Clinical Study Protocol	
Study Intervention	Fasenra® (Benralizumab)
Study Code	D3250C00093
Version	Version 1.0
Date	09 Mar 2021

A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma with Eosinophilic Phenotype in India

Sponsor Name: AstraZeneca Pharma India Limited

Legal Registered Address: Block N1, 12th Floor, Manyata Embassy Business Park

Rachenahalli, Outer Ring Road, Bangalore-560045

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Amendment Number: Not Applicable
Study Intervention: Fasenra® (Benralizumab)
Study Phase: 4

Short Title:

Postmarketing, Phase 4, Safety Study of Fasenra (Benralizumab) in India

Acronym:

FAST: **FA**senra **S**afety **T**rial in India

Study Physician Name and Contact Information will be provided separately

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma With Eosinophilic Phenotype in India

Short Title:

Postmarketing, Phase 4, Safety Study of Fasenra® (Benralizumab) in India

Rationale:

The treatment options for patients with severe asthma with eosinophilic phenotype who remain uncontrolled on inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) are limited. Fasenra (benralizumab) is a humanised, afucosylated, monoclonal antibody that binds specifically to the human interleukin-5 (IL-5) receptor alpha subunit (IL-5Rα) of eosinophils and basophils. Administration of benralizumab results in rapid and near-complete depletion of eosinophils in the peripheral blood and in the airways with associated clinical improvement in patients with severe eosinophilic asthma. Benralizumab was approved as an add-on maintenance treatment for patients of severe asthma with an eosinophilic phenotype by the United States (US) Food and Drug Administration (FDA) in November 2017 (for those aged 12 years and older), and by the European Medicines Agency (EMA) in January 2018 (for adult patients). As on August 2020, benralizumab has been approved in 58 countries.

The recent European Respiratory Society/American Thoracic Society guidance recommends anti–IL-5 and anti–IL-5Rα agents for severe uncontrolled adult eosinophilic asthma phenotypes, and recognises the long-term safety of these therapies. The Global Initiative for Asthma (GINA) 2020 guidelines recommend add-on anti-IL-5 and anti–IL-5Rα treatment for severe eosinophilic asthma that is uncontrolled on step 4-5 treatment (Evidence level A). The safety of benralizumab is well established based on the pivotal SIROCCO, CALIMA, and ZONDA trials. Integrated analyses (BORA) of approximately 1600 patients with asthma (about 1000 of whom were exposed to benralizumab for up to 2 years) suggest that eosinophil depletion by benralizumab treatment does not increase risk of infections or malignancies. The MELTEMI study (open-label safety extension study of BORA) reported that benralizumab was well tolerated and the most frequently reported treatment-emergent adverse events (TEAEs) were nasopharyngitis, asthma, headache, viral upper respiratory tract infection, and bronchitis, reported by 131 (29.4%), 55 (12.3%), 53 (11.9%), 48 (10.8%), and 45 (10.1%) patients, respectively(MELTEMI D3250C00037 clinical study report [CSR], 2020). The cumulative worldwide post-approval patient exposure to benralizumab since launch is estimated to be 79,307 patient-years, and the combined analyses of the cumulative efficacy and safety data available continue to indicate a positive benefit-risk balance of

benralizumab (Periodic Benefit-Risk Evaluation Report, 2020).

Fasenra (benralizumab) has been recently approved in India with the condition to conduct a Phase 4 postmarketing study in the Indian population, as previous studies did not include patients from India. This prospective postmarketing safety study is planned to meet the regulatory mandate and assess the safety of benralizumab treatment in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks. This interventional study will provide insights into the potential risks of eosinophil-lowering therapies when used in routine clinical care in India. The study will also evaluate the effectiveness of benralizumab in reducing asthma exacerbations.

Objectives and Endpoints

Primary Objective	**Primary Endpoints**
To assess the safety and tolerability of Fasenra (benralizumab) in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks	• percentage of AEs [a], SAEs, and TEAEs • nature, incidence, and severity of AEs, including unexpected adverse drug reactions • percentage of patients with AEs that lead to study treatment discontinuations or modifications
Secondary Objective	**Secondary Endpoints**
To assess the effectiveness of Fasenra (benralizumab) in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks	• time to first asthma exacerbation[b] • annualised exacerbation rate • overall investigator's assessment on the outcome of the treatment: "well controlled", "partly controlled", "uncontrolled" • change in blood eosinophil levels from baseline at Weeks 4, 16, and 24

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] AEs that are reported and observed

[b] where an asthma exacerbation is defined by a worsening of asthma requiring

- Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depot-injectable dose of corticosteroids will be considered equivalent to a 3 day course of corticosteroid OR
- An emergency room/urgent healthcare visit (defined as evaluation and treatment for <24 hours in an emergency room or urgent care centre) due to asthma that required systemic corticosteroids (as per above) OR
- An inpatient hospitalisation due to asthma (defined as admission to an inpatient facility and or evaluation and treatment in a healthcare facility for ≥24 hours).

Overall Design

This is a prospective, single-arm, multicentre, interventional, Phase 4 study investigating the safety, tolerability, and effectiveness of Fasenra (benralizumab) in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks.

Disclosure Statement: This is a single-arm, postmarketing safety, tolerability, and effectiveness study with no masking.

Number of Participants:

Considering a dropout rate of 5%, a total of 147 participants from 10 centres across India will be enrolled into the study, for the purpose of obtaining data from at least 139 participants.

(Refer to Section 9.2 for details).

Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Male or female patients 18 to 75 years of age inclusive, at the time of signing the informed consent
2. Patients with physician's confirmed diagnosis of severe asthma with an eosinophilic phenotype, ie, a diagnosis of severe asthma in preceding at least 12 months, with an eosinophil count of ≥300 cells/µL at screening, requiring treatment with high-dose ICS (>500 µg fluticasone propionate dry powder formulation, or >800 µg budesonide dry powder formulation, or equivalent total daily dose) and a LABA as maintenance treatment for at least 3 months prior to enrolment
3. A decreased lung function with prebronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV1) of <80% predicted, demonstrated by spirometry at screening
4. At least 2 documented asthma exacerbations in the preceeding12 months, except in 30 days before the date of informed consent, that required the use of a systemic corticosteroid or temporary increase from the patient's usual maintenance dose of oral corticosteroid (OCS)
5. Documented postbronchodilator (post-BD) reversibility in FEV1 of ≥12% and ≥200 mL in FEV1 within 12 months before first dose. If historical documentation is not available, reversibility must be demonstrated and documented at screening or Day 1 before first dose
6. Benralizumab naïve patients who have not previously received benralizumab prior to the start of this study
7. Patients who are willing and capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis etc.) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary

aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome), which can confound the outcome assessment

2. Patients currently enrolled in an interventional clinical study in parallel including those with any biologic treatment
3. Patients who have received any biologic within 30 days prior to the date of informed consent.
4. Known history of allergy or reaction to the benralizumab formulation or excipients (L-histidine, L-histidine hydrochloride monohydrate, α-trehalose dihydrate, polysorbate 20, water for injection)
5. History of anaphylaxis to any biologic therapy
6. A helminth parasitic infection diagnosed within 24 weeks before the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy
7. Acute asthma exacerbation 30 days before the date informed consent
8. Acute asthma exacerbation between screening and first dose of study dose administration.
9. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days before the date informed consent
10. Patients with malignancy within 5 years prior to enrolment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal, or squamous cell carcinoma or non-melanomatous skin cancer with active or recent malignancy
11. Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis, which, in the opinion of the investigator, may put the participant at risk because of his/her participation in the study
12. History of current alcohol, drug, or chemical abuse or past abuse that would impair or risk the participant's full participation in the study, in the opinion of the investigator
13. Female patients who are pregnant or lactating or planning a family during the study period.

Intervention Groups and Duration:

Adult patients of severe asthma with eosinophilic phenotype requiring high dose of ICS plus LABA, who are prescribed Fasenra (benralizumab) 30 mg, subcutaneously, as an add-on therapy in line with the local prescribing information and are scheduled to initiate treatment with Fasenra (benralizumab) within 2 weeks will be enrolled in the study. The recommended dose of Fasenra (benralizumab) is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen as per local prescribing information (Appendix D). The study drug, Fasenra (benralizumab), will be provided by AstraZeneca Pharma India Ltd. for the duration of the study.

The total study duration will be 24 weeks, including 16 weeks of study treatment.

- Screening duration: 2 weeks
- Study period: 24 weeks
    - Treatment duration (4 doses): 16 weeks (Day 1, Week 4, Week 8, and Week 16)
    - Post-treatment follow-up duration: 8 weeks (Week 24)

Statistical Methods

Statistical analyses will be primarily descriptive in nature. Data from all participating sites will be pooled for analysis. Standard method of imputation will be applied for any missing/partial dates.

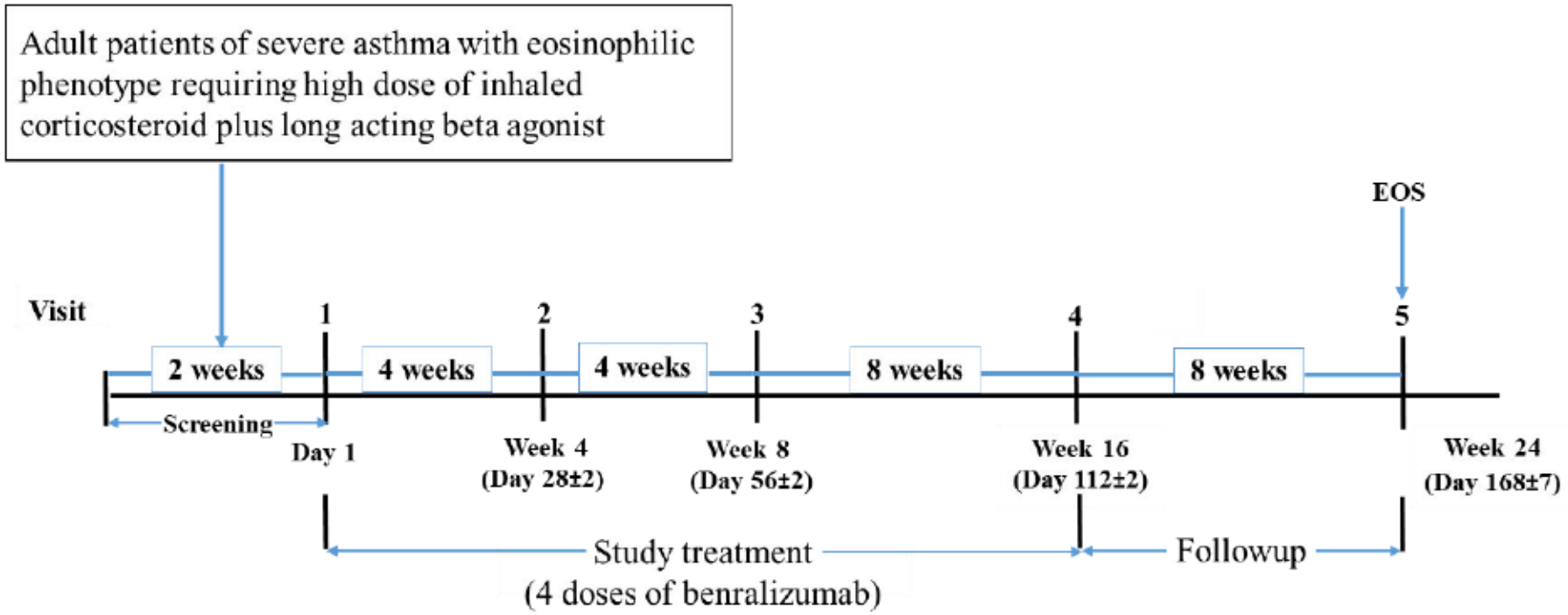
According to the objectives, the relevant parameters will be summarised descriptively with appropriate statistical methods: categorical variables will be presented using frequencies, percentages, and corresponding 95% confidence intervals (CIs) (using Clopper-Pearson exact method, where appropriate) and continuous variables using number of observations, arithmetic mean, standard deviation (SD), median, 25th and 75th percentiles, and minimum and maximum values. The last measurement prior to first dose of study treatment will serve as the baseline measurement.

The safety parameters including AEs, deaths, treatment discontinuation/modification, patient discontinuation, laboratory data, etc. will be reported using safety analysis set.

The time-to-event endpoint shall be summarised using Kaplan-Meier (KM) method along with the corresponding 95% CIs (as appropriate) and the KM curve will be plotted.

1.2 Schema

Figure 1 Study Design



EOS = end of study

1.3 Schedule of Activities

The schedule of activities is provided in Table 1.

Table 1 Schedule of Activities

Procedure	Screening (Up to 14 Days Before Day 1)	Intervention Period				Follow-up
		Day 1	Week 4	Week 8	(Last Dose)Week 16	EOS Week 24
			Day 28±2	Day 56±2	Day 112±2	Day 168±7
Visit		1	2	3	4	5
Informed consent	X					
Inclusion and exclusion criteria[a]	X					
Demography, anthropometry including BMI	X					
Significant medical history	X					
Clinical safety laboratory assessments[b]	X					X
Serum/urine pregnancy test (WOCBP only)[c]	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X
ECG	X		X			X
Targeted physical examination	X	X	X	X	X	X
Blood eosinophil count	X		X		X	X
Prebronchodilator FEV1	X					
Postbronchodilator FEV1[e]	X					
Administration of benralizumab		X	X	X	X	
Recording Use of concomitant asthma medication (OCS/ICS/LABA)	X	X	X	X	X	X
Adverse events and Serious adverse events[f] (reported[g] and observed)	X	X	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X	X	X

Abbreviations: BMI = body mass index; EOS = end of study; ECG= Electrocardiogram; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; OCS = oral corticosteroid; UPT = urine pregnancy test; WOCBP = women of childbearing potential (after menarche)

[a] Recheck clinical status before first dose of benralizumab.

[b] Clinical safety laboratory assessment will include clinical chemistry, haematology, and urinalysis. Clinical chemistry will include serum alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, lactate dehydrogenase, total protein, total bilirubin, albumin, and serum creatinine. Haematology will include haematocrit, leucocyte count, leucocyte differential count (absolute count), platelet count, and haemoglobin. Urinalysis (dipstick) will assess urine haemoglobin/erythrocytes/blood, protein/albumin, and glucose.

[c] Serum pregnancy test will be done at baseline and UPT will be done at Day 1, Week 4, 8, 16, 24.

[d] The vital signs (pulse, blood pressure, respiration rate, and body temperature) will be taken before benralizumab administration, and, if possible, blood drawing and usual asthma controller medication. If it is not logistically possible, sufficient time as per clinician discretion should be allotted between phlebotomy and vital signs assessment. For details, please refer to Section 8.1.3.

[e] When historical proof of postbronchodilator reversibility in FEV1 is not documented within 12 months before Visit 1, the reversibility test by spirometry will need to be performed either during screening or on Day 1 before first dose.

[f] While on study drug treatment and within 2 months after the end of study treatment/discontinuation of the study drug.

[g] Participants will be provided a patient diary to record any undesirable health-related experience or adverse events occurring during the study. Adverse events and serious adverse events mentioned both in the patient diary and verbally communicated by the participant will be recorded.

2 INTRODUCTION

Benralizumab is a humanised, afucosylated, monoclonal antibody that binds specifically to the human interlukin-5 (IL-5) receptor alpha subunit (IL-5Rα) of target cells such as eosinophils and basophils (Takatsu et al, 1994; Toba et al, 1999; Pelaia et al, 2020).

Interlukin-5, major pro-inflammatory cytokine, binds to IL-5R and results in an increased eosinophilic recruitment and activation resulting in airway inflammation (Takatsu et al, 1994; Toba et al, 1999; Pelaia et al, 2020). Targeting IL-5R by monoclonal antibodies such as benralizumab is a novel way to decrease eosinophilic airway inflammation (GINA, 2020).

Severe eosinophilic asthma accounts for over 50% of cases with severe asthma, and is associated with increased disease severity, exacerbation frequency, and decreased lung function (Pavord, 2013; Walford et al, 2014; Gonzalez et al, 2019). Current guidelines recommend the addition of anti-IL-5 therapies such as mepolizumab or reslizumab or anti-IL-5 receptor therapy such as benralizumab for patients with severe eosinophilic asthma (GINA, 2020). Benralizumab was approved as an add-on maintenance treatment for patients of severe asthma with an eosinophilic phenotype by the United States (US) Food and Drug Administration (FDA) in November 2017 (for those aged 12 years and older) (Fasenra® [benralizumab] United Stated Prescribing Information [USPI], 2017), and by the European Medicines Agency (EMA) in January 2018 (for adult patients) (Fasenra™ [benralizumab] Summary of Product Characteristics [SmPC], 2019). As on August 2020 it has been approved in 58 countries.

Benralizumab was generally well tolerated by patients in clinical trials, with no apparent safety concerns.

2.1 Study Rationale

The treatment options for patients with severe eosinophilic asthma who remain uncontrolled on inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) are extremely limited. In clinical studies, benralizumab administration resulted in rapid and nearly complete depletion of eosinophils in the peripheral blood and in the airways of patients with severe eosinophilic asthma, with associated improvements in clinical symptoms and lung function (Kolbeck et al, 2010; Bleecker et al, 2016; Fitzgerald et al, 2016; Busse et al, 2019).

The recent European Respiratory Society/American Thoracic Society guidance recommends anti–IL-5 and anti–IL-5Rα agents for severe uncontrolled adult eosinophilic asthma phenotypes, and recognises the long-term safety of these therapies. The Global Initiative for Asthma (GINA) 2020 guidelines recommend add-on anti-IL-5 and anti–IL-5Rα treatment for severe eosinophilic asthma that is uncontrolled on step 4-5 treatment (Evidence level A). The safety of benralizumab is well established based on the pivotal SIROCCO, CALIMA, and ZONDA trials. Integrated analyses (BORA) of approximately 1600 patients with asthma (about 1000 of whom were exposed to

benralizumab for up to 2 years) suggest that eosinophil depletion by benralizumab treatment does not increase risk of infections or malignancies. (Jackson et al, 2020). The recently completed MELTEMI study (open-label safety extension study of BORA) reported that benralizumab was well tolerated and the most frequently reported mild to moderate treatment-emergent adverse events (TEAEs) were nasopharyngitis, asthma, headache, viral upper respiratory tract infection, and bronchitis, reported by 131 (29.4%), 55 (12.3%), 53 (11.9%), 48 (10.8%), and 45 (10.1%) patients, respectively(MELTEMI D3250C00037 CSR, 2020). The cumulative world-wide post-approval patient exposure to benralizumab since launch is estimated to be 79,307 patient-years, and the combined analyses of the cumulative efficacy and safety data available continue to indicate a positive benefit-risk balance of benralizumab (Periodic Benefit-Risk Evaluation Report, 2020). An ongoing prospective, observational, pregnancy registry (D3250R00026) will examine pregnancy and infant outcomes in women with asthma exposed to benralizumab anytime during pregnancy, and an ongoing malignancy post-authorisation safety study (D3250R00042) will assess incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics and those not receiving biologics.

Fasenra (benralizumab) has been recently approved in India with the condition to conduct a Phase 4 postmarketing study in the Indian population, as previous studies did not include patients from India. The current prospective, interventional, postmarketing safety study is planned to meet the regulatory mandate and assess the safety of benralizumab over a period of 24 weeks in adult patients of severe asthma with eosinophilic phenotype in India.

2.2 Background

Asthma affects about 339 million people worldwide and an estimated 5% to 10% have disease that remains severe and uncontrolled despite maximal treatment with ICS and LABA (Chung et al, 2014; GINA, 2020). Patients who suffer from severe or uncontrolled asthma have a reduced quality of life, with increased risk of hospitalisation and mortality, in addition to increased health care costs (Rogliani et al, 2020). The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen and primarily centres on ICS, tiotropium, leukotriene receptor antagonists with addition of LABA in severe asthma (GINA, 2020). Despite treatment management as per guidelines, a significant number of patients have asthma that is not well controlled, and therein lies the unmet medical need within this therapeutic area.

With identification of specific biomarkers for different asthma phenotypes, biological drugs are currently indicated for severe eosinophilic asthma not controlled on maximal doses of ICS plus LABA (GINA, 2020). By targeting inflammatory molecules, these novel monoclonal antibodies are proven to reduce asthma exacerbations, maintain symptom control, and reduce use of systemic steroids (Rogliani et al, 2020).

Benralizumab is an anti-eosinophil, humanised afucosylated, monoclonal antibody (IgG1, kappa). Benralizumab binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with high affinity (16 pM) and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity (45.5 nM) for FcγRIII receptors on immune effector cells such as natural killer (NK) cells leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) (Benralizumab India package insert (PI)).

The safety and efficacy of benralizumab have been demonstrated in 3 Phase 3 randomised trials, SIROCCO, CALIMA, and ZONDA. Benralizumab was well tolerated as shown by low discontinuation rate (2%) in both the pivotal SIROCCO and CALIMA studies, with 90% of patients assigned to benralizumab still receiving treatment at 48 weeks in SIROCCO. The long-term efficacy and safety of benralizumab was evaluated in a Phase 3, 56-week extension trial, BORA, and the MELTEMI trial (open-label safety extension study of BORA). The reduction in annual rate of asthma exacerbations observed in SIROCCO and CALIMA were maintained over the second year of treatment. In addition, no new consequences of long-term eosinophil depletion occurred, and incidences of AE including opportunistic infections were similar during the second year (Busse et al, 2018).

However, previous studies did not include patients from India. Fasenra has been recently approved in India with the condition to conduct a Phase 4 postmarketing study in the Indian population. This prospective postmarketing safety study will generate safety data to meet the regulatory mandate in India.

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab is provided in the PI.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Benralizumab has been well tolerated, with the most frequently observed adverse events (AEs) from the Phase 3 controlled studies being generally reflective of asthmatic patient population.

Potential risks of benralizumab are as follows:

- Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.
- Malignancies have been reported at a low incidence in the completed and ongoing studies of benralizumab. Eosinophils have been found in association with solid tumours, especially tumours of epithelial origin (breast and colon), and may play an active role in tumour defence by modulating host defences, or may be a bystander effect. However, the cause and consequences (ie, pro-tumourigenic versus anti-tumourigenic) of eosinophil recruitment and accumulation into tumours are unclear (Jacobsen et al, 2012). The overall

incidence of malignant neoplasms AEs in benralizumab-treated patients during the SIROCCO/CALIMA studies and the BORA extension was low (< 1%), with no apparent trends in organs or tissue types affected. (Jackson et al, 2020). Risk minimisation measures include exclusion of patients with active or recent malignancy and routine pharmacovigilance activities.

- Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimisation includes observation period at the clinical site following benralizumab administration in line with clinical practice for the appearance of any acute drug reactions.
- Development of antidrug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA may include decreased drug efficacy and hypersensitivity reactions (e.g. anaphylaxis or immune complex disease). There was no apparent impact of ADA on overall benralizumab safety or efficacy in the previous Phase◦3 studies in severe eosinophilic asthma patients.
- Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites. Risk minimisation measures include exclusion of patients with an untreated parasitic infection, in conjunction with the performance of routine pharmacovigilance activities.

2.3.2 Benefit Assessment

Patients with severe uncontrolled asthma, enrolled in this trial are expected to benefit from the benralizumab therapy for symptomatic relief, improved lung function, fewer exacerbations and fewer hospital visits. For enrolling in this study, the physician would have already determined the eligibility of the patient who would be prescribed and derive benefit from benralizumab. The cost of the study treatment will be borne by AstraZeneca for 4 doses. Data generated from this study will help evaluate the safety of benralizumab in clinical settings in India. It will help provide a safer alternative to patients with severe uncontrolled asthma, reducing their dependency on high doses of long-term systemic steroids.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the overall benefit-risk profile of benralizumab, and the unmet need of the patients of severe asthma with eosinophilic phenotype, the anticipated benefits outweigh the risks for the participants in the study.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints are provided in Table 2.

Table 2 Objectives and Endpoints

Primary Objective	Primary Endpoints
To assess the safety and tolerability of Fasenra (benralizumab) in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks	• percentage of AEs [a], SAEs, and TEAEs • nature, incidence, and severity of AEs including unexpected adverse drug reactions • percentage of patients with AEs that lead to study treatment discontinuations or modifications
Secondary Objective	**Secondary Endpoints**
To assess the effectiveness of Fasenra (benralizumab) in adult patients of severe asthma with eosinophilic phenotype over a period of 24 weeks	• time to first asthma exacerbation[b] • annualised exacerbation rate • overall investigator's assessment on the outcome of the treatment: "well controlled", "partly controlled", "uncontrolled" • change in blood eosinophil levels from baseline till Weeks 4, 16, and 24

Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] AEs that are reported and observed

[b] where an asthma exacerbation is defined by a worsening of asthma requiring

- Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depot-injectable dose of corticosteroids will be considered equivalent to a 3 day course of corticosteroid OR
- An emergency room/urgent care visit (defined as evaluation and treatment for <24 hours in an emergency room or urgent care centre) due to asthma that required systemic corticosteroids (as per above) OR
- An inpatient hospitalisation due to asthma (defined as admission to an inpatient facility and or evaluation and treatment in a healthcare facility for ≥24 hours).

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 4, single-arm, prospective, multicentre, interventional study, designed to assess the safety, tolerability, and effectiveness of benralizumab in adult patients of severe asthma with eosinophilic phenotype in India. The study is planned to meet the postapproval commitment as a regulatory requirement.

Ten centres across India will participate in this study. The investigators will be pulmonologists or chest physicians treating asthma patients. Informed consent will be obtained from all the patients at screening before any study-related procedures are performed. Adult patients of severe asthma with eosinophilic phenotype, who are prescribed benralizumab as an add-on therapy by the treating physician, will be enrolled in the study.

The total study duration will be 24 weeks, including 16 weeks of study treatment, and 8 weeks follow-up (Figure 1).

- Screening duration: 2 weeks
- Study period: 24 weeks
    - Treatment duration (4 doses): 16 weeks (Day 1, Week 4, Week 8, and Week 16)
    - Post-treatment follow-up duration: 8 weeks (Week 24)

Benralizumab will be provided by AstraZeneca Pharma India Ltd. for the duration of the study.

Participants will be maintained on their currently prescribed therapies including ICS-LABA therapy(ies), throughout the study duration.

4.2 Scientific Rationale for Study Design

This proposed Phase 4 single-arm study will fulfil the regulatory requirement as a postmarketing study to assess the safety of 30-mg benralizumab administered subcutaneously in Indian patients of severe asthma with eosinophilic phenotype who remain uncontrolled on high doses of ICS plus LABA. Owing to the recent marketing approval, there are no data available from real-life studies in the Indian population. Participants included in this study will be as per the indicated patient profile in the local prescribing information, specifically taking into consideration the contraindications, warnings, and special precautions for use.

4.3 Justification for Dose

The study will enrol patients who have been prescribed benralizumab as per the local prescribing information. The recommended dose is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh,

or abdomen by the study physician. Four doses of benralizumab will be administered as part of the study.

4.4 End of Study Definition

A participant is considered to have completed the study when he/she has completed his/her end of study (EOS) visit at Week 24, 8 weeks after end of treatment (EOT), as per the schedule of activities (SoA) in Section 1.3.

The EOS is defined as the last expected visit of the last participant undergoing the study.

See Appendix A for guidelines about dissemination of study results.

5 STUDY POPULATION

Study population will include adult (18 to 75 years of age) male or female patients who have severe asthma with eosinophilic phenotype requiring high dose of ICS and LABA.

Each participant should meet all the inclusion criteria and none of the exclusion criteria to be eligible for the study. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures, refer to Section 5.4.

"Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study after completion of the informed consent process. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Male or female patients 18 to 75 years of age inclusive, at the time of signing the informed consent
2. Patients with physician's confirmed diagnosis of severe asthma with an eosinophilic phenotype, ie, diagnosis of severe asthma in preceding at least 12 months, with an eosinophil count of ≥300 cells/µL at screening, requiring treatment with high-dose ICS (>500 µg fluticasone propionate dry powder formulation, or >800 µg budesonide dry powder formulation, or equivalent total daily dose) and a LABA as maintenance treatment for at least 3 months prior to enrolment
3. A decreased lung function with prebronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV1) of <80% predicted, demonstrated by spirometry at screening
4. At least 2 documented asthma exacerbations in the preceeding12 months, except in 30 days before the date of informed consent, that required the use of a systemic corticosteroid or temporary increase from the patient's usual maintenance dose of OCS
5. Documented postbronchodilator (post-BD) reversibility in FEV1 of ≥12% and ≥200 mL in FEV1 within 12 months before first dose. If historical documentation is not available, reversibility must be demonstrated and documented at screening or Day 1 before first dose
6. Benralizumab naive patients who have not previously received benralizumab prior to the start of this study
7. Patients who are willing and capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis etc.) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome), which can confound the outcome assessment
2. Patients currently enrolled in an interventional clinical study in parallel including those with any biologic treatment
3. Patients who have received any biologic within 30 days prior to the date of informed consent.
4. Known history of allergy or reaction to the benralizumab formulation or excipients (L-histidine, L-histidine hydrochloride monohydrate, α-trehalose dihydrate, polysorbate 20, water for injection)
5. History of anaphylaxis to any biologic therapy
6. A helminthic parasitic infection diagnosed within 24 weeks before the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy
7. Acute asthma exacerbation 30 days before the date informed consent
8. Acute asthma exacerbation between screening and first dose of study dose administration.
9. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days before the date informed consent
10. Patients with malignancy within 5 years prior to enrolment, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal, or squamous cell carcinoma or non-melanomatous skin cancer with active or recent malignancy
11. Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis, which, in the opinion of the investigator, may put the participant at risk because of his/her participation in the study
12. History of current alcohol, drug, or chemical abuse or past abuse that would impair or risk the participant's full participation in the study, in the opinion of the investigator
13. Female patients who are pregnant or lactating or planning a family during the study period.

5.3 Lifestyle Considerations

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

For patients who were excluded due to asthma exacerbation, rescreening can be done post 30

days of completion of treatment of asthma exacerbation provided other inclusion criteria are met. Rescreened participants should be assigned the same participant number as for the initial screening

6 STUDY INTERVENTION

6.1 Study Intervention Administered

6.1.1 Study Drug

Study drug information is provided in Table 3.

Table 3 Study Drug

Intervention name	Benralizumab
Type	Biologic
Dose formulation	Prefilled syringe
Unit dose strength	30 mg/mL
Dosage levels	30 mg administered once every 4 weeks for the first 3 doses and then once every 8 weeks thereafter
Route of administration	Subcutaneous injection into the arm, upper arm, thigh, or abdomen
Sourcing	Benralizumab will be provided by AstraZeneca Pharma India Ltd. for the duration of the study (4 doses)
Packaging and labelling	Benralizumab will be provided in single-dose prefilled syringe. Each syringe will be labelled in accordance with Good Manufacturing Practices (GMP) Annex 13 and as per Indian regulatory requirement
Current/former names	Fasenra®, MEDI-563

All doses of the study drug will be administered at the study clinics. Serious hypersensitivity reactions (including anaphylaxis) are an identified risk for benralizumab. After administration of the study drug, the patients will be observed at the clinical site in line with clinical practice for the appearance of any acute drug reactions.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Benralizumab is to be stored at the study centre in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature-monitoring log.
5. Benralizumab must be kept in the original package and under conditions specified on the label (between 2°C to 8°C (36°F to 46°F), protected from the light).
6. The syringe may be kept at room temperature up to 25°C for a maximum of 14 days. After removal from the refrigerator, benralizumab must be used within 14 days or discarded.
7. Before administration, warm the syringe by leaving carton at room temperature generally for 30 minutes. Visually inspect for particulate matter and discolouration and if cloudy and discoloured, should not be used.
8. Do not use in the following cases:
   - temperature excursion on receipt or during storage at the study
   - damaged kit on receipt
   - damaged syringe

The centre staff should not use affected benralizumab and should immediately contact an AstraZeneca representative for further guidance.

More detailed information about the dosage, preparation, and administration of benralizumab may be found in the abridged prescribing information of benralizumab (Appendix D).

6.3 Measures to Minimise Bias

This is an open-label study; potential bias will be reduced by enrolling consecutive participants fitting into the inclusion criteria from the respective sites in an effort to reduce the selection bias.

If a participant withdraws from the study, they will not be replaced.

AstraZeneca or designee may access participant level data for monitoring purposes.

6.4 Limitations of the Study

This study has no control group and will follow about 147 patients during the period of 24 weeks. Given these conditions, the safety and effectiveness data available for collection may be limited compared with randomised clinical trials. The data generated by the study will be used to meet the post-approval commitment and presented in descriptive way. The descriptive data will be published only locally. This study will generate results from a wider range of data than those previously derived from the more limited clinical trial setting. This study will provide information on the Indian patient population that is treated with Fasenra.

6.5 Study Intervention Compliance

The administration of the study intervention should be recorded in the appropriate sections of the electronic case report form (eCRF).

The study intervention will be administered at the study centre on treatment visits and within visit windows as specified in Table 1. Participants will receive study intervention directly from the investigator/designee, under medical supervision. The date and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Concomitant Therapy

Information about any treatment in the 3 months before the date of informed consent, and all concomitant treatments including treatment/medications for asthma that the participant is receiving at the time of enrolment or receives during the study, must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Background Medication

Participants in the study are required to be treated with high-dose ICS (>500 µg fluticasone propionate dry powder formulation, or >800 µg budesonide dry powder formulation, or equivalent total daily dose) and a LABA as maintenance for at least 3 months prior to enrolment. Systemic or ICS should not be abruptly discontinued upon initiation of therapy with benralizumab. Reduction in corticosteroid doses, if appropriate, should be gradual.

The aim of this study is to review the safety and effectiveness of benralizumab as add-on therapy in up to 147 patients in India in the postmarketing setting. Therefore, the background asthma controller medications should be maintained at a stable dose from Visit 1 until the end of the study. If changing the ICS-LABA dose is judged as necessary by the investigator, the justification should be documented in the source and the change in the doses should be reflected in the eCRF.

Background medication will not be provided by AstraZeneca.

Additional controllers that are labelled for asthma and allowed as per protocol will not be provided by AstraZeneca.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and effectiveness parameters. Evaluations and safety assessments at the time of discontinuation of study intervention may be performed as per study physician discretion.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. Participants will be discontinued from benralizumab in the following situations:

- Participant is free to discontinue treatment at any point of time, without prejudice to further treatment (see Section 7.2)
- Development of any study-specific criteria for discontinuation:
    a. anaphylactic reaction to benralizumab requiring administration of epinephrine
    b. development of helminth parasitic infestations requiring hospitalisation
    c. intensive care unit admission with prolonged intubation and mechanical ventilation for asthma-related event
- Severe non-compliance to study protocol including if any dose of benralizumab is missed during the course of the study
- Eligibility requirement found not to be fulfilled (see Section 5.1, Section 5.2)
- Pregnancy (see Section 8.2.5)
- Lost to follow-up

Before a decision to discontinue a participant from benralizumab instituted, the investigator should carefully consider whether continuation on benralizumab or discontinuation of benralizumab will be in the best interest of the patient, and whether the issue can be mitigated by postponing or skipping the dose. It is highly recommended that the AstraZeneca study physician be consulted before the benralizumab discontinuation transaction takes place. In case of safety concerns benralizumab administration may be immediately withheld until the final decision is made.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

7.3 Lost to Follow up

Participant is considered lost to follow-up when any of the following attempts of contact have failed: 3 attempts of telephone calls, faxes, or emails; having sent 1 certified mail; one unsuccessful effort to check the vital status of the participant using publicly available sources, if allowed by local regulations.

At that visit, participants should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments or alternatively agree to be contacted by phone calls at monthly intervals to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information.

Reasons for withdrawal of benralizumab should be recorded in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- The investigator will ensure the accuracy and completeness of the data recorded on the eCRF.
- The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Blood sample collection and pregnancy test will be performed as per SoA.
- Postbronchodilator spirometry will be performed at screening for participants without prior documentation (documentation within 12 months before Visit 1) of reversibility.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.1.1 Physical Examinations

- A targeted physical examination will be performed including assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.
- Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.2.2 and Section 8.2.3.

Physical examination will be performed at time points as specified in the SoA.

8.1.2 Vital Signs

Vital signs (pulse, blood pressure, respiration rate, and body temperature) and electrocardiogram

(ECG) will be obtained in accordance with schedule provided in Table 1.

The vital signs will be taken before benralizumab administration, and, if possible, blood drawing and usual asthma controller medication.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.2.2 and Section 8.2.3.

8.1.3 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be collected at screening and at EOS (Day 168±7) as indicated in the SoA.

Clinical chemistry will include serum alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, lactate dehydrogenase, total protein, total bilirubin, albumin, and serum creatinine. Haematology will include haematocrit, leucocyte count, leucocyte differential count (absolute count), platelet count, and haemoglobin. Urinalysis (dipstick) will assess urine haemoglobin/erythrocytes/blood, protein/albumin, and glucose.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, and urinalysis will be performed at a local laboratory at or near the investigator site. Sample tubes may vary depending on laboratory method used and routine practice at the site.

8.1.4 Other Safety Assessments

Not applicable.

8.1.5 Adverse Events and Serious Adverse Events

The Principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or when appropriate by a caregiver, surrogate, or the participant's legally authorised representative). Participants will be provided a patient diary to record any undesirable health-related experience or adverse events occurring during the study. Adverse events and serious adverse events mentioned both in the patient diary and verbally communicated by the participant will be recorded.

The investigator and any designees are responsible for detecting, documenting, and recording

events that meet the definition of an AE.

8.1.6 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Adverse events and serious adverse events will be collected from time of signature of the ICF, throughout the treatment period and including the follow-up period (Week 24).

If the investigator becomes aware of any SAE with a suspected causal relationship to benralizumab that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.2 Follow-up of Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the follow-up in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

'The following variables will be collected for each AE:

- adverse event (verbatim)
- the date when the AE started and stopped
- maximum intensity of the AE
- whether the AE is serious or not
- investigator causality rating against Fasenra (benralizumab) (yes or no)
- action taken with regard to Fasenra (benralizumab)
- adverse event caused participant's withdrawal from study (yes or no)
- outcome

In addition, the following variables will be collected for SAEs:

- date AE met criteria for SAE
- date investigator became aware of SAE
- adverse event is serious due to
- date of hospitalisation
- date of discharge
- probable cause of death

- date of death
- autopsy performed
- causality assessment in relation to study procedure(s)
- causality assessment to other medication

8.2.1 Causality Collection

The investigator should assess causal relationship between Fasenra (benralizumab) and each AE and SAE, 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 Fasenra (benralizumab)?'

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.2.2 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.2.3 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with Fasenra (benralizumab) or are considered clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital signs is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital signs will be considered as additional information.

8.2.4 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the benralizumab, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar** days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative or investigator/delegated study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

8.2.5 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for the study participant whose pregnancy is discovered before receiving any study drug.

8.2.5.1 Maternal Exposure

If a participant becomes pregnant during the study, benralizumab should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that benralizumab 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 termination of pregnancy 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 participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later**

than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.2.4) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

8.2.5.2 Paternal Exposure

Pregnancy of the participant's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3 Effectiveness Assessments

8.3.1 Assessment of Asthma Exacerbations

For the protocol, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depot-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.
- An ER/Urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above).
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

Time to first asthma exacerbation will be calculated from baseline (Day 1) to time of first exacerbation. The start of an exacerbation is defined as the start date of systemic corticosteroids, ER or urgent care visits requiring systemic corticosteroids, or hospital admissions due to asthma, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or ER/Urgent care/hospital discharge, whichever occurs later.

In order to calculate the number of exacerbations experienced by a patient during the study period, the following rule will be applied. The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of a temporary increase in a stable OCS background dose, or start date of hospital admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable OCS background

dose, or the date of discharge from a hospital, whichever occurs later. Additional systemic corticosteroid treatments, ER/urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted for as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

Maximum follow-up time for a participant is approximately 24 weeks; defined as the time from enrolment to the date of EOS visit. For a participant lost to follow- up, this will be defined as the time from enrolment to the time point after which an exacerbation could not be assessed, (ie, the last contact date). Any exacerbations after this time point will not be included in analyses.

Proportion of participants with ≥ 1 asthma exacerbation(s) between baseline and end of study will be summarised.

8.3.2 Prebronchodilator FEV1 Through Spirometry

Pre-BD FEV1 will be recorded by spirometry and performed at screening to confirm the diagnosis of severe asthma.

8.3.3 Change in Blood Eosinophils

Change in blood eosinophil levels from baseline at Week 4, Week 16, and Week 24 will be assessed.

8.3.4 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.2.4) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.3.5 Device Constituent Deficiencies

- In a combination drug-device study drug (e.g. accessorised prefilled syringe), the device constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

- For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.4 Overdose

For this study, any dose of benralizumab greater than 30 mg within 4 weeks will be considered an overdose. As benralizumab is given by a healthcare professional in a medical setting, an overdose is unlikely to occur.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel must inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.2.4) and **within 30 days** for all other overdoses.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study- specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity assessments will not be done in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.6 Collection of Human Biological Sample Biomarkers

Biomarkers will not be evaluated in this study.

8.7 Collection of Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable to this study.

8.8 Health Economics OR Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters will not be evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no statistical hypothesis to be tested in this study.

9.2 Sample Size Determination

The primary objective of this study is to assess safety and tolerability of benralizumab in adult (18 to 75 years of age) male or female patients who have severe asthma with eosinophilic phenotype requiring high dose of ICS and LABA. Based on the literature review, the below table is created for listing the key AEs (headache, pyrexia, pharyngitis and injection site reactions) and hypersensitivity reactions (e.g. anaphylaxis, angioedema, urticaria, urticaria papular, rash) which were included in the USPI, SmPC and the India PI, all in the range of 1% to 10%.

	Incidence Rate (%)		
Key AE Terms	**SmPC/ India label**	**USPI**	**SIROCCO**
Headache	Common (1%-10%)	8%	7%-9%
Pharyngitis		5%	4%-6%
Pyrexia		3%	3%-4%
Injection site reactions		2.2%	2%-4%
Hypersensitivity		3%	3%

effectiveness $n = \frac{Z^2 P(1-P)}{d^2}$

where n = calculated sample size, Z = tabulated Z statistic value for α level of confidence, P = expected proportion of AEs and d = absolute precision level (half-width of the confidence interval [CI]).

Considering the maximum limit of the incidence rate of AEs to be 10%, approximately 139 evaluable participants will be required to present 95% CI around the estimated AE incidence rate with absolute precision level of 0.05. Considering dropout rate of 5%, a total of 147 participants will be required to be enrolled into the study.

9.3 Populations for Analyses

For purpose of analysis, the following populations/analysis sets are defined, as presented in Table 4

Table 4 Populations for Analysis

Population/Analysis set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorised representative's, agreement by signing the ICF to participate in a clinical study following completion of the informed consent process.
Assigned to study intervention	Potential participants who fulfil the eligibility criteria and are assigned with the study identification number.
Evaluable	All participants assigned to study intervention and receiving at least 1 dose of study intervention and provide at least one post baseline assessment.
Safety	All participants assigned to study intervention and who take at least 1 dose of study intervention.

Abbreviation: ICF= Informed Consent Form

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised before data base lock. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Statistical analyses will be primarily descriptive in nature. All tabulations, figures, and listings will be produced using the Statistical Analysis Software (SAS) System (Version 9.2 or higher). Data from all participating sites will be pooled for analysis. Standard method of imputation will be applied for any missing/ partial dates.

According to the objectives, the relevant parameters will be summarised descriptively with appropriate statistical methods: categorical variables will be presented using frequencies, percentages and corresponding 95% CI (using Clopper-Pearson exact method, where appropriate) and continuous variables using number of observations, arithmetic mean, standard deviation (SD), median, 25th and 75th percentiles, and minimum and maximum values. The last measurement prior to first dose of study treatment will serve as the baseline measurement.

The safety parameters including AEs, SAEs, deaths, treatment discontinuation/modification, patient discontinuation, laboratory data, etc. will be reported using safety analysis set.

The time-to-event endpoint will be summarised using Kaplan-Meier (KM) method along with the corresponding 95% CIs (as appropriate) and the KM curve will be plotted.

9.4.2 Safety

9.4.2.1 Primary Endpoints

In order to assess safety and tolerability of benralizumab in participants with severe eosinophilic asthma, following results will be presented:

Frequency, percentage, and 95% CIs (using Clopper-Pearson exact method) will be reported for the following:

- AEs
- SAEs
- TEAEs
- Participants with unexpected Adverse Drug Reactions (ADRs)
- Participants with AEs that lead to study treatment discontinuations or modifications.

The AE profiles in participants will be presented as summaries showing the number of participants (n, %) along with number of events by System Organ Class and Preferred Terms assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA) for the following:

- TEAEs
- SAEs
- Related and non-related TEAEs
- Serious and non-serious TEAEs
- TEAEs based on severity (Mild, Moderate, Severe)
- Unexpected ADRs based on severity (Mild, Moderate, Severe)

The physical examination, vital signs, and laboratory parameters (if available) will be summarised descriptively for actual values and change from baseline values for each visit using the number of observations, arithmetic mean, SD, median, 25th and 75th percentiles, and minimum and maximum values.

9.4.2.2 Other Safety Endpoints

None

9.4.3 Effectiveness

In order to assess effectiveness of benralizumab in participants of severe asthma of eosinophilic phenotype, following results will be presented using Evaluable Analysis Set:

Annualised exacerbation rate per 24-week period will be reported as percentage, and 95% CI (exact Poisson method), and will be presented in the SAP.

The proportion of participants with ≥1 asthma exacerbation during the study period will be described using the frequency and the percentage. The proportion of such participants will be calculated as: (number of participants with ≥1 asthma exacerbation during the 24 week study period)/(total number of participants in the study).

Overall investigator's assessment on the outcome of study treatment will be summarised using frequency and percentage.

Time from first dose of study treatment to the first asthma exacerbation will be calculated as follows: Start Date of first asthma exacerbation minus Date of first dose of study treatment plus 1. The time to first asthma exacerbation for participants who do not experience an asthma exacerbation during the study period will be censored at 24 weeks, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up participants). The data will be summarised through median time to the first asthma exacerbation along with the 95% CI of median (as per availability of data) and displayed graphically using a KM plot.

The absolute values of blood eosinophil levels and the change from baseline at Week 4, Week 16, and Week 24 will be summarised descriptively using number of observations, arithmetic mean, SD, median, 25th and 75th percentiles, and minimum and maximum values.

9.4.4 Other Analyses

None

9.5 Interim Analyses

No interim analyses is planned for this study.

9.6 Data Monitoring Committee

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, prescribing information, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or Prescribing Information and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study. AstraZeneca is responsible for furnishing the details of the contract with the investigator about financial support, fees, honorarium and payments made in kind, to the appropriate regulatory authorities.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of, local regulations, ICH guidelines, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://ctri.nic.in/Clinicaltrials/login.php as will the summary of the study results when they are available. The clinical trial and/or summary of the study results may also be available on other websites according to the locally prevalent regulations in India.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, New Drugs and Clinical Trial Rules 2019, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site initiation visit (SIV) and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will be discontinued from the study and will be provided with standard of care as determined appropriate by the study investigator.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), 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 and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse events for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room (ER) is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life- threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an ER or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- Mild: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- Moderate: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Severe: Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B.

B 3 Definition of Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the drug treatment or any event already present that worsens in either intensity or frequency following exposure to the drug treatment.

B 4 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if after a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 5 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication

- Wrong drug administered to participant

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

Appendix D Benralizumab, prefilled syringe (India-specific package insert) Fasenra™

Therapeutic indications

Fasenra™ is indicated as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients.

Posology and method of administration

Posology

The recommended dose is 30 mg of Fasenra™ by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter.

Elderly patients

No dose adjustment is required for elderly patients (see Section 5.2).

Renal and hepatic impairment

No dose adjustment is required for patients with renal or hepatic impairment (see Section 5.2).

Administration

Fasenra™ is administered as a subcutaneous injection by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended.

Administer Fasenra™ into the upper arm, thighs, or abdomen. Do not administer into areas where the skin is tender, bruised, erythematous, or hardened (Appendix D).

Contraindications

Fasenra™ is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients.

Special warnings and special precautions for use

Fasenra™ should not be used to treat acute asthma exacerbations.

Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Abrupt discontinuation of corticosteroids after initiation of Fasenra™ therapy is not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

Hypersensitivity reactions

Hypersensitivity reactions (e.g. anaphylaxis, angioedema, urticaria, urticaria papular, rash) have occurred after administration of Fasenra™. These reactions may occur within hours of administration, but in some instances, have a delayed onset (ie, days).

In the event of a hypersensitivity reaction, Fasenra™ should be discontinued.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if Fasenra™ may influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with Fasenra™. If patients become infected while receiving treatment with Fasenra™ and do not respond to antihelminth treatment, discontinue treatment with Fasenra™ until infection resolves.

Effects on ability to drive and use machines

Fasenra™ has no or negligible influence on the ability to drive and use machines.

Special precautions for storage

Store in a refrigerator (2°C to 8°C). Store the prefilled syringe in the original package to protect from light. Do not freeze.

Nature and contents of container

One mL solution in a sterile, single-use prefilled syringe made from type I glass with a staked 29 gauge ½ inch stainless steel needle, rigid needle shield, and Fluorotec-coated stopper in a passive safety device.

Fasenra™ is available in a pack containing 1 single dose prefilled syringe.

Instructions for use, handling and disposal

Do not shake. Do not use if frozen.

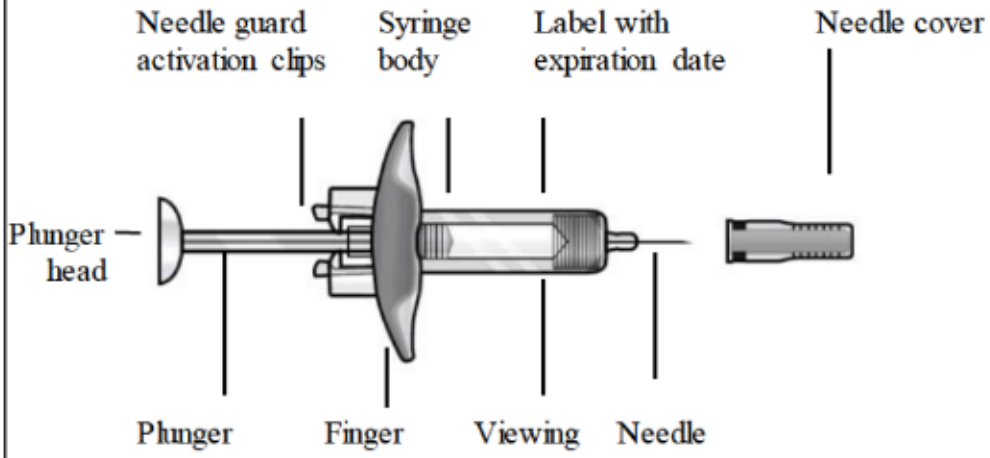
Instructions for administration

Before administration, warm Fasenra™ by leaving carton at room temperature. This generally takes 30 minutes. Administer within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

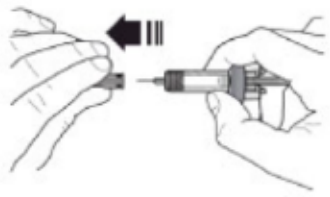
Refer to figure below to identify the prefilled syringe components for use in the administration steps.

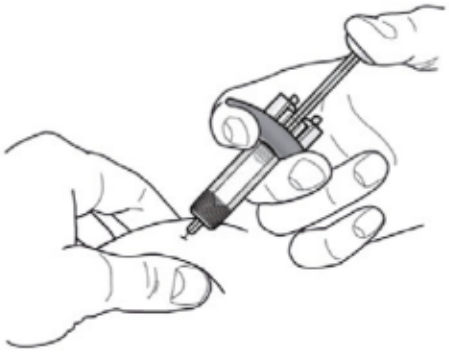
Figure:



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect Fasenra™ for particulate matter and discoloration before administration. Fasenra™ is clear, colourless to yellow, and may contain translucent or white to off-white particles. Do not use Fasenra™ if liquid is cloudy, discoloured, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble before administration.

2 	Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.
3	Gently pinch the skin and insert the needle at the

	recommended injection site (ie, upper arm, thigh, or abdomen)
4 	Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**
5 	After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**
6 Discard the used syringe into a sharps container.	

Appendix E Coronavirus Disease-19 Vaccination Guidance

In response to the current pandemic and approval/emergency use authorization (EUA) of novel SARS-CoV-2 (COVID-19) vaccines, AstraZeneca has developed the following guidance for benralizumab (Fasenra) trials:

- The trials continue as per approved Clinical Study Protocol.
- Ongoing participants in clinical trials may receive an approved/EUA COVID-19 vaccine when made available to them.
- Vaccine administration must be at least 7 days apart from IP injection, longer interval is advised when possible. If needed, IP dose can be re-scheduled to allow for sufficient interval prior/post COVID vaccination.
- Subsequent IP dose should be given a different location from the vaccine.
- Patients who received COVID-19 vaccination prior to the study start should not be randomized until >30 days after the last vaccine dose.
- COVID vaccination must be recorded on Concomitant Medication module in eCRF clearly indicating the vaccine brand. That applies to any COVID-19 vaccine received prior to or during the study.
- Use of experimental and/or non-approved and /or non-authorised COVID-19 vaccines is disallowed.
- The decision to vaccinate should be based on the risks and benefits for each individual patient and on what is in the patient's best interest according to the Investigator's clinical judgement.
- Any questions should be addressed to the study Medical Team through the QA log, or direct communication if urgent.

Appendix F Abbreviations

Abbreviation or special term	Explanation
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRO	contract research organisation
ECG	electrocardiogram
EDC	electronic data capture
ER	Emergency Room
eCRF	electronic case report form
EOS	End of Study
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-5	interlukin-5
IL-5Rα	interlukin-5 receptor alpha subunit
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
KM	Kaplan–Meier
LABA	long-acting beta-agonist
OCS	8.1.steroid
PI	Package Insert
Pre-BD	prebronchodilator
Post-BD	postbronchodilator
SAE	serious adverse event
SD	standard deviation
SAP	statistical analysis plan
SmPC	Summary of product characteristics
SoA	schedule of activities

Abbreviation or special term	Explanation
TEAE	treatment-emergent adverse event
USPI	United States Prescribing Information

11 REFERENCES

AstraZeneca Fasenra™ (benralizumab) Summary of Product Characteristics
AstraZeneca. Fasenra™ (benralizumab) summary of product characteristics. 2019. Available at www.ema.europa.eu/en/documents/product-information/fasenra-epar-product-information_en.pdf. Accessed 04 Sep 2020.

AstraZeneca Fasenra® (benralizumab) US Prescribing Information
AstraZeneca. US FDA 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761070s005lbl.pdf. Accessed 04 Sep 2020.

AstraZeneca
A Safety Extension Study with Benralizumab for Asthmatic Adults on Inhaled Corticosteroid Plus Long-acting β2 Agonist (MELTEMI): NCT2808819. Available at https://clinicaltrials.gov/ct2/show/NCT2808819. Accessed 14 December 2020.

AstraZeneca
Observational Study of Characteristics, Treatment and Outcomes With Severe Asthma in the United States (CHRONICLE): NCT03373045. Available at https://clinicaltrials.gov/ct2/show/NCT03373045. Accessed 14 December 2020.

Bagnasco et al, 2017
Bagnasco D, Ferrando M, Varricchi G, et al. Anti-interleukin 5 (IL-5) and IL-5Ra biological drugs: efficacy, safety, and future perspectives in severe eosinophilic asthma. Front Med (Lausanne). 2017;4:135.

Bleecker et al, 2016
Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27

Busse et al, 2019
Busse WW, Bleecker ER, Fitzgerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. Lancet Respir Med 2019;7:46-59

Chung et al, 2014
Chung KF, Wenzel SE, Brozel JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373

Clinical Study Report D3250C00037. A Multicenter, Open-label, Safety Extension Study with Benralizumab (MEDI-563) for Asthmatic Adults on Inhaled Corticosteroid Plus Long-acting β2 Agonist (MELTEMI). AstraZeneca. 26 Oct, 2020.

Fitzgerald et al, 2016
Fitzgerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatszch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388:2128-41

GINA 2020
Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2020. Available from: www.ginaasthma.org

Gonzalez et al, 2019
Gonzalez ID, Benitez FM, Quirce S. Benralizumab: A New Approach for the Treatment of Severe Eosinophilic Asthma. J Investig Allergol Clin Immunol 2019;29:84-93.

ISAR
International Severe Asthma Registry (ISAR). Available at https://isaregistries.org/ Accessed 14 December 2020.

Jackson et al, 2020
Jackson DJ, Korn S, Mathur SK, et al, Safety of Eosinophil-Depleting Therapy for Severe, Eosinophilic Asthma: Focus on Benralizumab. Drug Saf. 2020;43:409-425.

Kolbeck et al, 2010
Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol 2010;125:1344-1353

Pavord et al, 2013
Pavord ID. Eosinophilic phenotypes of airway disease. Ann Am Thorac Soc 2013;10 Suppl:S143-9

Pelaia et al, 2020
Pelaia C, Busceti MT, Crimi C, Carpagnano GE, Lombardo N, Terracciano R, et al. Real-Life effects of benralizumab on exacerbation number and lung hyperinflation in atopic patients with severe eosinophilic asthma. Biomed Pharmacother 2020;129:110444 doi: 10.1016/j.biopha.2020.110444. Online ahead of print.

Periodic Benefit-Risk Evaluation Report. Fasenra™ (benralizumab). AstraZeneca. 19 Dec, 2020.

Rogliani et al, 2020
Rogliani P, Calzetta L, Matera MG, Laitano R, Ritondo BL, Hanania NA, et al. Severe Asthma and Biological Therapy: When, Which, and for Who. Pulm Ther 2020;6:47-66

Takatsu et al, 1994
Takatsu K, Takaki S, Hitoshi Y. Interleukin-5 and its receptor system: implications in the immune system and inflammation. Adv Immunol. 1994;57:145-90.

Toba et al, 1999
Toba K, Koike T, Shibata A, Hashimoto S, Takahashi M, Masuko M, et al. Novel technique for the direct flow cytofluorimetric analysis of human basophiles in unseparated blood and bone marrow, and the characterization of phenotype and peroxidase of human basophiles. Cytometry. 1999;35:249-59

Walford et al, 2014
Walfor HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma Allergy 2014;7:53-65

ASTRAZENECA SIGNATURE(S)

A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma with Eosinophilic Phenotype in India

This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

Mar 11, 2021

Name and Affiliation

PPD
(Study Director)
VP - Medical Affairs & Regulatory
AstraZeneca Pharma India Ltd.
Block N1, 12th Floor,
Manyata Embassy Business Park,
Bangalore, Karnataka 560045

Date (Day Month Year)

ASTRAZENECA SIGNATURE(S)

A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma with Eosinophilic Phenotype in India

This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

Mar 11, 2021

Name and Affiliation

Date (Day Month Year)

PPD
Therapy Area Lead-Respiratory
AstraZeneca Pharma India Ltd.
Block N1, 12th Floor,
Manyata Embassy Business Park,
Bangalore, Karnataka 560045

ASTRAZENECA SIGNATURE(S)

A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma with Eosinophilic Phenotype in India

This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

Mar 10, 2021

Name and Affiliation Date (Day Month Year)

PPD
(Study Delivery Team Leader)
Senior Manager-Trials, Publications & Medical Excellence
AstraZeneca Pharma India Ltd.
Block N1, 12th Floor,
Manyata Embassy Business Park,
Bangalore, Karnataka 560045
Mobile no. -PPD

ASTRAZENECA SIGNATURE(S)

A Postmarketing, Phase 4, Multicentre, Prospective, Single-arm Study to Assess the Safety of Fasenra® (Benralizumab) in Adult Patients of Severe Asthma with Eosinophilic Phenotype in India

This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

Mar 10, 2021

Name and Affiliation Date (Day Month Year)

PPD
(Study Physician)
Medical Affairs
AstraZeneca Pharma India Ltd.
Block N1, 12th Floor,
Manyata Embassy Business Park,
Bangalore, Karnataka 560045
Mobile No: PPD