Clinical Study Protocol	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00025
Version	5.0
Date	22 February 2022

An Open-label Study to Evaluate the Pharmacokinetics and Pharmacodynamics and Long-term Safety of Benralizumab Administered Subcutaneously in Children with Severe Eosinophilic Asthma

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Local Sponsor in Japan:

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Regulatory Agency Identifying Number(s):

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Version 5.0)	22 February 2022
Amendment 3 (Version 4.0)	01 July 2020
Amendment 2 (Version 3.0)	22 August 2019
Amendment 1 (Version 2.0)	22 July 2019
Original Protocol (Version 1.0)	22 June 2018

Amendment 4 (22 February 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to update: the estimated study completion date; the benefit/risk assessment; storage of ECG readings; to add information regarding to medical device malfunctions; and to align with current CSP template requirements.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.2, Synopsis	Estimated date of last patient completed was changed from May 2022 to September 2022.	The last patient's first dose was mid-September 2021. If this patient completes the study, the estimated date of completion would be in September 2022.	Non-substantial
Section 2.3 Benefit/risk assessment	The minimum observation period at the clinical site following IP administration was changed to 1-hour from 2-hours.	Typographical correction to align with Section 6.3.3	Non-substantial
Section 6.1.1, Investigational products, Table 3 Study treatments	Aligned information presented with current CSP template.	Clarification	Non-substantial
Section 8.2.4 Electrocardiograms	Clarification that ECG readings can be stored as physical copies in subject's source files.	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.4.6 Medical device deficiencies; Section 8.4.6.1 Time period for detecting medical device deficiencies; Section 8.4.6.2 Follow-up of medical device deficiencies; Section 8.4.6.3 Prompt reporting of medical device deficiencies to Sponsor; Section 8.4.6.4 Regulatory reporting requirements for device deficiencies; Appendix G Medical device AEs, ADEs, SAEs, SADEs, USADEs and medical device deficiencies: definitions and procedures for recording, evaluating, follow-up, and reporting in medical device studies	New sections added to discuss device constituent deficiencies.	New sections to discuss device deficiencies in line with new EU/US regulations and CSP template.	Substantial

Version 4.0, 01 July 2020

In this amendment to the protocol:

- Section 4.1.1 (Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis), Section 8 (Study assessments and procedures), Section 9.7 (Sensitivity analyses), and Appendix B:
  - New text was added to clarify how the study could continue in the event of a serious disruption, including details of mitigations that could be employed to ensure study continuity.
- Section 5.1 (Inclusion criteria):
  - The duration of mandatory contraception use during the study was updated: contraception to be used for 12 weeks (rather than 4 months) after the last dose of IP.

- Section 6.3.3 (After investigational product administration) and Section 8.4.4 (Management of investigational product-related reaction):
  - The minimum observation time (for the appearance of acute drug reactions) following investigational product administration was shortened to 1 hour.
- Section 6.6 (Concomitant therapy):
  - The study period during which the use of live attenuated vaccines was prohibited was updated: live attenuated vaccines use prohibited for 12 weeks (rather than 4 months) after the last dose of IP.
- Section 7.1 (Discontinuation of study treatment):
  - Criteria for discontinuation due to missed doses of IP updated to specify applicable to Part A only.
- Section 8.1.1.2 (Spirometry technique)
  - The procedure for performing a forced expiratory manoeuvre in children aged <10 years was clarified.
- Section 8.2.1 (Clinical safety laboratory assessments [Table 8]):
  - Procedures hepatitis B surface antigen screening updated.
- Section 8.4.3 (Overdose):
  - Section updated to specify dose considered as an overdose.
- Title page:
  - Sponsor details updated to include AstraZeneca Japan.
- Minor editorial changes throughout the document to clarify text, improve consistency, and to align the language and terminology used in the latest Clinical Study Protocol template.

Version 3.0, 22 August 2019

In this amendment to the protocol, the requirement that patients aged 12 to 14 years must weigh at least 35 kg has been removed. This change has been applied to the Synopsis and to Sections 4.1, 5.1, 6.1, 6.1.1 (Table 3) and 9.5.2. The rationale for this change has been added to Section 4.3.

Text to describe the cohort of Japanese patients aged 12 to 14 years has been added to the Synopsis and to Sections 4.1 and 9.2.

Minor changes have been made throughout to clarify text and improve consistency.

Version 2.0, 22 July 2019

In this amendment to the protocol:

Table 1:

- The window for the screening visit has been updated.
- Windows for Visit 3, Visit 4, and Visit 5 have been updated to be consistent with the window for the PK sample at these visits.
- Interviewer-administered Asthma Control Questionnaire (ACQ-IA) has been added at Visit 2, Visit 4, Visit 5, Visit 11, Visit 12, and Visit 14.
- Interviewer-administered Patient Global Impression of Change (PGIC-IA) has been added at Visit 9, Visit 10, Visit 11, Visit 13 and at the early discontinuation (DXD)/early withdrawal (WD) visit.
- Clinician Global Impression of Change (CGIC) has been added at Visit 9, Visit 10, Visit 11, Visit 13 and at the DXD/WD visit.
- Forced expiratory volume in 1 second (FEV_1) has been added at Visit 2.
- Urinalysis has been added at screening and at Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 13, and at the DXD visit, to be consistent with the text of Section 8.2.1.
- Asthma exacerbation has been added to all visits except Visit 1 and Visit 2.
- Pregnancy test, pharmacokinetic (PK) sampling and anti-drug antibody (ADA) sampling assessments have been updated with a corresponding footnote added to indicate when these assessments should be performed pre-dose.
- The schedule of ADA sampling has been updated
- Sampling for neutralizing antibodies (nAb) has been deleted from the ADA sampling row, and from the table footnotes.
- The table has been reorganised to follow the recommended sequence for the completion of assessments at each visit.

Synopsis

- PPD has been added as the international co-ordinating investigator.

Synopsis and Section 2.2, Section 4.1, Section 4.2, Section 5.1, and Section 9.5.2

- Inclusion of patients aged 12 to 14 years and weighing at least 35 kg in Japan has been added.

Synopsis and Section 3:

- Presence of neutralizing antibodies has been deleted from the secondary objectives.
- ACQ-IA has been added at Weeks 1, 2, 32, and 40 and at the follow-up visit in the secondary endpoints.
- PGIC-IA has been added at Week 16 (Part A), and Weeks 24, 32 and 48 (Part B) and at the DXD/WD visit.
- CGIC has been added at Week 16 (Part A), and Weeks 24, 32 and 48 (Part B) and at the DXD/WD visit.
- Annualized asthma exacerbation rate (AAER) has been added as an exploratory objective.

Synopsis and Section 4.1, Section 6.1, Section 6.1.1, and Section 9.5.2:

- Stratification by body weight <40 kg / ≥40 kg has been changed to stratification by body weight <35 kg / ≥35 kg.
- The dose of [redacted] mg to be administered to patients in the lower weight stratum (previously <40 kg) has been changed to [redacted] mg for the updated lower weight stratum of <35 kg.

Synopsis and Section 4.1:

- A statement has been added to allow the screening period to be extended if necessary.
- The statement that any of the first 4 patients in each cohort will be replaced if the patient misses a dose or a scheduled assessment has been deleted.

Section 2.3:

- A statement has been added concerning the risk related to hypersensitivity reactions.

Section 4.1:

- A statement has been added to clarify the requirements for patients in Part A to be evaluable, and that non-evaluable patients in Part A will be replaced.

Section 4.3:

- The justification for the dose of benralizumab has been updated to provide a rationale for the use of [redacted] mg in patients weighing <35 kg.

Section 5.1:

- The Japanese Pediatric Asthma Guidelines have been added to inclusion criterion 3.
- Definition of inhaled corticosteroid relevant to Japan has been added to inclusion criterion 6.

Section 6.1.2:

- Section 6.1.2 Medical Devices has been deleted, as it is not applicable to this study.

Section 6.2

- Further information has been added relating to storage of the investigational product (IP) and to actions to be taken in case of temperature excursions or damage to the IP or IP packaging.

Section 6.6:

- 'Five-lipoxygenase inhibitors' has been deleted from the table of prohibited medications.

Section 8:

- A recommended sequence for the completion of assessments at each visit has been added.
- Table 7 has been updated to include detail of the type of samples to be taken at each visit in addition to the volume of blood to be taken at each visit.

Section 8.1.2:

- A rationale has been added for the completion of the ACQ-IA at all visits during the treatment and post-treatment periods.

- A description of the PGIC-IA has been added.
- A description of the CGIC has been added.

Section 8.2.1, Section 8.3.8, Section 11 (Appendix D):

- References to liver enzyme elevations and to Hy's Law have been deleted.

Section 8.2.5.3:

- Reference to patients older than 9 years of age has been deleted.

Section 8.2.5.5:

- A section describing asthma exacerbation has been added.

Section 8.4.6:

- Section 8.4.6 Medical Device Malfunctions has been deleted, as it is not applicable to this study.

Section 8.5.1:

- Further detail has been added concerning the time and date of blood sampling for PK analysis.

Section 8.10.1:

- Testing for neutralizing antibodies has been deleted.

Section 8.10.2:

- Reference to neutralizing antibodies has been deleted.

Section 9.3

- The definition of patient evaluability has been updated.

Section 9.5.4.4

- PGIC-IA and CGIC have been added.

Section 9.5.6

- A description of the analysis of asthma exacerbation has been added.

Section 9.6.2:

- Reference to the SRC charter has been added, and detail of possible SRC recommendations has been deleted.

Throughout:

- Minor changes have been made to clarify text and improve consistency.

Version 1.0, 22 June 2018

Initial creation

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.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of assessments

	Part A – PK, PD, Safety									**Part B- Safety**					**DXD/ WD**	
Visit Visit windows	**1** SCRN Days –28 to -14	**2**	**3** +1 day	**4** ±3 day	**5** ±4 day	**6** ±7 day	**7** ±7 day	**8** ±7 day	**9** ±7 day	**10** ±7 day	**11** ±7 days	**12** ±7 days	**13** EOT ±7 day	**14** F/U ±7 day		For details see Section
Week	**-**	**0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**-**	**Section**
Day	**-**	**0**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**168**	**224**	**280**	**336**	**362**	**-**	**-**
Written informed consent/assent	X															Appendix A 3
Inclusion/ exclusion criteria	X	X														5.1, 5.2
ACQ-IA	X	X		X	X	X	X	X	X	X	X	X	X	X	X	8.1.2
PGIC-IA									X	X	X		X		X	8.1.2
CGIC									X	X	X		X		X	8.1.2
Body weight and height	X								X	X			X		X	8.2.5.1
Patient stratification	X															6.1
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.3
Medical/surgical history	X	X														8.2.5.2
12-lead ECG	X								X				X		X	8.2.4

Table 1 Schedule of assessments

	Part A – PK, PD, Safety									Part B- Safety					DXD/ WD	
Visit Visit windows	**1** SCRN Days –28 to -14	**2**	**3** +1 day	**4** ±3 day	**5** ±4 day	**6** ±7 day	**7** ±7 day	**8** ±7 day	**9** ±7 day	**10** ±7 day	**11** ±7 days	**12** ±7 days	**13** EOT ±7 day	**14** F/U ±7 day		For details see Section
Week	**-**	**0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**-**	**Section**
Day	**-**	**0**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**168**	**224**	**280**	**336**	**362**	**-**	**-**
Complete PE (pre-dose)	X	X							X				X		X	8.2.2
Brief PE (pre-dose)						X	X	X		X	X	X				8.2.2
FEV_1	X	X				X	X	X	X	X			X		X	8.1.1
Clinical chemistry assessments	X[a]	[a]				X	X	X	X	X			X		X	8.2.1
Haematology (CBC + differential)	X[a]	[a]				X	X	X	X	X			X		X	8.2.1, 8.6.1
Serology (hepatitis B, C, HIV)	X															8.2.1
Urinalysis	X					X	X	X	X	X			X		X	8.2.1
Pregnancy test	X	X[b]				X[b]	X[b]	X	X[b]	X[b]	X[b]	X[b]	X		X	8.2.5.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.5.4
Asthma exacerbation			X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.5.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
PK sampling		X[b]	X	X	X	X[b]	X[b]	X	X[b]	X[b]			X		X	8.5

Table 1 Schedule of assessments

	Part A – PK, PD, Safety									Part B- Safety					DXD/ WD	
Visit Visit windows	**1** SCRN Days –28 to -14	**2**	**3** +1 day	**4** ±3 day	**5** ±4 day	**6** ±7 day	**7** ±7 day	**8** ±7 day	**9** ±7 day	**10** ±7 day	**11** ±7 days	**12** ±7 days	**13** EOT ±7 day	**14** F/U ±7 day		For details see Section
Week	**-**	**0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**-**	**Section**
Day	**-**	**0**	**1**	**7**	**14**	**28**	**56**	**84**	**112**	**168**	**224**	**280**	**336**	**362**	**-**	**-**
ADA sampling		X[b]					X[b]		X[b]	X[b]			X		X	8.10
Single-dose IP injections		X				X	X		X	X	X	X				6.1

[a] The screening clinical chemistry/haematology samples at Visit 1 (Day -28 to Day -14) will constitute baseline values provided that Visit 2 (Day 0) is done ≤ 28 days after Visit 1. If so, no safety laboratory samples will need to be collected at Visit 2.

[b] To be performed before IP is administered at these visits.

Abbreviations: ACQ-IA interviewer-administered asthma control questionnaire, ADA anti-drug antibody(ies), CBC complete blood count, CGIC clinician global impression of change, DXD early discontinuation, ECG electrocardiogram, exam examination, EOT end of treatment, FEV_1 forced expiratory volume in 1 second, F/U follow-up, HIV human immunodeficiency virus, IP investigational product, PD pharmacodynamics, PE physical examination, PGIC-IA interviewer administered patient global impression of change, PK pharmacokinetics, SCRN screening, std standard, WD early withdrawal.

1.2 Synopsis

International co-ordinating investigator:

PPD

St. Louis, Missouri 63110

Protocol Title:

An Open-label Study to Evaluate the Pharmacokinetics and Pharmacodynamics and Long-term Safety of Benralizumab Administered Subcutaneously in Children with Severe Eosinophilic Asthma

Rationale:

Severe asthma appears to be related to increased blood concentrations of eosinophilic cells in adults, adolescents, and children aged 6 to 11 years (Fitzpatrick et al 2011). Eosinophilic cells have been shown to be a mediator in the pathophysiology of asthma in adults, adolescents, and children aged 6 to 11 years. Yet, it is unclear whether the pathophysiology is identical in these three age groups.

The absolute eosinophilic count in blood can be reliably measured in all the age groups concerned, thus a pharmacokinetic (PK)/pharmacodynamic (PD) relationship can be evaluated. Previous clinical studies of benralizumab in adult asthma patients have shown an association between depletion of eosinophilic cells in blood and improvement of asthma exacerbation rate, lung function, and asthma symptoms. Although an improvement in these asthma parameters was not demonstrated in the adolescent population, a PK/PD relationship similar to adults in eosinophil depletion was observed. However, the sample size was limited, and considerable efficacy was also seen in the placebo group.

The population PK analysis of benralizumab in asthma patients found that the clearance of the drug increased with body weight (AstraZeneca 2016, AstraZeneca 2017). In addition, age was not found to be a significant covariate in PK; the PK of adolescents was consistent with that of adults after accounting for weight difference. Thus, benralizumab can be expected to show PK properties proportional to body weight in children aged 6 to 11 years, as well as in adolescents and in adults, thus making a modelling approach based on adolescent and adult data possible to project an efficacious dose in children by matching the exposure of the adult efficacious dose. Moreover, there have been no safety signals detected in previous benralizumab clinical studies that would preclude administration to children aged 6 to 11 years.

This study will evaluate the PK, PD and long-term safety of benralizumab in 30 children aged 6 to 11 years with severe eosinophilic asthma. Up to 3 additional Japanese patients aged 12 to 14 years will be enrolled.

Objectives and endpoints

Primary objectives:	**Endpoints/variables:**
To evaluate the pharmacokinetics (PK) of benralizumab administered subcutaneously (SC) in children from 6 to 11 years of age with severe eosinophilic asthma	• Clearance • Area under concentration time curve to Day 28 (AUC_{0-28}) • Maximum serum concentration (C_{max}) • Terminal phase elimination half-life ($t_{1/2}$) • Time to reach C_{max} (T_{max})
To evaluate the pharmacodynamics (PD) of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma	Change from baseline in peripheral blood eosinophil count at Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B)
Secondary objectives:	**Endpoints/variables:**
To characterize the PK of benralizumab	Body weight-adjusted clearance
To evaluate the immunogenicity of benralizumab	Presence of anti-benralizumab antibodies
To evaluate the effect of benralizumab on pulmonary function	Change from baseline in pre-dose (when applicable), pre-bronchodilator, forced expiratory volume in 1 second (FEV_1) measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B)
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics	Change from baseline in Interviewer-administered Asthma Control Questionnaire (ACQ-IA) score, measured at screening and Weeks 1, 2, 4, 8, 12, and 16 (Part A), and Weeks 24, 32, 40 and 48, and at follow-up (Part B) Interviewer-administered Patient Global Impression of Change (PGIC-IA), measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD/WD visit Clinician Global Impression of Change (CGIC), measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD/WD visit
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability of benralizumab	Adverse events (AEs) Vital signs Collection of clinical chemistry/haematology parameters and urinalysis
Exploratory objective:	**Endpoints/variables:**
To evaluate exacerbations experienced	Annualized asthma exacerbation rate (AAER)

Overall design:

This is an open-label, parallel group study designed to evaluate the PK and PD, and long-term safety of benralizumab administered SC in 30 children from 6 to 11 years of age with severe eosinophilic asthma. Up to 3 additional Japanese patients aged 12 to 14 years will be enrolled.

Patients aged 6 to 11 years will be stratified by body weight at screening (<35 kg / ≥35 kg). Patients with a body weight <35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Patients with a body weight ≥35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Japanese patients aged 12 to 14 years will receive the CCI mg dose, and their visit schedules will be the same as patients aged 6 to 11 years throughout the study.

The study will be conducted in 2 parts, Part A and Part B. Part A will consist of 16 weeks of treatment to evaluate the PK/PD, and safety of benralizumab. Part B will consist of 32 weeks of continued treatment to evaluate the safety of benralizumab. All study data will be summarised together, not separately by study part.

After initial enrolment and confirmation of entry criteria, patients will proceed to a screening period of up to 28 days to allow adequate time for the eligibility criteria to be evaluated. The screening period may be extended if necessary after discussion with the AstraZeneca Study Physician. Patients who meet the eligibility criteria will enter the 48-week treatment period.

Staggered inclusion will occur for patients aged 6 to 11 years in which 4 patients with a body weight <35 kg and 4 patients with a body weight ≥35 kg will complete Part A then progress directly into Part B. Each treatment/weight group will be assessed separately by the Safety Review Committee (SRC) in accordance with the charter, so the treatment/weight groups can progress independently into Part B. After evaluation of all available PK and safety data from the initial 4 evaluable patients in each treatment/weight group, the remaining enrolled patients will enter the treatment phase. The 4 patients in each treatment/weight group in Part A must have received at least 1 dose of benralizumab and at least 3 post-first IP dose PK serum samples must have been collected to be evaluable. If any of the patients in Part A do not meet these criteria, then that patient will be replaced. Japanese patients aged 12 to 14 years may be enrolled in parallel with the staggered inclusion for the first 8 patients aged 6 to 11 years.

Study Period:

Estimated date of first patient enrolled: November 2019

Estimated date of last patient completed: September 2022

Number of Subjects:

Approximately 30 evaluable patients aged 6 to 11 years will be treated with benralizumab across the 2 combined weight strata, with a minimum of 8 patients in each stratum. Up to 3 additional Japanese patients aged 12 to 14 years will be enrolled.

Treatments and treatment duration:

Patients aged 6 to 11 years will receive either [redacted] mg or [redacted] mg of benralizumab (MEDI-563) based on baseline body weight for SC injection and the dose for each patient will not change during the study. Patients aged 12 to 14 years will receive [redacted] mg of benralizumab (MEDI-563) for SC injection during the study. Study treatment will be provided in an accessorised pre-filled syringe. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

In Part A, patients will receive 4 doses of study treatment (the first 3 doses every 4 weeks and the fourth dose 8 weeks after) depending on body weight. In Part B, 8 weeks after completing Part A, patients will receive an additional 3 doses of study treatment every 8 weeks (Q8W). The total duration of the study for most patients will be up to 56 weeks and will include a screening period of up to 28 days and a treatment period of 48 weeks, and a safety follow-up visit at Week 52. The total duration of the study may be longer if the screening period is extended.

Data Safety Monitoring Board:

A Data Safety Monitoring Board (DSMB) will oversee specific aspects of this study.

Statistical methods:

The sample size is not based on a formal sample size calculation. A sample size of 30 evaluable patients aged 6 to 11 years, with a minimum of 8 patients in each weight stratum, was chosen to provide sufficient data across the dosing and weight categories for PK parameter estimations using noncompartmental analysis (NCA) criteria assuming 30% for percent of coefficient of variation (CV%). Evaluable patients are defined as those patients with at least 3 post-first investigational product (IP) dose PK assessments above the lower limit of quantification. A cohort of up to 3 Japanese patients aged 12 to 14 years has been added following discussion with the PMDA.

PK parameters will be derived using either NCA or PK analysis set. PK analysis will, where possible, be carried out using actual time recorded in the raw data. If actual times are missing, nominal times will be used. A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Serum concentrations and PK parameters will be summarised using appropriate descriptive statistics. Figures showing individual and mean of PK concentration-time profiles will be produced on both semi-log and linear scales. Serum concentration data associated with positive anti-drug antibody (ADA) status will be flagged in

the PK concentration listings and may be excluded from the summary statistics and/or mean profiles. The observed paediatric PK will be compared with the projection from the population PK model in adult and adolescent asthma patients.

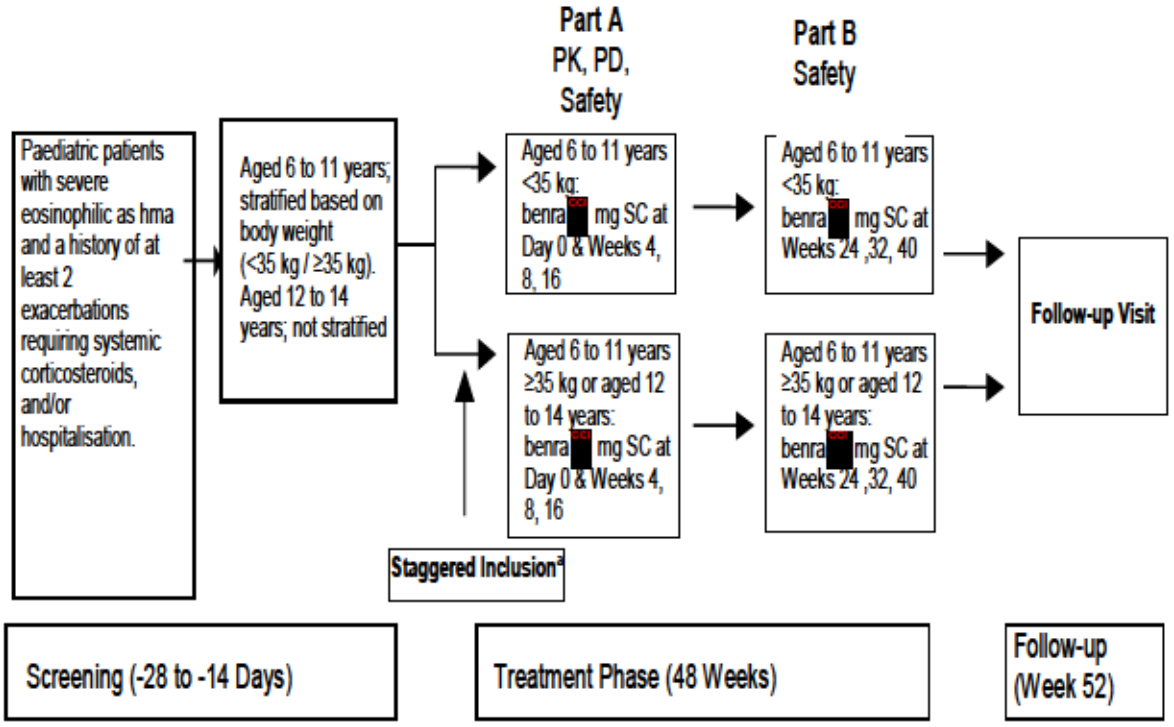
Peripheral blood eosinophils values and changes from baseline at each visit will be summarised using descriptive statistics for each treatment/weight group.

Other variables will be summarised, as appropriate, using descriptive statistics.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



[a] After the first 4 patients in each weight group have completed Part A (after evaluation of the PK and safety from Part A in these patients by the safety review committee), the remaining patients wi hin the weight group will enter the treatment phase.

benra benralizumab; PK pharmacokinetics; PD pharmacodynamics; SC subcutaneously

2 INTRODUCTION

2.1 Study rationale

Severe asthma appears to be related to increased blood concentrations of eosinophilic cells in adults, adolescents, and children ages 6 to 11 years (Fitzpatrick et al 2011). Eosinophilic cells have been shown to be a mediator in the pathophysiology of asthma in adults, adolescents, and children ages 6 to 11 years. Yet, it is unclear whether the pathophysiology is identical in these three age groups.

The absolute eosinophilic count in blood can be reliably measured in all the age groups concerned, thus a PK/PD relationship can be evaluated. Previous clinical studies of benralizumab in adult asthma patients have shown an association between depletion of eosinophilic cells in blood and improvement of asthma exacerbation rate, lung function, and asthma symptoms. Although an improvement in these asthma parameters was not demonstrated in the adolescent population, a PK/PD relationship similar to adults in eosinophil depletion was observed. However, the sample size was limited, and considerable efficacy was also seen in the placebo group.

The population PK analysis of benralizumab in asthma patients found that the clearance of the drug increased with body weight (AstraZeneca 2016, AstraZeneca 2017). In addition, age was not found to be a significant covariate in PK; the PK of adolescents was consistent with that of adults after accounting for weight difference. Thus, benralizumab can be expected to show PK properties proportional to body weight in children ages 6 to 11 years, as well as in adolescents and in adults, thus making a modelling approach based on adolescent and adult data possible to project an efficacious dose in children by matching the exposure of the adult efficacious dose.

2.2 Background

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction, and airway hyper responsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma affects children and adults of all ages. Asthma is a major cause of chronic morbidity and mortality throughout the world, with a higher prevalence in children as compared to adults (Fitzpatrick et al 2011, GINA 2018). Asthma often starts during childhood and may persist into adulthood. Current treatment strategies for controlling asthma are primarily aimed at reducing inflammation, with corticosteroids being the mainstay of treatment for patients with persistent asthma due to their powerful anti-inflammatory effects (GINA 2018, NAEPP 2007). However, the suppression of inflammation is incomplete in a considerable proportion of adults and children with severe asthma, despite treatment with corticosteroids in addition to or in combination with other long-term controller medications (Davies and Holgate 2002). This results in considerable

impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an urgent unmet medical need for patients, particularly children, whose severe asthma is not controlled by existing therapies (Alonso and Saglani 2017).

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Weiss and Ware 1996). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics) with the degree of eosinophilia associated with clinical severity including the risk of asthma exacerbations (Bousquet et al 1990, Di Franco et al 2003, Louis et al 2000, Sampson et al 2006, Scott and Wardlaw 2006, Zhang and Wenzel 2007).

Interleukin-5 (IL-5) is a key cytokine essential for eosinophil trafficking and survival (Molfino et al 2011). Benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody (mAb) that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell, which is expressed on the surface of eosinophils and basophils (Takatsu et al 1994, Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity, which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2012). Single and repeated doses of benralizumab in mild to severe asthma patients has resulted in depletion of blood eosinophils; repeated doses of benralizumab administered SC also markedly reduced airway wall and sputum eosinophil levels (Busse et al 2010, Gossage et al 2012, Laviolette et al 2013, Pham et al 2016). Since benralizumab has an anti-eosinophil mechanism of action with resultant tissue eosinophil depletion, it could reduce the disease burden in children with severe asthma.

The clinical efficacy of benralizumab 30 mg SC in adults was confirmed in 2 large Phase 3 global safety and efficacy studies in patients on high dose inhaled corticosteroids/long-acting β2 agonists (ICS/LABA) and blood eosinophil counts ≥300 cells/μL (Bleecker et al 2016, FitzGerald et al 2016). In these studies, that included patients ≥12 years, benralizumab was dosed Q8W for approximately 1 year and produced significant decreases in asthma exacerbations (up to 51%), and improvements in FEV_1 (up to 159 mL) and total daily asthma symptom scores in both studies. Additionally, the Phase 3 program also studied the efficacy of benralizumab in patients with blood eosinophil counts <300 cells/μL and in an oral corticosteroid (OCS)-dependent asthma population (FitzGerald et al 2017, Goldman et al 2017, Nair et al 2017). The results of these pre-specified and pooled analyses demonstrate broad efficacy in patients with blood eosinophil levels ≥150 cells/μL and support an enhanced response to benralizumab treatment when certain identifiable clinical features of the eosinophilic asthma phenotype are present, including OCS dependence and a history of frequent exacerbations.

To date, safety and tolerability has been evaluated in the paediatric population (≥12 years old) treated with benralizumab and patients (2 to 17 years old) treated with mepolizumab, a similar mAb that targets IL-5 and depletes eosinophils. In Phase 3 studies conducted in patients aged 12 years and older with severe uncontrolled asthma, benralizumab was generally well tolerated and depleted blood eosinophils, reduced exacerbation rates, and improved lung function in the overall population (Bleecker et al 2016, FitzGerald et al 2016). In patients with severe eosinophilic asthma, exacerbations decreased following treatment with mepolizumab (Ortega et al 2014, Pavord et al 2012); however, only a very small number of adolescents were included. A recently completed clinical study studying the pharmacological properties of SC administration of mepolizumab in children ages 6 to11 years with severe eosinophilic asthma further established the safety in younger children of mAbs that target eosinophils (NCT02377427). Further, children as young as 2 years have been included in clinical studies with mepolizumab for eosinophilic esophagitis (NCT00358449, Assa'ad et al 2011). Therefore, the PK/PD and safety profile of benralizumab in children is anticipated to be similar to adolescents and adults who demonstrate eosinophilic asthma.

The goal of this open-label, parallel group study Phase 3 study is to evaluate the PK and PD, and long-term safety of benralizumab administered SC in children from 6 to 11 years of age (or 6 to 14 years of age in Japan) with severe eosinophilic asthma.

2.3 Benefit/risk assessment

Benralizumab is currently approved for the treatment of severe eosinophilic asthma. This antibody is specific for the IL-5Rα subunit expressed predominantly on eosinophils and acts to deplete eosinophils. To date, trials of the efficacy of mAbs that deplete eosinophils either via targeting IL-5 (mepolizumab or reslizumab) or its receptor (benralizumab) have not been undertaken in children with severe asthma. Although it should be noted that paediatric severe asthma is markedly heterogeneous, eosinophils are the predominant inflammatory cell types present in the airway lumen and airway wall in children with severe asthma (Bossley et al 2012, Saglani and Lloyd 2014, Alonso and Saglani 2017). Benralizumab is beneficial for the treatment of adult severe asthma with an eosinophilic phenotype and thus there is a potential that benralizumab can be beneficial for the treatment of severe paediatric asthma at exposures that deplete eosinophils.

Overall, the AE profile in adolescents was generally similar to the overall population in Phase 3 studies conducted with benralizumab and mepolizumab. Additionally, during the benralizumab Phase 3 asthma exacerbation studies, extensive evaluation of immunoglobulins and flow cytometric assessment of cell subtypes demonstrated no differences between adolescent patients receiving benralizumab compared with placebo. Of note, mepolizumab had an acceptable AE profile in children with eosinophilic esophagitis as young as 2 years, and the PK in children was similar to adults (Assa'ad et al 2011). In summary, there have been no safety signals detected in previous clinical trials with benralizumab or other mAbs

that deplete eosinophils (mepolizumab) that would preclude administration of benralizumab to children ages 6 to 11 years.

Development of ADAs to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and increased hypersensitivity reactions (eg, anaphylaxis or immune complex disease). Anti-drug antibody development has not been associated with an increase in AEs.

Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumours. Therefore, there is a theoretical risk that sustained eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumours. Risk minimisation measures include exclusion of patients with untreated parasitic infection and active or recent malignancy.

Serious hypersensitivity reactions (including anaphylaxis) are a risk of treatment with biologic therapy including benralizumab. Anaphylaxis may be life-threatening. Risk minimisation includes a minimum of a 1-hour observation period at the clinical site following IP administration for the appearance of any acute drug reactions.

To date, benralizumab has exhibited a similar risk profile in adults and adolescents, one that is commensurate with placebo, and the important potential risks are manageable based on risk minimisation measures currently utilised in the clinical studies in conjunction with AstraZeneca routine pharmacovigilance activities.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of benralizumab may be found in the Investigator's Brochure.

See Section 9.6.1 and Appendix A for information regarding the DSMB.

3 OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are shown in Table 2.

Table 2 Study objectives and endpoints

Primary objectives:	**Endpoints/variables:**
To evaluate the pharmacokinetics (PK) of benralizumab administered subcutaneously (SC) in children from 6 to 11 years of age with severe eosinophilic asthma	• Clearance • Area under concentration time curve to Day 28 (AUC_{0-28}) • Maximum serum concentration (C_{max}) • Terminal phase elimination half-life ($t_{1/2}$) • Time to reach C_{max} (T_{max})
To evaluate the pharmacodynamics (PD) of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma	Change from baseline in peripheral blood eosinophil count at Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B)
Secondary objectives:	**Endpoints/variables:**
To characterize the PK of benralizumab	Body weight-adjusted clearance
To evaluate the immunogenicity of benralizumab	Presence of anti-benralizumab antibodies
To evaluate the effect of benralizumab on pulmonary function	Change from baseline in pre-dose (when applicable), pre-bronchodilator, FEV_1 measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B)
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics	Change from baseline in ACQ-IA score, measured at screening and Weeks 1, 2, 4, 8, 12, and 16 (Part A), and Weeks 24, 32, 40 and 48, and at follow-up (Part B) PGIC-IA, measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD/WD visit CGIC, measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD/WD visit
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability of benralizumab	AEs Vital signs Collection of clinical chemistry/haematology parameters and urinalysis
Exploratory objective:	**Endpoints/variables:**
To evaluate exacerbations experienced	Annualized asthma exacerbation rate (AAER)

4 STUDY DESIGN

4.1 Overall design

This is an open-label, parallel group study designed to evaluate the PK and PD, and long-term safety of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma, with an additional cohort of up to 3 Japanese patients aged 12 to 14 years.

Approximately 30 evaluable patients aged 6 to 11 years will be treated with benralizumab across the 2 combined weight strata, with a minimum of 8 patients in each stratum (Section 9.3). Up to 3 additional Japanese patients aged 12 to 14 years will be enrolled. Patients aged 6 to 11 years will be stratified by body weight at screening (<35 kg / ≥35 kg). Patients with a body weight <35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Patients with a body weight ≥35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Japanese patients aged 12 to 14 years will receive the CCI mg dose, and their visit schedules will be the same as patients aged 6 to 11 years throughout the study.

The study will be conducted in 2 parts, Part A and Part B. Part A will consist of 16 weeks of treatment to evaluate the PK and PD, and safety of benralizumab. Part B will consist of 32 weeks of continued treatment to evaluate the safety of benralizumab. All study data will be summarised together, not separately by study part.

After initial enrolment and confirmation of entry criteria, patients will proceed to a screening period of up to 28 days to allow adequate time for the eligibility criteria to be evaluated. The screening period may be extended if necessary after discussion with the AstraZeneca Study Physician. Patients who meet eligibility criteria will enter the 48-week treatment period. Patients will be maintained on their currently prescribed asthma maintenance therapy(ies) without change, from enrolment through screening, and through the treatment period.

Staggered inclusion will occur for patients aged 6 to 11 years in which 4 patients with a body weight <35 kg and 4 patients with a body weight ≥35 kg will complete Part A then progress directly into Part B. Each treatment/weight group will be assessed separately by the SRC in accordance with the charter, so the treatment/weight groups can progress independently into Part B. After evaluation of all available PK and safety data from Part A in the first 4 evaluable patients within each treatment/weight group, the remaining enrolled patients will enter the treatment phase (Section 9.6.2). The 4 patients in each treatment/weight group in Part A must have received at least 1 dose of benralizumab and at least 3 post-first IP dose PK serum samples must have been collected to be evaluable. If any of the patients in Part A do not meet these criteria, then that patient will be replaced. Japanese patients aged 12 to 14 years may be enrolled in parallel with the staggered inclusion for the first 8 patients aged 6 to 11 years.

The total duration of the study for most patients will be up to 56 weeks and will include a screening period of up to 28 days and a treatment period of 48 weeks, and a safety follow-up visit at Week 52. The total duration of the study may be longer if the screening period is extended.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3.

4.1.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis

The guidance given below supersedes instructions provided elsewhere in this Clinical Study Protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice (GCP), and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent and assent/reassent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form [ICF] should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure due to study disruption and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated Study Physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP administration: Performed by a site qualified HCP or HCP provided by a TPV. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix B.

4.2 Scientific rationale for study design

The aim of this study is to evaluate the PK and PD, and long-term safety of benralizumab administered SC as an add-on therapy in children (6 to 11 years old, or 6 to 14 years old in Japan) with severe eosinophilic asthma.

The sponsor considers the appropriate target population to be children ages 6 to 11 years with uncontrolled asthma despite adequate use of established asthma therapies (including ICS and LABA). Since PK and PD are objective measurements not assessed directly by the investigator or patient, and as such are not susceptible to investigator or patient bias, there is no need for a double-blind control in this study. The primary and secondary endpoints for this study (Section 3) are consistent with those in previously conducted studies and support the overall paediatric clinical development plan for benralizumab.

4.3 Justification for dose

Clinical asthma manifestations and treatment responses in children (6 to 11 years of age) and adolescents (12 to 17 years of age) are similar to the adult population (Weiss and Ware 1996). For several marketed or emerging therapeutic mAbs (adalimumab, basiliximab, canakinumab, eculizumab, and omalizumab), children typically receive the same fixed dose as for adults if their body weight is greater than 30 to 40 kg or the same weight-based intravenous dose (ie, infliximab and daclizumab) as in adults (Xu et al 2013). For the lower body weight strata, a dose is typically selected to match PK exposure of the adult efficacious dose using, for example, a population PK model.

A population PK model for benralizumab was previously developed with data from 8 clinical studies (SIROCCO, CALIMA, BISE, MI-CP158, MI-CP166, MI-CP186, MI-CP197 and MI-CP220). In this population PK model, weight was identified as a significant covariate. The PK profile for children 6 to 11 years of age weighing <35 kg was simulated using the weight distribution in the CDC growth chart assuming it was equally likely to recruit females and males at any age within the age group. The CCI mg dose was selected for children aged 6 to 11 years weighing <35 kg as the steady-state PK exposure was projected to be comparable to that of the adult efficacious dose, CCI mg. Based on the PK/PD relationship, blood eosinophils were predicted to attain near complete depletion.

In the pivotal Phase 3 studies, adult and adolescent (12 to 17 years old) patients were enrolled and randomised to receive placebo, 30 mg every 4 weeks (Q4W), and 30 mg Q8W. In these studies, there was no apparent advantage to more frequent dosing (Q4W). The safety profile in adolescents was consistent with the profile in adults and the more frequent regimen of 30 mg Q4W was well tolerated in both populations. Moreover, no exposure-related increase in TEAEs was observed in adult patients receiving 100 mg Q8W (more than three times the recommended clinical dose for the asthma indication).

Patients aged 12 to 14 years will receive [redacted] mg of benralizumab (MEDI-563) for SC injection during the study, irrespective of their body weight when enrolled, consistent with the approved dose of benralizumab in patients of this age.

The percentage and titre of ADAs and the impact of ADAs on the PK profile were assumed to be the same for children and for adults.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in Table 1.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study to be assigned to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are to be classed as screen failures, defined in Section 5.4.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Parent(s)/guardian are able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the patient must be able and willing to give assent to take part in the study according to the local requirement.

The ICF process is described in Appendix A 3.

Age

2 Patient must be 6 to 11 years of age inclusive (6 to 14 years of age inclusive in Japan), at the time of signing the ICF.

Type of subject and disease characteristics

3 Diagnosis of severe asthma, defined by the regional guidelines (ie, National Institutes of Health [NIH], Global Initiative for Asthma [GINA], American Thoracic Society [ATS], European Respiratory Society [ERS], Japanese Society of Pediatric Allergy and Clinical Immunology [JSPACI], etc.), for at least 12 months prior to Visit 1. If the patient is naïve to the study site, the patient/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the patient/guardian.

4 A previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids* and/or hospitalization in the 12 months prior to Visit 1, despite the use of ICS, or a persistent need for oral corticosteroid maintenance treatment to maintain asthma control, for at least 3 of the last 12 months prior to Visit 1, despite the use of ICS. *For patients receiving maintenance oral corticosteroids, the OCS treatment for the exacerbations must have been a two-fold increase or greater in the dose.

5 Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by peripheral blood eosinophil count of ≥150 cells / μL at Visit 1.

6 A well-documented requirement for regular treatment with ICS: total daily dose equivalent to ≥250 μg fluticasone propionate, or ≥400 μg budesonide (≥320 μg budesonide ex-actuator), or ≥200 μg fluticasone furoate, or ≥220 μg mometasone furoate, or ≥160 μg ciclesonide, or ≥1000 μg triamcinolone acetonide, or ≥500 μg beclomethasone dipropionate, or ≥200 μg beclomethasone dipropionate (HFA) in the 12 months prior to Visit 1, with or without maintenance oral corticosteroids. Medium dose ICS as per local guidelines will also satisfy the inclusion criterion after agreement with the Study Physician.

7 Current treatment with at least 1 additional controller medication, such as inhaled LABA, leukotriene receptor antagonist, long acting anti-muscarinic agent, or theophylline, since at least 3 months prior to Visit 1.

8 Forced expiratory volume in 1 second (FEV_1): Flow/ volume curve indicating airflow obstruction at either Visit 1 or 2 (performed prior to first dose of study medication), associated with: a pre-bronchodilator $FEV_1 \leq 110\%$ predicted normal, or, FEV_1/Forced Vital Capacity ratio ≤ 0.8.

Weight

9 Body weight ≥15 kg.

Sex

10 Male or female

Reproduction

11 Females of childbearing potential (FOCBP) who are sexually active, as judged by the investigator, must commit to consistent and correct use of an acceptable method of contraception for the duration of the study and for 12 weeks after the last dose of IP.

5.2 Exclusion criteria

Patients are eligible to be included in the study only if all of the inclusion criteria and none of the exclusion criteria apply:

Medical conditions

1 Any history of life-threatening asthma (eg, requiring intubation).

2 Clinically important pulmonary disease other than asthma such as active lung infection, bronchiectasis, pulmonary fibrosis, cystic fibrosis, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia.

3 Previous diagnosis of pulmonary or systematic disease, other than asthma, that is associated with elevated peripheral eosinophil counts such as allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), and hypereosinophilic syndrome.

4 Ever been diagnosed with malignant disease.

5 Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, immunological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could:

   (a) Affect the safety of the patient throughout the study.

   (b) Influence the findings of the study or their interpretations.

   (c) Impede the patient's ability to complete the entire duration of the study.

6 History of anaphylaxis to any biologic therapy.

7 Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening period, which in the opinion of the investigator may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete the entire duration of the study.

8 Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening period, which in the opinion of the investigator may put the patient at risk or interfere with study assessments.

9 Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol.

10 A helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent and assent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.

11 Alanine aminotransferase or aspartate aminotransferase level ≥1.5 times the upper limit of normal confirmed during the screening period.

12 A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.

Prior/concomitant therapy

13 Use of immunosuppressive medication, including, but not limited to, methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy, within 3 months prior to Visit 1. Chronic maintenance corticosteroid for the treatment of asthma is allowed.

14 Receipt of immunoglobulin or blood products within 30 days prior to Visit 1.

15 Receipt of any marketed (eg, omalizumab, mepolizumab, or off-label benralizumab) or investigational biologic within 4 months or 5 half-lives, whichever is longer, prior to Visit 1.

16 Receipt of live attenuated vaccines 30 days prior to the date of first dose of IP.

17 Initiation of new allergen immunotherapy is not allowed within 30 days prior to Visit 1. However, allergen immunotherapy initiated prior to this period can be continued provided there is a gap of 7 days between the immunotherapy and IP administration.

18 Current use of any oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol).

19 Planned surgical procedures during the conduct of the study.

Prior/concurrent clinical study experience

20 Participation in another clinical study with an investigational nonbiologic product administered in the last 30 days or 5 half-lives prior to enrolment, whichever is longer.

21 Known history of allergy or reaction to any component of the IP formulation.

22 Concurrent enrolment in another clinical study.

Other exclusions

23 Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (eg, inability to read, comprehend and write) which will limit the validity of consent to participate in this study.

24 Unwillingness or inability of the patient or parent/guardian to follow the procedures outlined in the protocol.

25 Children who are wards of the state or government.

26 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

27 Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

28 Previous treatment in the present study.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements.

5.3.2 Caffeine, alcohol, and tobacco

The patient must be a non-smoker.

5.3.3 Activity

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF 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 patients 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).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These patients should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

6 STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) intended to be administered to a study patient according to the study protocol. Study treatment in this study refers to benralizumab.

6.1 Treatments administered

Patients aged 6 to 11 years with a body weight <35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Patients aged 6 to 11 years

with a body weight ≥35 kg at screening will receive the following regimen of benralizumab: CCI mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by CCI mg at Weeks 24, 32, and 40 (Part B). Japanese patients aged 12 to 14 years will receive CCI mg, and their visit schedules will be the same as patients aged 6 to 11 years throughout the study.

6.1.1 Investigational products

Study treatments are outlined in Table 3.

Table 3 Study Treatments

	Aged 6 to 11 years and body weight <35 kg	Aged 6 to 11 years and body weight ≥35 kg, or aged 12 to 14 years
Study treatment name:	Benralizumab	Benralizumab
Type	Combination product	Combination product
Dose formulation:	CCI	CCI
Unit dose strength	CCI mg/mL	CCI mg/mL
Dosage level	Part A: CCI mg on Day 0, Weeks 4, 8 and 16. Part B: CCI mg on Weeks 24, 32 and 40.	Part A: CCI mg on Day 0, Weeks 4, 8 and 16. Part B: CCI mg on Weeks 24, 32 and 40.
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and labelling:	Study treatment will be provided in an APFS. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in an APFS. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Current/former name(s) or alias(es)	MEDI-563	MEDI-563

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

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.

Benralizumab must be kept in the original outer container and under conditions specified on the label (between 2°C to 8°C [36°F to 46°F], protected from the light).

In the following cases the centre staff should not use affected study treatment and should immediately contact an AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study
- Damaged kit upon receipt
- Damaged syringe/cartridge

Damaged study treatment should be documented via interactive web response system (IWRS)/interactive voice response system (IVRS) (refer to IWRS/IVRS manual for further details).

6.3 Investigational drug administration

6.3.1 Before investigational product administration

Study treatment is stored refrigerated and should be allowed to warm to room temperature before administration. Prior to each IP administration:

- Investigator/authorised delegate will assess injection site as per standards of medical care;

- For FOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative. A FOCBP is defined as a premenopausal female capable of becoming pregnant.

6.3.2 Investigational product administration

The IP will be administered by the investigator/authorised delegate.

Investigational product should be administered into the upper arm, thighs, or the abdomen. It is suggested that the site of injection is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, or hardened.

6.3.3 After investigational product administration

After IP administration, the sponsor recommends that the patient should be observed for a minimum of 1 hour in case of any acute drug reactions.

6.3.4 Conditions requiring investigational product administration rescheduling

If any of the following occur, the investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The patient has an intercurrent illness, that in the opinion of the investigator may compromise the safety of the patient in the study (eg, viral illnesses);
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration.

6.4 Measures to minimise bias: randomisation and blinding

Not applicable as this is an open-label study.

6.5 Treatment compliance

Any change from the dosing schedule and dose discontinuations should be recorded in the eCRF.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

6.6 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient 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.

Restricted medications are listed in Table 4.

Table 4 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Bronchodilator medication: SABA or SAMA Twice daily LABA or LAMA Once daily therapies containing LABA or LAMA	Should be withheld prior to scheduled spirometry for: 6 hours 12-24 hours ≥24 hours
Topical immunosuppressive medication	May be administered at the discretion of the investigator after discussion with the AstraZeneca Study Physician
Allergen immunotherapy injection	Should not be administered within 7 days of IP administration
Inactive/killed vaccines (eg, inactive influenza)	Should not be administered 7 days before or 7 days after IP administration

Abbreviations: IP investigational product, LABA long-acting β2 agonists, LAMA long-acting anti-muscarinic, SABA short-acting β2 agonists, SAMA short-acting anti-muscarinic

Prohibited medications are listed in Table 5.

Table 5 Prohibited medications

Prohibited medication/class of drug:	Duration
Immunosuppressive medication other than prior stable systemic corticosteroid for the maintenance treatment of asthma and for asthma exacerbations	Study period
Live attenuated vaccines	Within 30 days prior to first dose of IP, during the treatment period, and for 12 weeks (5 half-lives) after the last dose of IP
Oral or ophthalmic non-selective β-adrenergic antagonist (eg, propranolol)	Study period
Any marketed or investigational biologic (monoclonal or polyclonal antibody)	4 months or 5 half-lives (whichever is longer) prior to Visit 1, during the treatment period, and 4 months or 5 half-lives (whichever is longer) after the last dose of the IP
Other IP	30 days or 5 half-lives (whichever is longer) prior to first dose of IP and during the study period

Abbreviations: IP investigational product

6.6.1 Background medication

The patient's usual pre-study ICS and/or OCS formulations, doses and regimens, and any other additional allowed asthma controllers that they may have been taking prior to enrolment, should be continued throughout the screening and treatment periods. All changes in the patient's background medication should be documented in source along with the rationale for the change and recorded in the eCRF.

6.6.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.6.3 Rescue medication

Worsening of asthma symptoms should be treated according to standard practice.

6.7 Dose modification

No dose modification is allowed in this study. Patients aged 6 to 11 years will receive the same dose of benralizumab throughout the study based on their weight at screening. Patients aged 12 to 14 years will receive the [redacted] mg dose of benralizumab throughout the study.

6.8 Treatment after the end of the study

The patient should continue their usual asthma medication at the discretion of the investigator.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Patient or guardian decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event
- Severe non-compliance with the CSP
- Eligibility requirement found not to be fulfilled
- Positive pregnancy test at any time during the study
- Lost to follow-up
- Development of any study specific criteria for discontinuation:
  - Anaphylactic reaction to the IP requiring administration of epinephrine

- Development of helminth parasitic infestations requiring hospitalization
- If 2 consecutive doses of IP are missed or more than 2 scheduled doses of IP are missed during Part A dosing
- An asthma-related event requiring mechanical ventilation.

See Table 1 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last administration of study treatment should be documented in the eCRF. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

All patients who prematurely discontinue IP should return to the study site and complete the procedures described for the Early Discontinuation (DXD) Visit within 4 weeks after the last dose of IP. At that visit, although no longer on IP, patients should be encouraged to remain in the study. Although only AEs, SAEs, and concomitant medication are required to be collected after the DXD Visit, safety data collection should continue according to the study protocol. Note that in this case, the DXD Visit replaces the nearest regular visit while the following visits continue as possible. If the patient or guardian does not agree to continue in-person study visit(s), a modified follow-up, such as telephone contact with the patient or guardian, should be arranged to ensure the collection of safety information through the 48-week time point.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or guardian and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, certified letter to the patient´s or guardian’s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient’s medical record.
- Efforts to reach the patient or guardian should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be

lost to follow-up with unknown vital status at end of study and censored at the latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (IP **and** assessments) at his/her own request, without prejudice to further treatment.

If the patient 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 patient withdraws from the study, he/she or his/her guardian may request destruction of any samples taken, and the investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow-up patients as medically indicated.

See Table 1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a patient withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn patients may be replaced if they discontinue within Part A of the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in Table 1.

The investigator will ensure that data are recorded in the eCRF. The Web Based Data Capture system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRF and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site. Additional data to assess the impact of civil crisis, natural disaster, or public health crisis will be collected.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of

all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1.

The recommended sequence for completion of assessments at each visit is:

- Complete ACQ-IA, PGIC-IA, CGIC
- Measure vital signs, ECG, conduct physical examination
- Conduct spirometry assessment
- Take blood samples
- Administer benralizumab.

Based on the European Medicines Agency's (EMA) Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population (EMA 2008), the maximum amount of blood collected, including any losses in the manoeuvre, from each patient should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time during the study (Table 6).

Table 6 Maximum volume of blood to be withdrawn from a patient

Patient weight (kg)	Total blood volume (mL)[a]	Maximum blood volume (mL) to be withdrawn at any visit	Maximum blood volume (mL) to be withdrawn within a 4-week period
15-20	1200-1600	12.0-16.0	36.0-48.0
21-25	1680-2000	16.8-20.0	50.4-60.0
26-30	2080-2400	20.8-24.0	62.4-72.0
31-35	2480-2800	24.8-28.0	74.4-84.0
36-40	2880-3200	28.8-32.0	86.4-96.0
41-45	3280-3600	32.8-36.0	98.4-108.0
46-50	3680-4000	36.8-40.0	110.8-120.0
51-55	4080-4400	40.8-44.0	122.4-132.0
56-60	4480-4800	44.8-48.0	134.4-144.0
61-65	4880-5200	48.8-52.0	146.4-156.0
66-70	5280-5600	52.8-56.0	158.4-168.0
71-75	5680-6000	56.8-60.0	170.4-180.0
76-80	6080-6400	60.8-64.0	182.4-192.0

Table 6 Maximum volume of blood to be withdrawn from a patient

Patient weight (kg)	Total blood volume (mL)[a]	Maximum blood volume (mL) to be withdrawn at any visit	Maximum blood volume (mL) to be withdrawn within a 4-week period
81-85	6480-6800	64.8-68.0	194.4-204.0
86-90	6880-7200	68.8-72.0	206.4-216.0
91-95	7280-7600	72.8-76.0	218.4-228.0
96-100	7680-8000	76.8-80.0	230.4-240.0

[a] The total blood volume is estimated at 80 mL/kg body weight.
Source: EMA 2008

The total maximum volume of blood that will be withdrawn from each patient at each study visit is listed in Table 7.

Table 7 Maximum volume of blood to be withdrawn from each patient

Visit	Samples required	Total maximum volume (mL)[a]
Visit 1 (Screening)	clinical chemistry; haematology; serology	13.0
Visit 2	PK; ADA	5.0
Visit 3	PK	2.5
Visit 4	PK	2.5
Visit 5	PK	2.5
Visit 6	clinical chemistry; haematology; PK	7.0
Visit 7	clinical chemistry; haematology; PK; ADA	9.5
Visit 8	clinical chemistry; haematology; PK	7.0
Visit 9	clinical chemistry; haematology; PK; ADA	9.5
Visit 10	clinical chemistry; haematology; PK; ADA	9.5
Visit 11		0
Visit 12		0
Visit 13 (End of Treatment)	clinical chemistry; haematology; PK; ADA	9.5
Visit 14 (Follow-up)		0
Early discontinuation (DXD)	clinical chemistry; haematology; PK; ADA	9.5
Total (mL)		87.0

[a] Volumes exclude serum pregnancy testing and excludes any re-testing requirements. If serum pregnancy testing is needed, it will be analysed from samples collected at Visit 1, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, Visit 13, and the DXD Visit. If serum pregnancy testing is to be analysed at other visits then an additional 2.5mL blood collection will be required.

8.1 Efficacy assessments

This is a PK/PD study; therefore, the primary outcome measures are described in Section 8.5 and Section 8.6.

8.1.1 Spirometry

8.1.1.1 General requirements

Lung function (FEV_1) at the study centre will be measured by spirometry using the site's own equipment. Spirometry should be performed by the investigator or authorised delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

Important! Patients should withhold their bronchodilator medications prior to scheduled spirometry per Section 6.6. The patient's usual asthma medications may be administered following completion of the lung function procedures.

8.1.1.2 Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the centre. Forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

The forced expiratory manoeuvre (FEV_1) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds (3 seconds for children aged <10 years). It is important to encourage the patient to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred:

- coughing during the first second
- glottis closure
- leak or
- obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded in the eCRF. The best efforts will be based on the highest FEV_1. The absolute measurement (for FEV_1), and the percentage of predicted normal

value will be recorded using the local spirometer at the site with predicted values derived from the reference value of choice, eg, Nair et al 2017, NHANES III 2010, Quanjer et al 2012, etc.

8.1.2 Clinical outcome assessments

Asthma Control Questionnaire-Interviewer Administered

The Asthma Control Questionnaire (ACQ) is a 7-item assessment comprised of 6 patient-reported items and a single clinical item pertaining to pre-bronchodilator FEV_1 % predicted (Juniper et al 1999). The ACQ was developed for self-administration by adults and adolescents. Patients are asked to record their experience with 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and use of short-acting β2 agonist (SABA) over the previous week using a 7-point scale (0 = no impairment; 6 = maximum impairment). The final item pertaining to FEV_1 uses a similar 7-point response scale. Shortened versions of the ACQ can be produced by omitting the FEV_1 item (ACQ-6) or the FEV_1 and SABA items (ACQ-5) from the assessment or scoring (Wyrwich et al 2011). The ACQ score is calculated by taking the mean of the 7 equally weighted items. The ACQ score range is 0 (well controlled) to 6 (extremely poorly controlled). Individual score change of at least 0.5 is meaningful and is used to support the responder definition (Juniper et al 2005). Mean ACQ scores ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and a score >1.5 indicates poorly controlled asthma (Juniper et al 2006).

An interviewer-administered version of the ACQ, which was developed for use with children aged ≥6 years (ACQ-IA), will be used in this study with the omission of item 7. The only difference between the ACQ-IA and the ACQ is the mode of administration. The ACQ-IA is administered by trained individuals according to standardized instructions to help the child understand concepts like "during the last week" and the 7-point scale. Per the assessment instructions, help from parents/caregivers is sought only as a last resort. Thresholds for defining poor asthma control and responder status have been evaluated but not to the extent of the self-administered version for adults and adolescents. The estimated threshold indicating poor asthma control is an ACQ-IA score ≥1.25 in patients ages 6 to 17 years (Nguyen et al 2014). The estimated minimal clinically important difference is 0.5 (Juniper et al 2010, Nguyen et al 2014).

The questionnaire will be completed at the study centre during every study visit except Visit 3 on Day 1 (Table 1). This will capture the early onset of effect and the effect of maintenance treatment. Completion of the ACQ-IA may also provide early insight into potential safety concerns.

Patient Global Impression of Change Interviewer Administered

The Patient Global Impression of Change (PGIC) question captures the patient's overall evaluation of response to treatment (Guy 1976). The PGIC is included to assess how a patient perceives their overall change in health status since the start of study treatment(s). This item is useful in characterizing the overall impact of the treatment. The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point scale ('Much Better', to 'About the same', to 'Much worse'). The patient is instructed to select the one response that gives the most accurate description of his/her state of health (overall status).

An interviewer administered PGIC (PGIC-IA) will be used in this study to help the child understand what is being asked. The PGIC-IA will be administered by trained individuals according to standardized instructions to help the child understand the question and response options. Help from caregivers/parents is sought only as a last resort. The PGIC-IA will be completed at the study centre at Visits 9, 10, 11 and 13 (Table 1).

Clinician Global Impression of Change

The Clinician Global Impression of Change (CGIC) question captures the patient's overall evaluation of response to treatment from the perspective of the clinician (Busner and Targum 2007; Guy 1976). The CGIC is included to assess how the clinician interprets and perceives the patients overall change in health status since the start of study treatment(s). This item is useful in characterizing the overall impact of the treatment from the clinician's perspective. It provides a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study medication.

The clinician is asked to report the degree to which they perceive the patient has changed since entering the treatment period using a 7-point scale ('Much Better', to 'About the same', to 'Much worse'). The CGIC will be completed by the clinician at the study centre at Visits 9, 10, 11 and 13 (Table 1).

8.2 Safety assessments

Planned time points for all safety assessments are provided in Table 1.

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and Table 1 for the timing and frequency. All protocol-required laboratory assessments, as defined in Table 8, must be conducted in accordance with the laboratory manual and Table 1.

The investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded in the eCRF and reported, see Section 8.3.7.

Local clinical routine procedures to reduce pain and discomfort from blood sampling in children will be followed, eg, offering topical anaesthesia, coordinated sampling to avoid repeated punctures and use of in-dwelling catheters as appropriate in accordance with ethical and instruction guidelines for paediatric blood sampling. Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

The clinical chemistry, haematology, virology, and urinalysis will be performed at a central laboratory.

Table 8 Laboratory safety variables

Haematology (complete blood counts with differential)	Clinical chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-basophil count differential count (absolute count)	S/P-Bilirubin, total
B-lymphocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
B-eosinophil count differential count (absolute count)	S/P-Alanine transaminase (ALT)
B-monocytes differential count (absolute count)	S/P-Glucose
B-neutrophils differential count (absolute count)	S/P-C-reactive protein
White blood cell (WBC) count	S/P-Urea
	S/P-Albumin
Urinalysis (dipstick)	S/P-Potassium
U-Hb/Erythrocytes/Blood	S/P-Calcium, total
U-Protein/Albumin	S/P-Sodium
U-Glucose	S/P-Creatine kinase (CK)
	S-hCG test (Section 8.2.5.3)
Virology screen	
Hepatitis B surface antigen (HBsAG)[a]	
Hepatitis C virus (HCV)	
Human immunodeficiency virus (HIV)	

[a] If a positive antibody test from Hepatitis B surface antigen (HBsAG) is received, standard reflex confirmation testing is to be carried out.

8.2.2 Physical examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), and neurological systems.

A brief physical examination will include the following: general appearance, respiratory, cardiovascular, and abdomen systems.

Complete and brief physical examinations will be performed at timelines as specified in Table 1. Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital signs

- Body temperature, pulse rate, and blood pressure (BP) will be assessed.
- Blood pressure and pulse measurements will be assessed sitting with a completely automated device with a calibrated manometer using an appropriate paediatric cuff. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute). The average of the 3 BP readings will be recorded in the eCRF.

8.2.4 Electrocardiograms

A 12-lead ECG will be obtained as outlined in Table 1 using the site's own ECG machines after the patient has rested in the supine position for at least 10 minutes.

The investigator or authorised delegate will judge the overall ECG as normal or abnormal and report this evaluation. If abnormal, it will be further documented as to whether the abnormality is clinically significant by the Principal Investigator. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF if applicable.

The investigator or authorised delegate may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents. Additionally, ECG readings can be printed and placed in the subject's source file.

8.2.5 Other safety assessments

8.2.5.1 Weight and height

Weight and height will be measured at timelines as specified in Table 1.

Weight and height measurements will be performed in light clothing and with shoes off, using calibrated weighing scales and stadiometer.

The patient's weight will be recorded in kilograms; height will be recorded in centimeters.

8.2.5.2 Medical/surgical history

Details of each patient's medical and/or surgical history will be recorded in the eCRF at timelines as specified in Table 1.

8.2.5.3 Pregnancy test

A serum pregnancy test will be done for FOCBP at screening (Visit 1), and a urine pregnancy test must be performed for FOCBP at each treatment visit prior to IP administration. A positive urine test result must be confirmed with a serum pregnancy test. If the serum test at screening is positive, the patient should be excluded. If a urine pregnancy test at a treatment visit and the confirmatory serum pregnancy test are positive, IP treatment must be discontinued.

Females of childbearing potential will be determined at the discretion of the investigator.

8.2.5.4 Concomitant medications

A list of a patient's concomitant medications will be recorded in the eCRF at timelines as specified in Table 1.

8.2.5.5 Asthma exacerbation

In this study, an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids (or an increase in oral steroid dose for those already on systemic corticosteroids) and/or an emergency department (ED) visit requiring use of systemic corticosteroids and/or an in-patient hospitalization due to asthma. An asthma exacerbation that occurs ≤ 7 days following the last dose of systemic steroid, prescribed for a prior exacerbation, will be recorded in the eCRF as the same exacerbation event. Asthma exacerbation information will be collected with a recall period of 'since the last scheduled visit'.

Information on in-patient hospitalizations, number of days in the hospital, and ED visits will be collected by the investigator/authorised delegate at each visit (as shown in Table 1) and recorded in the eCRF. Asthma-related hospitalization and ED visit information will be collected with a recall period of 'since the last scheduled visit'.

A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study centres (eg, by the primary care health care provider or at an ED/hospital) and details entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the eCRF.

8.3 Collection of adverse events

The 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 C.

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE in the eCRF. For information on how to follow up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse events and SAEs will be collected from the time of signature of the ICF throughout the treatment period and including the follow-up period (Visit 14).

All SAEs will be recorded in the eCRF and reported to the sponsor or designee within 24 hours, as indicated in Appendix C. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient’s last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix C.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE/non-serious AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last AE assessment 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE 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

8.3.5 Causality collection

The investigator will assess causal relationship between IP and each AE, 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 the IP?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix C to the CSP.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: 'Have you/the child 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.

8.3.7 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.8.

8.3.8 Disease-under study (DUS)

Symptoms of the DUS are those which might be expected to occur as a direct result of asthma. Events which are unequivocally due to the disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel 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 works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 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 is undertaken immediately. Investigators or other site personnel 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.

If the EDC system is not available, then the investigator or other 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.

For further guidance on the definition of a SAE, see Appendix C of the CSP.

8.4.2 Pregnancy

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

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal

birth or congenital abnormality) should be followed up and documented even if the patient 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 1day 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 8.3.2) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study. However, information on a pregnancy of a partner will be collected.

8.4.3 Overdose

For this study, any dose of benralizumab greater than 200 mg will be considered an overdose.

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

- 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 drug occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.4.1. For other overdoses, reporting must occur within 30 days.

8.4.4 Management of investigational product-related reaction

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available at the clinical research site where IP is administered. Study personnel must be trained to recognize

and treat anaphylaxis (Laviolette et al 2013, Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

Anaphylaxis will be defined as a serious reaction that is rapid in onset (minutes to hours) and that may result in death (Sampson et al 2006). Anaphylaxis to an IP that the patient has not been previously exposed to (such as benralizumab) is deemed highly likely when Sampson criterion 1 is fulfilled. Sampson criteria 2 and 3 are also listed for completeness:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, AND AT LEAST 1 of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction.

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient including: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms and/or persistent gastrointestinal symptoms.

3. Reduced BP after exposure.

Patients will have had a pre-assessment (ie, vital signs) prior to IP administration and the sponsor recommends that patients should be observed after IP administration for a minimum of 1 hour for the appearance of any acute drug reactions.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator.

8.4.5 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 8.3.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix C.

8.4.6 Medical device deficiencies

Medical devices (APFSs) are being utilised to deliver the IMP under study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

The definition of a Medical Device deficiency can be found in Appendix G.

NOTE: Incidents and deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix G of the protocol.

8.4.6.1 Time period for detecting medical device deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Appendix G.

8.4.6.2 Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.6.3 Prompt reporting of medical device deficiencies to sponsor

- Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The Medical Device Deficiency Paper Report Form will be sent to the sponsor.
- The sponsor will be the contact for the receipt of medical device deficiency reports.

8.4.6.4 Regulatory reporting requirements for device deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.
- For further guidance on the definition of an SAE, see Appendix G of the CSP.

8.5 Pharmacokinetics

8.5.1 Collection of samples

Blood samples for determination of PK parameters in serum will be taken at timelines as specified in Table 1. Blood samples taken at visits when a dose of benralizumab is administered must be taken pre-dose. Blood samples taken at visits when no benralizumab dose is administered may be taken at any time during the day of the visit. The time and date of blood samples taken for PK analysis must be recorded in the eCRF.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.2 Determination of drug concentration

Samples for determination of drug concentration in serum will be analysed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Full details of the analytical method used will be described in the bioanalytical report.

8.5.3 Storage and destruction of pharmacokinetic samples

The PK samples will be destroyed within 5 years of the CSR finalisation.

8.6 Pharmacodynamics

8.6.1 Collection of samples

Samples for analysis of peripheral blood eosinophils will be collected as part of standard haematology assessment (complete blood count [CBC], Section 8.2.1) at timelines as specified in Table 1. Sampling will occur pre-dose on visits when IP is administered.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.6.2 Storage, re-use and destruction of pharmacodynamic samples

The PD samples will be destroyed after analysis.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Additional biomarkers are not evaluated in this study.

8.9 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 Immunogenicity

8.10.1 Collection of samples

Serum samples for the determination of ADA in serum will be taken at the study visits indicated in Table 1. Sampling will occur pre-dose on visits when IP is administered.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Samples will be analysed using validated bioanalytical methods. Details of the analytical methods used will be described in a separate validation report.

8.10.2 Storage and destruction of immunogenicity samples

The ADA samples will be destroyed within 5 years of the CSR finalisation.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Data will be summarised descriptively. No formal statistical hypotheses will be tested in this study.

9.2 Sample size determination

The sample size is not based on a formal sample size calculation. A sample size of 30 evaluable patients, with at least 8 patients in each weight stratum, was chosen to provide sufficient data across the dosing and weight categories for PK parameter estimations using NCA criteria assuming 30% for CV%. In addition, a cohort of up to 3 Japanese patients aged 12 to 14 years will be enrolled.

9.3 Patient evaluability

For the purpose of the initial safety review by the SRC, evaluable patients are defined as those patients receiving at least one dose of study medication, with at least 3 post-first IP dose PK assessments above the lower limit of quantification. Any patients discontinuing the study in Part A due to a treatment-related safety reason will also be considered evaluable for safety assessment.

9.4 Populations for analyses

For purposes of analysis, the following populations are defined in Table 9. All data (including PD) except for PK data will be analysed using the safety analysis set. PK data will be analysed using the NCA or PK analysis set.

Table 9 Analysis populations

Population	Description
Pharmacokinetic analysis set	All patients who received at least 1 dose of benralizumab and from whom PK blood samples are not assumed to be affected by factors such as protocol violations (eg, restricted medications) and who had at least one quantifiable serum PK observation post first IP dose
Non-compartmental analysis set	All patients who received the first dose of benralizumab and from whom PK blood samples are not assumed to be affected by factors such as protocol violations (eg, restricted medications) and who had at least 3 quantifiable serum PK observations post-dose on Days 1, 7, 14, and 28
Safety analysis set	All patients who receive at least one dose of benralizumab

9.5 Statistical analyses

9.5.1 Overview

The statistical methodology below describes the high-level statistical analysis principles as foreseen when the study is being planned. The statistical analysis plan (SAP) will be prepared prior to the first patient entering the treatment period, and any subsequent amendments will be documented with the final amendments completed prior to database lock.

9.5.2 General statistical methodology

Summary data for patients aged 6 to 11 years will be presented in tabular format by treatment/weight groups (benralizumab CCI mg in patients <35 kg at screening and benralizumab CCI mg in patients ≥35 kg at screening). Categorical data will be summarised by the number and percentage of patients in each category. Continuous variables for parametric data will be summarised by descriptive statistics including n, mean, standard deviation, median, minimum value, and maximum value (unless stated otherwise) for non-PK data. For the summary of PK concentration levels, in addition, geometric mean and CV% based on log-transformed data will be presented.

Up to 3 Japanese patients aged 12 to 14 years will be enrolled. Exploratory analyses including both patients aged 12 to 14 years and patients aged 6 to 11 years will be conducted. In addition, subgroup analyses for Japanese and for non-Japanese patients will be conducted.

9.5.3 Primary variables

9.5.3.1 Pharmacokinetics

PK parameters will include clearance, body weight-adjusted clearance, area under concentration time curve to Day 28 (AUC_{0-28}), maximum serum concentration (C_{max}), terminal phase elimination half-life ($t_{1/2}$), and time to reach C_{max} (T_{max}).

PK parameters will be derived using either NCA or PK analysis set. PK analysis will, where possible, be carried out using actual time recorded in the raw data. If actual times are missing, nominal times will be used.

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Serum concentrations and PK parameters will be summarised using appropriate descriptive statistics. Figures showing individual and mean of PK concentration-time profiles will be produced on both semi-log and linear scales. Serum concentration data associated with positive ADA status will be flagged in the PK concentration listings and may be excluded from the summary statistics and/or mean profiles. The observed paediatric PK will be compared with the projection from the population PK model in adult and adolescent asthma patients (AstraZeneca 2016, AstraZeneca 2017).

9.5.3.2 Pharmacodynamics

Peripheral blood eosinophils values and changes from baseline at each visit will be summarised using descriptive statistics for each treatment/weight group.

9.5.4 Secondary variables

9.5.4.1 Pharmacokinetics

Body weight-adjusted clearance will be computed, based on a population PK model.

9.5.4.2 Immunogenicity

Anti-drug antibodies (ADA) to benralizumab will be summarised using descriptive statistics at each visit by treatment/weight group. Anti-drug antibody titres-time profiles of benralizumab by treatment/weight group will be generated. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety will be evaluated. Any hypersensitivity AEs reported during the on-study period will be evaluated by ADA status.

9.5.4.3 Spirometry

FEV_1 measurements and changes from baseline at each visit will be summarised using descriptive statistics for each treatment/weight group.

9.5.4.4 Asthma Control Questionnaire

ACQ-IA scores and changes from baseline at each visit will be summarised for each time point using descriptive statistics for each treatment/weight group.

9.5.4.5 Global Impression of Change Questionnaires

PGIC-IA and CGIC scores at each visit will be summarised for each time point using descriptive statistics for each treatment/weight group.

9.5.5 Safety variables

All safety analyses will be performed on the safety analysis set.

Adverse events will be listed for each patient and summarised by System Organ Class and Preferred Term assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory safety variables (haematology, clinical chemistry, and urinalysis) and changes from baseline will be summarised using standard summary statistics as appropriate. Shift tables using normal ranges (baseline to most extreme post-baseline value) will also be presented. Change from baseline of eosinophils count will also be summarised and be recorded in the eCRF as part of standard haematological assessments.

The results of the vital signs measurements will be listed and summarised.

Results of the physical examination and 12-lead ECG will be documented as normal or abnormal for each patient.

Other safety variables will be summarised as appropriate.

9.5.6 Exploratory variables

9.5.6.1 Annualized asthma exacerbation rate

Exacerbations experienced during the treatment period will be summarised descriptively for each treatment/weight group, including the number of exacerbations associated with an ED visit or hospitalization. For the production of summary statistics, the AAER will be calculated using the time-based risk approach:

*AAER = 365.25*Total number of exacerbations /Total duration of at risk treatment period (days)*

In addition, the number of patients experiencing at least one exacerbation will be summarised. Kaplan-Meier plots may also be considered to describe the time to first exacerbation.

9.6 Interim analyses

CCI [redacted]

9.6.1 Data Safety Monitoring Board

A DSMB will be utilized for this study. Appendix A, Section A 5 provides more details on the rationale for and the remit of the DSMB.

9.6.2 Safety Review Committee

In addition to the DSMB, the SRC will monitor safety in the study. The SRC will consist of 3 core members: Principal Investigator (or delegate), Study Physician/Global Clinical Lead (or delegate) and Global Safety Physician (or delegate). The Study Clinical Pharmacologist, Study Statistician, Patient Safety Scientist, Study Delivery Leader and other experts may also be invited as appropriate.

9.7 Sensitivity analyses

Additional analyses assessing the impact of civil crisis, natural disaster, or public health crisis may be included in the SAP.

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