational, real-life study and its documentation procedure will not affect the routine treatment situation in any way.
Site staff will collect all necessary information from the patient’s medical record to determine eligibility for enrolment. Consecutively, adult patients with a diagnosis of severe asthma according to the American Thoracic Society/European Respiratory Society (ATS/ERS) and local German guidelines will be screened and those who meet all inclusion criteria and none of the exclusion criteria will be invited to participate, consented and enrolled.

The investigator will collect data from medical records, examination results or conducting interviews at every study visit. All data will be collected and documented in an electronic Case Report Form (eCRF). In addition, the patient will be asked to provide PRO data on HRQL (SGRQ) and asthma control (ACT, ACQ-6) questionnaires. In addition, patient asthma control (ACQ-6), treatment satisfaction level and symptoms (how bothersome) will be captured on day 7 and 14 (home-recorded) and throughout the study. For those patients with cough being a bothersome symptom at baseline, severity of cough will be also recorded. Patient physical activity levels (in anti-IL5/IL5R naïve patients) will be measured as steps per day, recorded on a dedicated armband device (a minimum of 4 days baseline data will be required for patients to participate in this sub-study).

3.2 Study Population

Male and female patients aged $\geq$ 18 treated by pulmonary specialists with diagnosed asthma defined severe according to the ATS/ERS and local German guidelines [2,3], that are intended to be treated with benralizumab biologic treatment for severe eosinophilic asthma, and require a change in treatment for severe eosinophilic asthma (initiation of biologic/switch from one biologic to another)

The decision to change (initiate or switch) to a biologic treatment has to be made by the investigator according to the subject’s medical need and a positive benefit/risk balance. The decision is not part of the study, lies with the treating physician and is taken according to the standard of current best medical practice and national guidelines.

3.3 Inclusion Criteria

Patients will only be included in the study if they meet the following Inclusion criteria:

- Male or female patients aged 18 years or older with confirmed diagnosis of severe asthma according to the ATS/ERS and local German guidelines [2,3]
- Decision was made by the investigator (regardless of this NIS) to start treating the patient with benralizumab according to severe eosinophilic asthma indication (NB: can include patients that are switched from another EU approved biologic treatment if required for a medical reason).
- Patients must be able and willing to read and comprehend written instructions, and comprehend and complete the questionnaires required by the protocol
- After full explanation, patients must have signed an informed consent document indicating that they understand the purpose of and the procedures required for the study and are willing to participate in the study.
3.4 **Exclusion Criteria**

Patients who meet any of the following criteria will not be eligible to participate in the study:

- Concomitant treatment with any other biologic for any indication
- Patients already treated with benralizumab
- Clinically important pulmonary disease other than asthma including: chronic obstructive pulmonary disease (as main diagnosis), bronchiectasis, idiopathic pulmonary fibrosis, pulmonary hypertension, alpha-1-antitrypsin-deficiency, and malignancy of any kind (NB: the following conditions are permitted: nasal polyposis, allergic rhinitis, atopic dermatitis, non-idiopathic pulmonary fibrosis).
- An acute or chronic condition that, in the investigator’s opinion, would limit the patient’s ability to complete questionnaires or participate in this study or impact the interpretations of results.
- Concurrent biologics for asthma are not allowed except for stable allergen immunotherapy (defined as a stable dose and regimen at the time of enrolment). Acceptable wash-out periods for other asthma biologics:
  - ≥30 days from last dose of previous biologic
- Pregnancy or lactation period
- Participation in an observational trial that might, in the investigator’s opinion, influence the assessment for the current study, or participation in a randomized clinical trial in the last 3 months

3.5 **Participant Follow-up**

The patient follow-up period will be from the screening/baseline visit when consent is provided to collect baseline data until death, loss to follow-up, withdrawal of consent or study end date at 12 months (whichever occurs earlier). The key follow-up period for primary endpoint data collection will be from the first dose of biologic therapy (Day 0 at Visit 1) to 6 months. During the study period, patients who switch to another therapy due to a medical need will be considered drop-outs and will not be followed up during the study. Patients may withdraw consent at any time without prejudice to their further treatment.

4. **VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS**

4.1 **Exposures**

The imPROve asthma study is an observational study that will be conducted in a real-life setting in Germany and is not designed to evaluate specific medicinal products given according to a specific randomized schedule. Exposure data collected in this study will be on benralizumab biologic treatment indicated for severe eosinophilic asthma as part of routine medical care; the decision to prescribe it will be made by the investigator according to the subject’s medical need...
and a positive benefit/risk balance. The decision is not part of the study, lies with the treating physician and is taken according to the standard of current best medical practice and national guidelines.

4.2 Data collection

Data captured in this study will be derived from primary and secondary data collection. Primary data collection includes PROs, patients’ interview and physical activity. All other data will be documented based on the existing medical records (secondary data collection), either historically or throughout the study. Timing and type of visit is described in Table 1 (Section 6.1.1).

4.2.1 Primary data collection

Primary data collection includes the following:

- Investigator-reported reasons for initiating/switching to benralizumab treatment and treatment discontinuation, using a pre-defined checklist
- Treatment adherence during study period (date of benralizumab injections; investigator-assessed)
- Patient reported asthma control assessed using the ACT and ACQ-6.
- Patient-reported HRQL assessed using the SGRQ
- Patient-reported satisfaction with treatment using a VAS
- Patient-reported assessment of symptoms (how bothersome) using VAS
- Patient-reported assessment of severity of cough using VAS (only evaluated in patients with cough being reported as bothersome symptom at baseline)
- Patient-reported nasal polyposis symptoms and sense of smell using VAS (only evaluated in patients with nasal polyposis according to medical records)
- Investigator-reported treatment effectiveness using GETE
- Physical activity assessed by number of steps per day in anti-IL5/IL5R naïve patients (a minimum of 4 days baseline data will be required for patients to participate in this sub-study)
- As benralizumab is an AstraZeneca (AZ) product, serious adverse events and adverse drug reactions will be monitored during the study

4.2.2 Secondary data collection

Secondary data collection will be documented from the patients’ medical records and includes:

- Patient baseline characteristics (demographics, smoking history, physical examination)
- Asthma medication during prior 12 months and during the study including dose and start/stop dates including but not limited to: All EU-approved and standard of care treatments for asthma (e.g., short-acting beta agonists, ICS, LABA, long-acting muscarinic antagonists, short-acting muscarinic antagonists, ICS/LABA, leukotriene inhibitors, OCS)
- Concomitant medications
4.3 Outcomes

Due to the real life setting of this study, the outcome measurements will be kept as close as possible to the routine assessments conducted in Germany. Most of the tools are either commonly used by severe asthma centers to assess treatment response or have been explicitly recommended by the independent scientific committee to complement existing treatment tools by the additional use of simple tools to allow assessment of early response or change in physical activity.

4.3.1 Asthma control

4.3.1.1 Asthma Control Test (ACT)

The ACT will be used to assess change from baseline in asthma control during the study period and will be the variable used to assess the primary outcome measure of change from baseline in asthma control after 6 months treatment in patients initiated with benralizumab biologic therapy. ACT is a simple, validated, 5-item tool giving a total score from 5 (worst control) to 25 (best control) [22] (Appendix 1). Scores of 20 to 25 denote well-controlled asthma, scores ≤19 identifies patients with poorly controlled asthma [23]. The minimum clinically important difference (MCID) is reported to be 3 points [24]. ACT will be collected during routine clinic visits during the study (Baseline/Day 0, 1 month, 2 months, 4 months, 6 months and 12 months).

4.3.1.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 will be used to assess change from baseline in asthma control during the study period and will also be used to assess the primary outcome measure of change from baseline in asthma control after 6 months treatment. ACQ-6 is a validated questionnaire based on 5 symptoms questions (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing), and daily rescue bronchodilator use [25] (Appendix 2). Each item is scored on a 7-point scale (0=no impairment; 6=maximum impairment), and the ACQ score is the mean of
these items. The MCID is greater than or equal to 0.5 [25]. ACQ-6 will be collected during routine clinic visits during the study (Baseline/Day 0, 1 month, 2, 4, 6 and 12 months) and at home on day 7 and 14 of treatment using an ePRO.

4.3.2 Health-related quality of life (HRQL)

4.3.2.1 St George’s Respiratory Questionnaire

HRQL will be measured using the SGRQ to assess the change from baseline in HRQL after 6 months. SGRQ is a validated, 50-item questionnaire, giving scores ranging from 0 (best health status) to 100 (worst health status) [26] (Appendix 3). The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. A difference of four units in the SGRQ total score is considered the MCID [27]. SGRQ will be collected during routine clinic visits during the study (Baseline/Day 0, 1 month, 6 months and 12 months).

4.3.3 Investigator-reported reasons for change in therapy

Investigator-reported reasons for initiating/switching to benralizumab treatment and discontinuation during the study will be documented, using a pre-defined checklist (investigators may choose up to 2 reasons, stipulating them in order of importance):

Reasons for benralizumab initiation in biologic naïve patients (i.e. has not received a biologic therapy for severe asthma ever):

What was the main reason/reasons to initiate biologic treatment (choose up to two marked in order of importance as 1 (most important) and 2 (second most important))?

- Patient is uncontrolled with previous treatment. If so, what's the most concerning aspect?
  - Recurring Exacerbations
  - Reduced Lung function
  - Ongoing Symptoms
  - Requires chronic use of OCS to maintain some control
- Patient is only partially controlled with previous treatment. If so, what's the most concerning aspect?
  - Recurring Exacerbations
  - Reduced Lung function
  - Ongoing Symptoms
  - Requires chronic use of OCS to maintain some control
- Need to reduce OCS treatment to avoid Side effects
- Availability of new precision medications (Biologics)
- Other (please specify)

What was the main reason to choose benralizumab (choose up to two marked in order of importance as 1 (most important) and 2 (second most important))?
• Near complete EOS depletion
• Patient’s characteristics may predict good response to benralizumab
• Convenience of use (dosing schedule, mode of administration)
• Patient's preference
• Other (please specify)

Reasons for Benralizumab initiation in Biologic experienced patients (received a biologic treatment for severe asthma at any time previously (at least one dose)):

What was the main reason to discontinue the previous biologic for severe asthma (choose up to two marked in order of importance as 1 (most important) and 2 (second most important))?

• Patient is uncontrolled with previous treatment. If so, what's the most concerning aspect?
  o Recurring Exacerbations
  o Reduced Lung function
  o Ongoing Symptoms
  o Requires chronic use of OCS to maintain some control
• Patient is only partially controlled with previous treatment. If so, what's the most concerning aspect?
  o Recurring Exacerbations
  o Reduced Lung function
  o Ongoing Symptoms
  o Requires chronic use of OCS to maintain some control
• Patient was not able to achieve OCS reduction goal
• Side effects with previous biologic
• I don’t know, decision taken by previous HCP
• Other (please specify)

What was the main reason to choose Benralizumab (choose up to two marked in order of importance as 1 (most important) and 2 (second most important))?  

• Near complete EOS depletion
• Patient’s characteristics may predict good response to benralizumab
• Convenience of use (dosing schedule, mode of administration)
• Patient's preference
• Availability of this new treatment option
• Other (please specify)

Reasons for Benralizumab discontinuation (choose up to two marked in order of importance as 1 (most important) and 2 (second most important)):

• Patient is uncontrolled. If so, what's the most concerning aspect?
  o Recurring Exacerbations
Patient-reported satisfaction and symptoms

During the study patients will be asked about their satisfaction with treatment and how bothersome they find their symptoms (including which is most bothersome symptom) using a VAS (Figure 2). Both will be recorded at each study visit in the clinic and at home on day 7 and 14 of treatment using an ePRO.

- Reduced Lung function
- Ongoing Symptoms
- Requires chronic use of OCS to maintain some control

- Patient is only partially controlled. If so, what's the most concerning aspect?
  - Recurring Exacerbations
  - Reduced Lung function
  - Ongoing Symptoms
  - Requires chronic use of OCS to maintain some control

- Patient was not able to achieve OCS reduction goal
- Side effects
- Other (please specify)
Figure 2 VAS assessments for patient satisfaction and asthma symptoms

**VAS Patient Satisfaction**
Overall how satisfied with your treatment are you today?

- Extremely satisfied
- Not at all satisfied

**VAS Symptoms**
Overall how much are your asthma symptoms bothering you today?

- Not at all bothersome
- Extremely bothersome

Which of these symptoms was most bothersome?

- Wheeze
- Shortness of breath
- None
- Cough
- Chest tightness or pain

Additionally, for those patients who at baseline report cough as a bothersome symptom, they will be required to assess the severity of their cough by means of a VAS scale (Figure 3). The cough VAS is a linear scale on which patients indicate the severity of their cough, from “worst cough ever”, to “no cough”. Patients will be requested to mark on the scale to indicate the severity of their cough in the last week.

**Figure 3: VAS Cough**
4.3.5 Nasal polyposis symptoms and sense of smell

In patients with nasal polyposis, based on medical records, nasal polyposis symptoms and sense of smell will be evaluated through a VAS. The following nasal polyposis symptoms will be evaluated: nasal blockage, difficulty with sleeping due to nasal symptoms, headache/pressure on the face. These symptoms and loss of smell will be scored on a VAS ranging from 0 to 10 with 0 being not at all bothersome and 10 being extremely bothersome (Figure 4).

The questionnaire will be completed at baseline (how bothersome over last 12 months) and at 6 months.
Figure 4: VAS assessments for nasal polyposis symptoms and sense of smell

How bothersome were the following symptoms in the past 12 months (baseline)/ last 6 months (Visit 5)?

1. Nasal blockage/nasal congestion

   0                      10
Not at all            Extremely

2. Headache/pressure on the face

   0                      10
Not at all            Extremely

3. Loss of smell

   0                      10
Not at all            Extremely

4. Difficulty with sleeping due to nasal symptoms

   0                      10
Not at all            Extremely

4.3.6 Administration of ePRO questionnaires

The following PRO questionnaires will be electronically administered in this study at site: ACT, SGRQ, VAS symptoms, VAS satisfaction, VAS cough (when cough is a bothersome symptom at baseline), VAS for nasal polyposis symptoms and smell (will only be evaluated in patients with nasal polyposis according to medical records).

ACQ-6 will be administered in paper format. In addition, patient asthma control (ACQ-6), treatment satisfaction level and symptoms will be captured on day 7 and 14 be by the patients at home using handheld devices provided on baseline visit by the investigator. Each study site must allocate the responsibility for the administration of the ePROs to a specific individual (e.g., a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent. Patients will complete the PROs (ACQ-6 (paper format) ACT, SGRQ, VAS symptoms, VAS satisfaction, VAS Cough (when cough is a bothersome symptom at baseline) and VAS for nasal polyposis symptoms and smell (in patients with nasal polyposis according to medical records) (electronic format) [see Section 6.1.1]) at study sites. Assessment on day 7 and 14 will be self-administered at home by the patient using handheld devices.
4.3.7  **Global evaluation of treatment effectiveness (GETE)**

At the end of 6 months of treatment during the study period, investigators will complete the GETE measure. GETE grades overall treatment effectiveness using the following criteria: excellent (complete control of asthma); good (marked improvement of asthma); moderate (discernible, but limited improvement in asthma); poor (no appreciable change in asthma); or worsening (of asthma).

4.3.8  **Treatment adherence**

The date of benralizumab injections will be captured during the study. In addition, adherence to other asthma medication will be confirmed by the investigator (yes/no) at each clinic visit during the study period.

4.3.9  **Physical activity**

Physical activity (step counts per day) will be measured from enrollment and continuously until the end of the study in anti-IL5/IL5R naïve patients who consent to record this measurement, using a dedicated armband device (activity tracker). To assess the change from baseline in steps per day, patients will be required to wear the dedicated activity tracker for minimum of 4 days before first benralizumab dose. Armbands will be handed out at enrollment, to allow physical activity measurements before first benralizumab dose, when applicable. The patients will wear an activity tracker (e.g. Fitbit, vivofit®) on the wrist during the entire observation period. The device (tracker) will be given to the patient at enrollment visit at study site. The devices are checked and calibrated and the date and time are set correctly. The time spent wearing the device will be recorded so that steps per wearing time can be calculated. Each tracker will have a unique number (serial no.), enabling clear assignment to the patient ID. Patients who are willing to participate need to install the tracker App (e.g. FitBit App) on their own mobile device which will facilitate the collection of data from the patient. The data will be transmitted subsequently to the App owner that will transmit only the steps per day to the study database via a secured interface. All unused devices will be returned to the sponsor. All used devices shall be returned to the sponsor. Before returning all settings need to be reset to factory settings by the sites to ensure that all patient’s data are deleted.

4.3.10  **Asthma exacerbations**

The number of asthma exacerbations in the last 12 months (prior to study) and during the 12 months study period will be collected. Asthma exacerbations are defined as a worsening of asthma symptoms that leads to one of the following: (1) use of systemic corticosteroids (i.e. hydrocortisone or methylprednisolone) for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids, (2) an emergency room visit (<24h) due to asthma that required systemic corticosteroids; or (3) hospitalization (≥24 hours). In addition, the length of hospitalizations (number of days) due to asthma will be documented.
4.4 Other Variables and Covariates

Not applicable

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

The analyses will be of purely descriptive character since no hypotheses have been pre-specified. Hence it is not necessary to correct for multiple testing. Variables will be analyzed with appropriate statistical methods; categorical variables by frequency tables and continuous variables by sample statistics (i.e. n, mean, standard deviation, minimum, median, maximum). The proportion of missing data will be reported for each measured variable in the study. Stratified analyses on baseline characteristics like gender, age and previous treatments (anti IL-5, anti-igE) will be done if reasonable (by patient number and distribution between sub groups). Apart from the mentioned analyses post-hoc analyses will be possible if the data give rise to scientifically interesting questions. Details of the planned analyses will be given in the statistical analysis plan (SAP).

The analysis populations will be:

- **ITT (intent-to-treat set) = SAF (safety set):** All patients who gave informed consent and received at least one dose of benralizumab.
- **Anti-IL5/IL5R naïve:** All anti-IL5/IL5R naïve patients who gave informed consent, received at least one dose of benralizumab and completed visit 2.
- **PES (primary endpoint set):** All anti-IL5/IL5 naïve patients who gave informed consent, received at least one dose of benralizumab and for whom asthma control data is available at baseline and after 6 months.
- **Biologic experienced:** All biologic experienced patients who gave informed consent and received at least one dose of benralizumab.

*Anti-IL5/IL5R naïve patients:*

- Severe eosinophilic asthma patients who have never received IL-5/IL-5R treatment for severe asthma, for whom the investigator had decided to initiate benralizumab biologic treatment. Patients in this group may have taken omalizumab previously if the last dose was received > 6 months prior to study inclusion. These patients will be stratified as:
  - Biologic naïve: patients who never received any biologic treatment
  - Anti-IL5/IL5R naïve, with former omalizumab experience: anti-IL5/ILR5 naïve patients who received their last dose of omalizumab > 6 months prior to study inclusion

*Biologic experienced patients:*

Last updated: 22 October 2018
Parent SOP: LDMS_001_00164328
Patients that previously received a biologic treatment for severe asthma (at least one dose). Patients in this group will be stratified for statistical analysis according to:

1. the time since the last biologic dose:
   - Direct switcher: last biologic dose received within last 12 weeks prior to benralizumab treatment (≤ 12 weeks)
   - Recent biologic experienced: last biologic dose received between 12 weeks to 6 months prior to benralizumab treatment (> 12 weeks and ≤ 6 months)
   - Former biologic experienced: last biologic dose received > 6 months prior to benralizumab treatment (NB patients who received omalizumab previously with the last dose received > 6 months ago that are also ‘anti-IL5/IL5R naïve patients’ will be analyzed in both groups.)

2. class of previous biologics:
   - Anti-IL5
   - Anti-IgE

5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

The primary objective of this study is to describe the change in asthma control after 6 months of treatment vs baseline in anti-IL5/IL5 naïve patients with severe eosinophilic asthma initiated with benralizumab biologic treatment in pulmonary care centres in Germany in a real-life setting. The mean change in asthma control from baseline to month 6 will be analyzed as difference of the ACT score and the ACQ score after 6 months and baseline, respectively. Sample statistics for the mean change will be provided as well as the 95% confidence interval. Furthermore the percentage of anti-IL5/IL5 naïve patients with a clinically meaningful improvement in ACT score respective ACQ after 6 months, (i.e. an increase from baseline of at least 3 points) and the percentage of anti-IL5/IL5 naïve patients with a clinically meaningful improvement ACQ-6 (i.e. a decrease from baseline of at least 0.5 unit), will be calculated.

5.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

- To describe the investigator reported treatment effectiveness after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment
- To describe the change in HRQL after 6 months of treatment in anti-IL5/IL5R naïve patients with severe eosinophilic asthma initiated with benralizumab treatment.
- To describe the early treatment response in anti-IL5/IL5R naïve patients initiated with benralizumab treatment.
- To describe the change of asthma control over time after initiation of benralizumab treatment in anti-IL5/IL5R naïve patients.
To assess the reasons for biologic treatment change, as reported by the investigator.

For all points in time of interest the 95% confidence interval will be shown for the mean change in asthma control and HRQL (SGRQ) from baseline to the respective point in time. The mean change in ACQ-6/ACT (calculated from the mean changes from baseline at each of visits 1 to 5) will be used to determine the time course of change (onset and maintenance of effect). In addition, the percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months and that maintain it after 12 months will be determined, as well as the percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (decrease of at least 0.5 points) in ACQ-6 after 6 months and that maintain it after 12 months. Besides, a cross table of months 6 and 12 will show, how many patients, respectively, did respond (improvement of ≥ 3 points), worsen (deterioration of ≥ 3 points) or show no change (change between -3 points and 3 points) according to ACT as well as how many patients, respectively, did respond (decrease of ≥ 0.5 points), worsen (increase of ≥ 0.5 points) or show no change (change between -0.5 points and 0.5 points) according to ACQ. In addition, the percentage of well-controlled (ACQ score <0.75 respective ACT score 20-25), partly controlled/not well-controlled (ACQ score ≥0.75 and <1.5/ ACT score 16-19) and poorly-controlled (ACQ score >1.5 respective ACT score 5-15) anti-IL5/IL5R naïve patients will be given at each point in time, respectively. Furthermore, the percentage of anti-IL5/IL5R naïve patients with a clinically meaningful improvement (decrease of at least 4 units) in SGRQ after 6 months will be derived. A cross table of months 6 and 12 will show, how many patients, respectively, did respond (improvement of ≥ 4 units), worsen (deterioration of ≥ 4 units) or show no change (change between -4 units and 4 units).

Additionally the maximum increase and the point in time it was reached will be calculated per patient and the percentage of patients with maximal increase will be given for each visit during the first 6 months, respectively. The level of response achieved at early time-point, measured as % of the maximal response achieved at Day 7 and Day 14 for ACQ-6 and patient satisfaction/symptoms VAS, in anti-IL5/IL5R naïve patients will be calculated.

The percentage of anti-IL5/IL5R naïve patients within each category of the GETE after 6 months of treatment will be described.

VAS will be analyzed giving mean, standard deviation, median, minimum and maximum. Questionnaires will be analyzed according to the respective manual.

5.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

- To describe the change in asthma control, HRQL, symptoms, patient satisfaction and treatment effectiveness at early timepoint and after 6 and 12 months treatment in biologic experienced patients (as defined in Section 5.1)
To describe the change of physical activity over time in patients with severe eosinophilic asthma treated with benralizumab in anti-IL-5/IL5R naïve patients.

It will also be analysed how many biologic experienced patients took which EU approved biologic treatment for severe eosinophilic asthma prior to benralizumab. The respective biologic experienced patient groups will be analysed descriptively for their change in asthma control, HRQL, symptoms, patient satisfaction and treatment effectiveness at early timepoint and after 6 and 12 months therapy. Furthermore the percentage of patients with a clinically meaningful improvement (increase of at least 3 points) in ACT after 6 months that maintain it after 12 months will be given as well as the percentage of patients with a clinically meaningful improvement (decrease of at least 0.5 units) in ACQ-6 after 6 months that maintain it after 12 months. Besides, a cross table of months 6 and 12 will show, how many patients, respectively, did respond (improvement of ≥ 3 points), worsen (deterioration of ≥ 3 points) or show no change (change between -3 points and 3 points) according to ACT as well as how many patients, respectively, did respond (decrease of ≥ 0.5 points), worsen (increase of ≥ 0.5 points) or show no change (change between -0.5 points and 0.5 points) according to ACQ. In addition, the percentage of well-controlled (ACQ score <0.75 respective ACT score 20-25), partly controlled/not well-controlled (ACQ score ≥0.75 and <1.5/ ACT score 16-19) and poorly-controlled (ACQ score ≥1.5 respective ACT score 5-15) biologic experienced patients will be given at each point in time, respectively. A cross table of months 6 and 12 will show, how many patients, respectively, respond (improvement of ≥ 4 units), worsen (deterioration of ≥ 4 units) or show no change (change between -4 units and 4 units). Additionally, the maximum increase and the point in time it was reached will be calculated per patient and the percentage of patients with maximal increase will be given for each visit during the first 6 months, respectively. The level of response achieved at early time-point, measured as % of the maximal response achieved at Day 7 and Day 14 for ACQ-6 and patient satisfaction/symptoms VAS will be calculated. Furthermore, the percentage of biologic experienced patients with a clinically meaningful improvement (decrease of at least 4 units) in SGRQ after 6 months will be derived as well as the percentage of biologic experienced patients within each category of the GETE after 6 months of treatment.

Physical activity will be analyzed as number of steps per day in anti-IL5/IL5R naïve patients. The median change from baseline of physical activity will be determined at each month, respectively (a minimum of 4 days baseline data will be required for patients to participate in this sub-study). Further details will be given in the SAP.

In addition to the exploratory objectives, the impact of

- Baseline OCS use (yes/no)
- History of nasal polyposis (yes/no)
- Lung function based on prebronchodilator FVC (<65% vs ≥65% predicted)
- Prior exacerbation history (≤2 vs ≥3)
- Age at asthma diagnosis (< vs ≥18 years)
on change from baseline in ACT after 6 months as well as on response (measured as (i) any increase of the ACT score of at least 3 points and (ii) any increase of the ACT score) in anti-IL5/IL5R naïve patients will be analyzed using regression models, if the respective size of the subgroup is sufficient, i.e. if 20 patients per variable are available.

5.2 Bias

5.2.1 Methods to Minimize Bias

- Despite the attempt to achieve a geographically diverse study cohort from a mix of hospital-based and office-based sites, the study sites will nonetheless be selected as a non-probability sample from the healthcare provider population of inference. As such, the generalizability of the study results will be unknown. However, representativeness of the study cohort will be examined in part by comparing provider and patient characteristics to other cohorts described in the medical literature or other sources.

- Recruitment through clinical practice could lead to enrolment bias in the study population towards those with more frequent healthcare utilization or with a greater interest in clinical research. In order to minimize selection bias at each site, eligible patients will be enrolled consecutively at each site with a maximum quota per site.

- The real-life setting within the study design prohibits predefined study visits and study examinations, therefore the findings generated from this study are subject to biases, for example patient recall bias and missing data from medical record review. Healthcare providers and patients will be actively engaged on an ongoing basis to minimize missing data.

- Use of the patient digital platform may be subject to biases by patients who own and are familiar with a suitable digital platform versus those who do not. However, a digital platform will be offered for patients that cannot or don’t want to use their own device, to minimize this bias.

5.2.2 Adjustment for Multiple Comparisons

The analyses will be of purely descriptive character since no hypotheses have been pre-specified. Hence it is not necessary to correct for multiple testing.

5.2.3 Strengths and Limitations

The major strength of this study is its real-world nature and the collection of data during routine clinical practice with minimal constraints of inclusion/exclusion criteria. In addition, the collection of data directly from the patients through the PRO questionnaires, plus the collection of data in the natural environment using a patient digital platform, will provide a unique
perspective and enables the collection of HRQL outcomes, symptom assessments, new endpoint of interest i.e. physical activity, as well as symptom assessments at day 7 and 14, that may not be recorded by healthcare providers.

The use of ACT will provide asthma control assessment using a tool that is most commonly used in the day to day clinical practice by Pulmonologists in Germany. This study will also provide an opportunity to explore the usefulness of new tools in assessing the early response to treatment as currently there are few established PRO tools available.

Despite the above-mentioned strengths of the study approach, this study is subject to limitations as all studies are:

- Biases mentioned in 5.2.1, which will occur although actions are taken to keep them small.
- As with any non-interventional study, testing and procedures are performed according to standard clinical practice and are not mandated. As a result, not all patients will contribute data to all outcomes of interest.
- Despite the planned large sample size, some subgroup sample sizes may be too small for meaningful interpretation of data.
- Interpretation of the results might be hampered by missing data. Therefore, the results have to be interpreted carefully. Potential sources and extent of bias will be discussed in detail in the study report.

5.3 Interim Analyses
An interim analysis is planned after the recruitment is finished. Descriptive analyses will be performed on accruing baseline data to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the cohort studied.

5.4 Sample Size and Power Calculations
With no formal a priori hypotheses, this study uses a hypothesis-free approach focused on descriptive analyses. Thus, power calculation for any specific outcome is not strictly relevant. It is planned to enroll approximately 500 patients, 250 anti-IL5/IL5R treatment naïve patients with diagnosis of severe eosinophilic asthma, with investigators decision to start biologic treatment for severe eosinophilic asthma in Germany, and up to 250 biologic experienced (refer to definition in Section 5.1) patients (minimum of 100 patients should be recruited to this group). The sample size of approximately 250 patients is driven by the need to enroll an adequate number of patients to address the mentioned objectives, also across various subgroups of interest.
with sufficient precision. The sample size will ensure that the descriptive data mandated by the primary and secondary endpoints are sufficiently precise and meaningful at a subgroup level.

6. **STUDY CONDUCT AND REGULATORY DETAILS**

6.1 **Study Conduct**
A summary of the procedures conducted at each study visit is shown in Table 1.
### 6.1.1 Study Plan

#### Table 1: Study Plan

<table>
<thead>
<tr>
<th>study Visits&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Enrollment</th>
<th>1/Baseline&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Home - recorded</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-point</td>
<td>≤0</td>
<td>0</td>
<td>Day 7 and Day 14</td>
<td>Month 1</td>
<td>Month 2</td>
<td>Month 4</td>
<td>Month 6</td>
<td>Month 12</td>
</tr>
</tbody>
</table>

#### General procedures and medical history

<table>
<thead>
<tr>
<th>Informed consent</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
</tr>
<tr>
<td>Medical and asthma history</td>
<td>X</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
</tr>
</tbody>
</table>

#### Asthma medication

| Asthma medication during last 12 months | X |
| Adherence to medication | X | X | X | X | X | X |
| Reason for initiation of benralizumab treatment | X |
| Reason for discontinuation of Benralizumab, if applicable | (X) | (X) | (X) | (X) | (X) |
| Change in concomitant medications (including all asthma medications and OCS use including dose) since last visit | X | X | X | X | X |
### Investigator-reported GETE

<table>
<thead>
<tr>
<th>Patient-reported outcomes</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ACQ-6</td>
<td></td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td>X³</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Patient treatment satisfaction VAS</td>
<td></td>
<td>X³</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient symptom VAS</td>
<td></td>
<td>X³</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient-reported nasal polyposis VAS</td>
<td></td>
<td></td>
<td></td>
<td>X³</td>
<td></td>
</tr>
</tbody>
</table>

### Lung function (if measurements available as part of routine care)

| FEV₁                                   |     |     | X³  |     | X   |
| FVC                                    |     |     | X³  |     |     |

### Biomarkers (if measurements available as part of routine care)

| EOS, IgE                               |     |     |     | X³  |     |
| FeNO                                   |     |     |     | X³  |     |

### Physical activity

| Number of steps per day                |     |     | X²  |     |     |
| Number of exacerbations                | X³  |     | X³  |     |     |

| Number of exacerbations (last 12 months) |     |     | X³  |     |     |

---

1. As described in study design, assessments are captured during routine study visits and at home.
2. Enrollment /baseline Visit and Visit 1 may be on same day.
3. Baseline measurements should be taken at the closest timepoint before the first injection.
4. VAS for severity of cough will be also assessed for those patients who report cough as a bothersome symptom at baseline.
5. Nasal polyposis symptoms and smell will only be evaluated in patients with nasal polyposis according to medical records.
6. Anti-IL5/IL5R naïve patients only; armbands will be handed out at enrollment, to allow physical activity measurements before first Benralizumab dose, when applicable. A minimum of 4 days baseline data will be required for patients to participate in this sub-study.
7. Exacerbations defined as a worsening of asthma symptoms that leads to one of the following: (1) use of systemic corticosteroids (i.e. hydrocortisone or methylprednisolone) for 3 days or more or a temporary increase in a stable, background dosage of oral corticosteroids, (2) an
emergency room visit (<24h) due to asthma that required systemic corticosteroids; or (3) hospitalization (≥24 hours). The length of hospitalizations (number of days) due to asthma will be documented.

ACQ-6: Asthma Control Questionnaire-6; ACT: Asthma Control Test; EOS: eosinophils; FU: Follow-up; FEV₁: forced expiratory volume in 1 sec; FVC: forced vital capacity; GETE: Global evaluation of treatment effectiveness; IgE: Immunoglobulin E; SGRQ: St George’s Respiratory Questionnaire; VAS: visual analogue scale
6.1.2 Procedures

Study procedures to be performed at each visit are summarized in the Study Plan, Section 6.1.1 with more details on individual outcomes given in Section 4.3. Details of the PRO questionnaires are shown in Appendices 1 (ACT), 2 (ACQ-6) and 3 (SGRQ).

6.1.2.1 Procedures for voluntary withdrawal/discontinuation

Patients may withdraw their consent to be in the study at any time without prejudice to their further treatment. Patients who discontinue should be asked about the reason(s) for their discontinuation. If possible, they should be seen and assessed by the Investigator according to current practice. Any home-collected data should be returned to the investigator where possible. The reason for withdrawal should be documented in the database (eCRF) (e.g. safety reason/change of address/death/voluntary withdrawal). If the reason for withdrawal is a safety event, the safety event must be reported as per Section 6.3. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient other than the reason for withdrawal.

6.1.2.2 Early termination of study

Should AZ decide to discontinue the study prior to the date established in this protocol, the patients, investigators, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date. The investigator will immediately notify the patients taking part in the study; they will continue to receive their treatment according to usual clinical practice.

6.1.3 Quality Control

6.1.3.1 Data management

AZ will develop a Data Management Plan (DMP) and a website database platform for the purpose of this study. DMP will be created before data collection begins and will describe 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. Investigators directly through eCRF will perform data entry, hence each of them will be provided with system credentials. Regional and Local Study team, National Coordinators and investigators will be system users allowing different functions on database according individual profiles. The investigator or appropriately authorized staff must enter all clinical study data for every subject. The patient questionnaires will be filled by the patient during the study visit in electronic versions. The principal investigator will sign and date the subject’s eCRF after completion. After completing eCRF, investigator should print the form for each patient. The investigator will store his/her copy with the rest of the original data as required.
6.1.3.2 Monitoring activities

Before the first subject is recruited into the study, the local Marketing Company (MC), MEOR Delivery Director, MEOR Operations Lead or Contract Research Organisation (CRO) representative will:

- Establish the adequacy of the facilities and the investigator’s capability to appropriately select the sample
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AZ or its representatives. This will be documented in an Observational Study Primary Agreement between AZ/delegate and the investigator.

During the study the local MC representative or delegate can implement different activities to assure compliance with AZ standards of quality. These activities could include but are not limited to:

**Contacts with the sites to:**

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the eCRFs
- Ensure that the subject informed consent forms are signed and stored at the investigator’s site
- Ensure that the eCRFs are completed properly and with adequate quality.

**Monitoring activities for:**

- Checking of Informed Consent Forms (ICFs)
- Checking that subjects exist in medical records

The extent and nature of monitoring will be decided during the study planning based on design, complexity, number of subjects, number of sites, etc. Observational Research Center (multi country) /Marketing Company will give some recommendations that could be locally adapted. Different signals (e.g. high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators.

If these or any other signal occurs or if the local coordinator is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

**Training of Study Site Personnel**

- At least one meeting with local CRO / local AZ Medical staff will be held prior to the study start, and periodical meetings may be held through the study with the CRO / AZ study team
- An investigator meeting will be held, Local AZ medical staff/CRO will be responsible of inviting and logistics. Training will be conducted by CRO / AZ study team.
- Initiation visits will be performed during the investigator meeting by CRO and will include detailed review of protocol, eCRF and patients’ questionnaires, study procedures and study calendar. For those principal investigators who cannot attend to the investigator
meeting, initiation will be performed remotely by phone (or as required by local regulations).

- The activation of centres will be done by mail and personally by phone. This would mean the kick off for enrolment. All regulatory and study files should be on place and initiation and investigator meeting performed.

The Principal Investigator will ensure that appropriate training relevant to the Observational Study is given to investigational staff, and that any new information relevant to the performance of this Observational Study is forwarded to the staff involved.

### 6.1.4 Storage and retention

Upon completion of Data Base Lock and at the agreed time point, data from the imPROve asthma Study database will be transferred to AZ via a secure file transfer portal in the pre-agreed format.

All original source documentation is expected to be stored at the site for the longest possible time as required by local applicable regulations or as specified in the contract, whichever is longer. The records must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived following the study conclusion, according to local regulations or as specified in the contract, whichever is longer.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national regulations. Essential documents include:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals for the study protocol and all amendments
- All source documents
- eCRF contents
- Patients’ or next of kin/legal representative’s ICFs (with study number and title)
- Any other pertinent study document.

AZ will notify the investigators/institutions when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify AZ.

### 6.2 Protection of Human Subjects

The Observational Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation, Good Clinical Practices, Good Pharmacoepidemiology Practice and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

The Investigator will perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how.
The final protocol of the Observational Study, including the final version of the Subject Informed Consent Form, must be approved or given a favourable opinion in writing by the IRB/IEC.

The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

### 6.2.1 Subject Informed Consent (Primary Data Collection Only)

The Investigator at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the Observational Study (Appendix 4). Subjects must also be notified that they are free to discontinue from the Observational Study at any time. The subjects should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject informed consent must be obtained before any specific procedure for the Observational Study is performed, including:
- Interview with the investigator
- Fulfil the questionnaires
- eCRFs completion.

The Investigator must store the original, signed Subject Informed Consent Form. A copy of the signed Subject Informed Consent Form must be given to the subject.

### 6.2.2 Confidentiality of Study/Subject Data (Primary Data Collection Only)

The Subject Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the Observational Study.

The Subject Informed Consent Form will explain that Observational Study data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The Subject Informed Consent Form will also explain that for quality check purposes, a monitor of AZ or a monitor of company representing AZ, will require direct access to the signed subject informed consent forms. In case source data verification will be planned as quality check, the Subject Informed Consent Form will explain that for data verification purposes, monitor of AZ or a monitor of company representing AZ may require direct access to source documents that are part of the hospital or practice records relevant to the Observational Study.

### 6.3 Management and Report of Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Drug Reactions (ADRs)

This study is non-interventional observational in nature and will not impact the physicians’ treatment or patient management decisions. However, the patient population considered for this study will be prescribed the following AZ Product: benralizumab.
6.3.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The term AE is used to include both serious and non-serious AEs.

6.3.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.

Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

6.3.3 Definition of Adverse Drug Reactions (ADR)

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the medicinal product. An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

6.3.4 Collection of Serious Adverse Events (SAEs), Adverse Events (AE) and Adverse Drug Reactions (ADRs)

The events defined in sections 6.3.1, 6.3.2 and 6.3.3 will be collected in this study.

All adverse events, serious adverse events, and adverse drug reactions occurring during benralizumab treatment until the first follow-up visit must be reported on the corresponding
subject specific eCRF pages. Benralizumab-associated adverse events have to be documented throughout the whole follow-up period.

For each SAE and ADR the following variables will be collected:

- Verbatim
- The date when the AE started
- The date the AE stopped
- Concomitant drug therapy
- Maximum intensity
- Max CTCAE grade
- Whether the AE is serious or not (see definitions of seriousness in 6.3.2)
- Investigator causality rating against the AZ medicinal product (yes or no)
- Action taken with regard to the AZ Product (e.g., dose reduction, discontinuation of AZ medicinal product, AZ Product continued without changes)
- Outcome (e.g., recovered, not recovered, etc.)

Causality collection

The Investigator will assess the causal relationship between the studied medicinal product(s) and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by benralizumab?’

6.3.5 Reporting of serious adverse events, adverse events and adverse drug reactions

If during the course of the NIS the physician becomes aware of an SAE or an ADR, he must immediately (within 24 hours) enter the data on the electronically available ADR/SAE form. After saving the form an automatically generated report will be send to Tata Consultancy Services (TCS). In the case that electronic reporting is not possible, paper form in the investigator's binder are at the doctor’s disposal for notification by conventional fax. All documentations in the ADR/SAE form must be in English.

Adverse events which are not causally related to benralizumab will be documented in the eCRF but will not be immediately reported by an automatically generated fax. Data concerning adverse events which are not related to benralizumab will be analysed for presentation in the non-interventional study report.
CRO will work with the investigator to compile all the necessary information.

**Reporting of spontaneously mentioned adverse drug reactions**

With regards to the reporting of ADRs observed in subjects participating in this study, the following guideline applies: ADRs should be reported to Health Authorities as stated in local regulations and/or, if the investigator considers it appropriate, to AZ (in case of an ADR related to an AZ-product other than benralizumab) or the corresponding marketing authorization holder of the drug.

**Time period for collection of adverse events**

Adverse Events will be collected from the time of starting the medicinal product(s) under study throughout the treatment period until the first follow-up visit.

**6.3.6 Pregnancy**

All pregnancies and outcomes of pregnancy should be reported to AZ.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the benralizumab treatment under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the physician or other site personnel informs the appropriate AZ or CRO representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ or CRO representative works with the physician to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.3.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The electronically available PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.
6.3.7 **Overdose**

If an overdose of the drug occurs in the course of the study, then the physician or other site personnel inform appropriate AZ / CRO representatives and/or AZ DES immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AZ / CRO representative works with the physician to ensure that all relevant information is provided to the AZ Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines of 24 hours apply. For other overdoses, reporting must occur within 30 days. All cases of overdose should be recorded in study CRF.
7. LIST OF REFERENCES


8. APPENDICES

Appendix 1: ACT Questionnaire

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☐ in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. During the past 4 weeks, how often have you had shortness of breath?

<table>
<thead>
<tr>
<th>More than once a day</th>
<th>Once a day</th>
<th>3 to 6 times a week</th>
<th>Once or twice a week</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

<table>
<thead>
<tr>
<th>4 or more nights a week</th>
<th>2 to 3 nights a week</th>
<th>Once a week</th>
<th>Once or Twice</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, Maxair® or Primatene Mist®)?

<table>
<thead>
<tr>
<th>3 or more times per day</th>
<th>1 or 2 times per day</th>
<th>2 or 3 times per week</th>
<th>Once a week or less</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

5. How would you rate your asthma control during the past 4 weeks?

<table>
<thead>
<tr>
<th>Not Controlled at all</th>
<th>Poorly Controlled</th>
<th>Somewhat Controlled</th>
<th>Well Controlled</th>
<th>Completely Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix 2: ACQ-6 questionnaire

Please answer questions 1-6.

Circle the number of the response that best describes how you have been during the past week:

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few minutes
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up in the morning**?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze**?
   - 0 Not at all
   - 1 Hardly any of the time
   - 2 A little of the time
   - 3 A moderate amount of the time
   - 4 A lot of the time
   - 5 Most of the time
   - 6 All the time

6. On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?
   - 0 None
   - 1 1 puff most days
   - 2 2 puffs most days
   - 3 3 puffs most days
   - 4 4 puffs most days
   - 5 5 puffs most days
   - 6 6 puffs most days
   - 7 7 puffs most days
   - 8 8 puffs most days
   - 9 9 puffs most days
   - 10 10 puffs most days
   - 11 11 puffs most days
   - 12 12 puffs most days
   - 13 13 puffs most days
   - 14 14 puffs most days
   - 15 15 puffs most days
   - 16 More than 16 puffs most days
Appendix 3: SGRQ questionnaire

ST. GEORGE’S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please choose one box to show how you describe your current health:

<table>
<thead>
<tr>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>Very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks. Please check (✓) one box for each question:

<table>
<thead>
<tr>
<th>Question</th>
<th>Frequency Options</th>
<th>Selected Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Over the past 4 weeks, I have coughed:</td>
<td>almost every day</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>several days a week</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>a few days a month</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>only with respiratory infections</td>
<td>☒</td>
</tr>
<tr>
<td></td>
<td>not at all</td>
<td>☐</td>
</tr>
<tr>
<td>2. Over the past 4 weeks, I have brought up phlegm (sputum):</td>
<td>almost every day</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>several days a week</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>a few days a month</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>only with respiratory infections</td>
<td>☒</td>
</tr>
<tr>
<td></td>
<td>not at all</td>
<td>☐</td>
</tr>
<tr>
<td>3. Over the past 4 weeks, I have had shortness of breath:</td>
<td>almost every day</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>several days a week</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>a few days a month</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>only with respiratory infections</td>
<td>☒</td>
</tr>
<tr>
<td></td>
<td>not at all</td>
<td>☐</td>
</tr>
<tr>
<td>4. Over the past 4 weeks, I have had wheezing attacks:</td>
<td>almost every day</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>several days a week</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>a few days a month</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>only with respiratory infections</td>
<td>☒</td>
</tr>
<tr>
<td></td>
<td>not at all</td>
<td>☐</td>
</tr>
<tr>
<td>5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?</td>
<td>more than 3 times</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>3 times</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>2 times</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>1 time</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>none of the time</td>
<td>☒</td>
</tr>
<tr>
<td>6. How long did the worst respiratory attack last? (Go to Question 7 if you did not have a severe attack)</td>
<td>a week or more</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>3 or more days</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>1 or 2 days</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>less than a day</td>
<td>☐</td>
</tr>
<tr>
<td>7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?</td>
<td>No good days</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>1 or 2 good days</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>3 or 4 good days</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>nearly every day was good</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>every day was good</td>
<td>☐</td>
</tr>
<tr>
<td>8. If you wheeze, is it worse when you get up in the morning?</td>
<td>No</td>
<td>☐</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>☒</td>
</tr>
</tbody>
</table>
PART 2

Section 1
How would you describe your respiratory condition?

Please check (√) one:

- The most important problem I have
- Causes me quite a lot of problems
- Causes me a few problems
- Causes no problems

If you have ever held a job:

Please check (√) one:

- My respiratory problems made me stop working altogether
- My respiratory problems interfere with my job or made me change my job
- My respiratory problems do not affect my job

Section 2
These are questions about what activities usually make you feel short of breath these days.

For each statement please check (√) the box that applies to you these days:

<table>
<thead>
<tr>
<th>Activity</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or lying still</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washing or dressing yourself</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking around the house</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking outside on level ground</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking up a flight of stairs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking up hills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Playing sports or other physical activities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PART 2

Section 3
These are more questions about your cough and shortness of breath these days.
For each statement please check (+) the box that applies to you these days:

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughing hurts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing makes me tired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am short of breath when I talk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am short of breath when I bend over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My coughing or breathing disturbs my sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get exhausted easily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Section 4
These are questions about other effects that your respiratory problems may have on you these days.
For each statement, please check (+) the box that applies to you these days:

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My cough or breathing is embarrassing in public</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My respiratory problems are a nuisance to my family, friends or neighbors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get afraid or panic when I cannot catch my breath</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel that I am not in control of my respiratory problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I do not expect my respiratory problems to get any better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have become frail or an invalid because of my respiratory problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise is not safe for me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everything seems too much of an effort</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Section 5
These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.
For each statement, please check (+) the box that applies to you these days:

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>My treatment does not help me very much</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I get embarrassed using my medication in public</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have unpleasant side effects from my medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My treatment interferes with my life a lot</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (√) the box that applies to you because of your respiratory problems.

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I take a long time to get washed or dressed</td>
<td></td>
</tr>
<tr>
<td>I cannot take a bath or shower, or I take a long time to do it</td>
<td></td>
</tr>
<tr>
<td>I walk slower than other people my age, or I stop to rest</td>
<td></td>
</tr>
<tr>
<td>Jobs such as household chores take a long time, or I have to stop to rest</td>
<td></td>
</tr>
<tr>
<td>If I walk up one flight of stairs, I have to go slowly or stop</td>
<td></td>
</tr>
<tr>
<td>If I hurry or walk fast, I have to stop or slow down</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim</td>
<td></td>
</tr>
<tr>
<td>My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports</td>
<td></td>
</tr>
</tbody>
</table>

Section 7

We would like to know how your respiratory problems usually affect your daily life.

For each statement, please check (√) the box that applies to you because of your respiratory problems.

<table>
<thead>
<tr>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>I cannot play sports or do other physical activities</td>
<td></td>
</tr>
<tr>
<td>I cannot go out for entertainment or recreation</td>
<td></td>
</tr>
<tr>
<td>I cannot go out of the house to do the shopping</td>
<td></td>
</tr>
<tr>
<td>I cannot do household chores</td>
<td></td>
</tr>
<tr>
<td>I cannot move far from my bed or chair</td>
<td></td>
</tr>
</tbody>
</table>
Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

- Going for walks or walking the dog
- Doing activities or chores at home or in the garden
- Sexual intercourse
- Going to a place of worship, or a place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

________________________________________________________________________

________________________________________________________________________

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

- It does not stop me from doing anything I would like to do
- It stops me from doing one or two things I would like to do
- It stops me from doing most of the things I would like to do
- It stops me from doing everything I would like to do

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.
Appendix 4: Patient Information Sheet and Informed Consent Form (ICF)