

Protocol: D3250C00030

- **Protocol number:** D3250C00030
- **Document title:** Multicenter, Randomized, Open-Label, Parallel Group Phase I Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers.
- **Version number:** 1.0, Amendment 1
- **Date of the document:** 07 July 2017
- **NCT number:** NCT02968914

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## Clinical Study Protocol

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# A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administered using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

<b>PAREXEL Study No.:</b>	230172
<b>Sponsor Study Code:</b>	D3250C00030
<b>IND No./Eudra CT No:</b>	2016-002955-52
<b>Study Type:</b>	Clinical Pharmacology, Pharmacokinetic Comparability Study
<b>Test Product:</b>	Benralizumab administered via Autoinjector (AI)
<b>Reference Product:</b>	Benralizumab administered via accessorized pre-filled syringe (APFS)
<b>Therapeutic Indication:</b>	Asthma and Chronic Obstructive Pulmonary Disease (COPD)
<b>Pharmacological Class:</b>	Anti-eosinophil monoclonal antibody
<b>Development Phase:</b>	Clinical pharmacology
<b>Sponsor:</b>	AstraZeneca AB 151 85 Södertälje Sweden
<b>Study Centers:</b>	PAREXEL Early Phase Clinical Unit Berlin On the premises of Klinikum Westend, Haus 31 Spandauer Damm 130 14050 Berlin Germany  PAREXEL Early Phase Clinical Unit London Level 7, Northwick Park Hospital Watford Road, Harrow Middlesex HA1 3UJ United Kingdom
<b>Date of Original Protocol:</b>	Final 1.0, 19 October 2016
<b>Amendment No. 1</b>	Final 1.0, 07 July 2017

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Version 1996) and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

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### Confidentiality Statement

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## PROTOCOL AMENDMENT

### Clinical Study Protocol Amendment No. 1, Final 1.0, Dated 07 July 2017

The following changes were made to the original clinical study protocol, Final 1.0, dated 19 October 2016, to replace MedImmune Clinical Pharmacology with PAREXEL Quantitative Clinical Development (QCD) as the pharmacokinetic (PK) analyses vendor for this clinical study.

1. The Sponsor's (Lead) Clinical Pharmacologist was changed to **PPD**, see [Section 4](#).
2. The Clinical Pharmacokineticist was changed to **PPD**, see [Section 4](#).
3. The physical examination text was updated to clarify that any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE see [Section 9.3.4](#).
4. The protocol text was updated to indicate that the non-compartmental pharmacokinetic analyses of the serum concentration data for benralizumab will be performed by PAREXEL QCD using Phoenix WinNonlin (version 6.3 or higher) in accordance to PAREXEL SOPs and the following sentence was deleted "Figures will be created using SigmaPlot for Windows (12.5, or higher, Systat Software Inc., Chicago, IL)" see [Section 11.9.2](#).
5. The protocol text was updated to indicate that serum concentration data associated with positive anti-drug antibody (ADA) status may be excluded from the non-compartmental analyses (NCA), see [Section 11.9.2](#).
6. The protocol text was updated to indicate that 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, see [Section 11.9.3](#).
7. The protocol text was updated to indicate that abnormal baseline/screening results of physical examination will be documented in medical history for each subject see [Section 11.10.4](#).
8. Added **PPD** (Lead Clinical Pharmacologist) in the signature [Section 16.3](#).

## PROTOCOL SYNOPSIS

### Title of the Study

A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administered using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

### Principal Investigators (PIs)

PPD and PPD

### Study Centers

PAREXEL Early Phase Clinical Unit Berlin,  
On the premises of Klinikum Westend, Haus 31,  
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Germany

PAREXEL Early Phase Clinical Unit London,  
Level 7, Northwick Park Hospital,  
Watford Road, Harrow,  
Middlesex HA1 3UJ,  
United Kingdom

### Study Rationale

Benralizumab is a humanized anti-eosinophil monoclonal antibody (mAb) and depletes eosinophils via a mechanism of enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). Benralizumab's unique mechanism of action induces direct, rapid and nearly complete depletion of eosinophils in the lung tissue, sputum, blood and bone marrow. Benralizumab has demonstrated pharmacodynamic (PD) activity and clinical efficacy in asthma control in Phase 1, 2 and 3 studies.

In global pivotal trials, benralizumab has been administered by health care providers using accessorized pre-filled syringe (APFS) device. The APFS combination product is a single-use, disposable system that is designed to administer the labeled dose into the subcutaneous (SC) space as 1 injection and automatically provides a safety mechanism to reduce the occurrence of accidental needle-sticks during disposal of the system. The functionality and reliability of APFS for home administration were evaluated in another study (GREGALE). The Autoinjector (AI) combination product is an automated, single-use, disposable system that is designed to administer the labeled dose into the SC space as 1 injection in a two-step operation and has a locking needle shield to reduce the occurrence of accidental needle-sticks during disposal of the system.

An open-label, single dose pharmacokinetic (PK) comparability study is required to demonstrate comparable drug exposure (AUC and  $C_{max}$ ) following SC benralizumab administration by using APFS or AI devices. As for other therapeutic immunoglobulin G (IgG) monoclonal antibodies, body weight was previously identified as a relevant PK covariate for benralizumab. In addition, the use of different anatomical regions for SC injections may influence the absorption of protein drugs. In this study, descriptive comparison of benralizumab PK by weight and injection site will be provided.

### Number of Subjects Planned

A total of 180 healthy subjects will be randomized to ensure at least 162 evaluable subjects at the end of the treatment period.

### Study Period

Estimated date of first subject enrolled: November 2016 (signing of informed consent)  
Estimated date of last subject completed: June 2017

## Study Objectives

### Primary Objective:

- To compare the PK exposure following single SC administration of benralizumab by using APFS or AI devices

### Secondary Objectives:

- To evaluate the PK of benralizumab administered to various anatomical injection sites and in subjects with different body weight ranges
- To evaluate the safety and tolerability of benralizumab
- To evaluate the immunogenicity of benralizumab

## Study Design

This study will be a multicenter, randomized, open-label, parallel group Phase 1 study designed to compare benralizumab PK exposure in healthy subjects following single SC administration of fixed 30 mg dose of benralizumab by using APFS and single-use AI. Eligible subjects will be healthy subjects aged 18 to 55 years, with a body weight of 55 to 100 kg and a body mass index of 18 to 29.9 kg/m<sup>2</sup>. A total of 180 subjects will be randomized. Randomization will be stratified by weight group (55 to 69.9 kg, 70 to 84.9 kg and 85 to 100 kg), and within each of the 3 weight groups, subjects will be randomized 1:1:1:1:1 to 1 of the 6 combinations of treatment (APFS or AI) with injection site (upper arm, abdomen or thigh), presented in Table 1. This study will be performed at 2 study centers.

**Table 1 Design of a Pharmacokinetic Comparability Study in Healthy Subjects for Benralizumab Accessorized Pre-Filled Syringe and Autoinjector Devices**

Number of Subjects		APFS			AI			Total
		Upper Arm	Abdomen	Thigh	Upper Arm	Abdomen	Thigh	
Body Weight	55.0 to 69.9 kg	10	10	10	10	10	10	60
	70.0 to 84.9 kg	10	10	10	10	10	10	60
	85.0 to 100.0 kg	10	10	10	10	10	10	60
Total		90			90			180

AI: Autoinjector; APFS: Accessorized pre-filled syringe device

The study will comprise of:

- A screening period of maximum of 28 days,
- One treatment period during which subjects will be resident from the day before dosing (Day -1), until 2 hours after dosing on Day 1. The subjects will then return to the center for ambulant visits on Days 2, 4, 5, 6, 8, 15, 29 and 43, and
- An End-of-Treatment visit on Day 57 (Week 8).

After a screening period of up to 28 days, eligible subjects will be admitted to the unit on Day -1 (1 day before dosing) to reassess their eligibility. Subjects who meet eligibility criteria will be randomized on Day 1 to receive a single dose of 30 mg benralizumab by either APFS or AI device. The study will be completed after the End-of-Treatment visit on Day 57 (Week 8).

## Expected Duration of the Study

Each subject will be involved in the study for 12 to 13 weeks (8 to 9 weeks active participation) and 28 days screening period.

## Targeted Study Population

This study will be conducted in healthy male and/or female subjects (of non-child-bearing potential), 18 to 55 years (inclusive) of age.

#### Identity of the Investigational Medicinal Product (Accessorized Pre-Filled Syringe)

<b>IMP:</b>	Benralizumab
<b>Formulation:</b>	30 mg/mL solution for injection in accessorized pre-filled syringe
<b>Strength/concentration:</b>	30 mg/mL
<b>Dose:</b>	30 mg
<b>Route of administration:</b>	SC
<b>Specific device for drug administration, if applicable:</b>	Accessorized pre-filled syringe
<b>Regimen:</b>	Single Dose
<b>Special handling requirements:</b>	Store between 2-8°C (36- 46°F), protected from the light
<b>Availability of the IMP:</b>	01 Nov 2016

#### Identity of the Investigational Medicinal Product (Autoinjector)

<b>IMP:</b>	Benralizumab
<b>Formulation:</b>	30 mg/mL solution for injection in Autoinjector
<b>Strength/concentration:</b>	30 mg/mL
<b>Dose:</b>	30 mg
<b>Route of administration:</b>	SC
<b>Specific device for drug administration, if applicable:</b>	Autoinjector
<b>Regimen:</b>	Single Dose
<b>Special handling requirements:</b>	Store between 2-8°C (36- 46°F), protected from the light
<b>Availability of the IMP:</b>	01 Nov 2016

#### Outcome Endpoints

##### *Pharmacokinetic Endpoints:*

Where possible, the following PK parameters will be assessed for benralizumab on serum concentrations.

- Primary PK parameters: AUC,  $C_{max}$
- Secondary PK parameters:  $T_{max}$ ,  $t_{1/2}$ , CL/F,  $V_z/F$

Additional PK parameters may be determined where appropriate.

##### *Safety and Tolerability Endpoints:*

- Safety and tolerability variables will include
- Adverse events (AEs)
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate and body temperature)
- Electrocardiograms (ECGs)
- Physical examination
- Laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology and drugs of abuse and alcohol will be assessed for eligibility. Follicle-stimulating hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

#### Statistical Methods

##### *Presentation and Analysis of Pharmacokinetic Data:*

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 summarized separately by treatment (device) only and by treatment (device), body weight and injection site, using appropriate descriptive statistics.

The analysis of variance (ANOVA) model will be employed on the log-transformed  $C_{max}$  and AUC separately, with fixed effects of treatment (device), body weight group and injection site in order to provide a descriptive comparison of the PK exposure between the 2 devices. The estimated treatment (device) differences and the 90% confidence interval (CI) (2-sided) on the log scale will be back-transformed to obtain the geometric mean ratios of AI to APFS and its corresponding 90% CI.

***Presentation and Analysis of Safety and Eligibility Data:***

Adverse Events will be summarized by means of counts summaries by study period (pre-treatment and treatment period). Adverse Events will be listed for each subject and summarized by System Organ Class and Preferred Term assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA). Laboratory safety variables will be summarized using standard summary statistics as appropriate.

Other safety variables will be summarized as appropriate.

***Presentation and Analysis of Immunogenicity Data***

For the analysis of immunogenicity data, anti-drug antibodies (ADAs) to benralizumab will be summarized using descriptive statistics at each visit by treatment group. Anti-drug antibody titers-time profiles of benralizumab by treatment 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. The hypersensitivity reported during the on-study period will be evaluated for ADA status.

**Determination of Sample Size**

While this study is not a formal bioequivalence study, a total of 162 subjects (81 subjects per treatment group) are required for this study to achieve with 80% power and a 90% 2-sided CI for geometric mean ratios of AUC and  $C_{max}$  being within a limit of 0.8 to 1.25 inclusive. The calculation is based on two one-sided tests (TOST) at 5% alpha level under an assumption of maximum 50% CV PK variability for primary endpoints of benralizumab AUC and  $C_{max}$ . Assuming 10% dropout rate, 180 subjects will be enrolled to provide adequate numbers of subjects to assess the primary and secondary objectives of the study.

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## 2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<b>Abbreviation or special term</b>	<b>Explanation</b>
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event (see definition in <a href="#">Section 12.1.1</a> )
AI	Autoinjector
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APFS	Accessorized pre-filled syringe device
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AZRand	AstraZeneca randomization system
beta-hCG	Beta human chorionic gonadotropin
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL/F	Apparent extravascular clearance
ClinBase™	PAREXEL's electronic source data capturing and information management system
C <sub>max</sub>	Maximum observed concentration
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CV	Coefficient of variation
DCF	Data clarification form
DGR	Dangerous Goods Regulation
DILI	Drug-Induced Liver Injury
DMP	Data management plan
DVS	Data validation specification
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone

<b>Abbreviation or special term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
ICD	Informed Consent Document
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL-5	Interleukin-5
IL-5R	Interleukin 5 receptor
IMP	Investigational medicinal product
IV	Intravenous
IUD	Intrauterine device
LABA	Long-acting $\beta$ 2-agonists
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of subjects
NCA	Non-compartmental analysis
OAE	Other significant adverse events
OTC	Over-the-counter
PD	Pharmacodynamic (s)
PDS	Protocol deviation specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic (s)
Q4W	Every 4 weeks

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<b>Abbreviation or special term</b>	<b>Explanation</b>
Q8W	Every 8 weeks
QCD	Quantitative Clinical Development
R&D	Research and Development
RA	Regulatory Authority
RBC	Red blood cell
SAE	Serious adverse event (see definition in <a href="#">Section 12.1.2</a> ).
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal half-life
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
$T_{max}$	Time when the maximum concentration is observed
TOST	Two one-sided test
TSH	Thyroid-stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
$V_z/F$	Apparent volume of distribution based on the terminal phase
WBC	White blood cell

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### **3. ETHICAL AND REGULATORY REQUIREMENTS**

#### **3.1. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (version 1996) and are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples.

#### **3.2. Subject Data Protection**

The Informed Consent Document (ICD) will incorporate wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The Investigator and members of his research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in PAREXEL's ClinBase™ system and other documents by their subject number, not by name. Documents that identify the subject (e.g., signed ICD) will be maintained in confidence by the Investigator.

Study data will be stored in accordance with local and global data protection laws.

#### **3.3. Ethics and Regulatory Review**

The study will be submitted to the national regulatory agency for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Independent Ethics Committee (IEC) for ethical review and approval, by PAREXEL in accordance with local procedures.

PAREXEL will provide the Ethics Committee and Principal Investigator (PI) with safety updates/reports according to local requirements, including Suspected Unexpected Adverse Reactions (SUSARs), where relevant.

AstraZeneca will provide the Regulatory Authority (RA) with safety updates/reports according to local requirements, including SUSARs, where relevant.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how participants will be compensated is contained in the ICD.

### **3.4. Insurance**

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

### **3.5. Informed Consent**

The subjects shall be informed of the nature, significance, implications and risks of the trial, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his free informed consent, prior to the start of the study.

In conformance with the law, the nature of the informed consent will comply with the Declaration of Helsinki (version 1996), the current requirements of GCP (CPMP/ICH/135/95) and local regulation, which ever affords the greater subject protection.

### **3.6. Changes to the Protocol and Informed Consent Document**

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol. The amendment should be approved by the IEC and the national RA, before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICD, the IEC should approve the revised ICD before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IEC.

#### 4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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A list and contact details of Investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating Investigators will be provided in the clinical study report (CSR).

## 5. INTRODUCTION

### 5.1. Background Information

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 is a leading cause of morbidity with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 to 450 million people worldwide by 2025 [14].

The current approach to anti-inflammatory controller therapy in asthma is based on a stepwise intensification of a daily maintenance regimen centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA), with the addition of long-acting  $\beta$ 2 agonists (LABA) in patients with more severe asthma [10, 16]. Despite treatment per management guidelines, up to 50% of patients have asthma that is not well controlled [1; 2]. 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 unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes [21]. 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 [4, 13, 7, 17, 22, 18]. Interleukin-5 (IL-5) is a key cytokine essential for eosinophil trafficking and survival [15].

Benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody (mAb) that binds specifically to the human IL-5 receptor alpha subunit (IL-5R $\alpha$ ) on the target cell. The IL-5 receptor (IL-5R) is expressed almost exclusively on the surface of eosinophils and basophils [19, 20]. Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis [11]. Single and repeated doses of benralizumab in mild to severe asthma patients have resulted in depletion of blood and airway eosinophils [5, 15, 12]. A dose-finding trial in severe asthma proved benralizumab to have benefit across a range of asthma outcomes including reductions in asthma exacerbations, improvements in lung function, and reduction in symptoms [6].

The efficacy and safety of benralizumab has been confirmed in 2 large Phase 3 trials, in severe asthmatics with a history of exacerbations and still symptomatic despite using medium-to-high dose ICS/LABAs with or without oral corticosteroids or additional controller

medications [3, 9]. The dose studied in these trials was 30 mg, a dose derived from pharmacokinetic/pharmacodynamic (PK/PD) modeling of the Phase 2 dose-finding study, administered in 2 dosing regimens – either 30 mg every 4 weeks (Q4W) or 30 mg Q4W for the first 3 doses followed by dosing every 8 weeks (Q8W) thereafter. The primary endpoint in each study was the annual rate of asthma-related exacerbations with key secondary endpoints being FEV<sub>1</sub> and asthma symptoms as defined by a daily patient diary.

## 5.2. Study Rationale

Benralizumab is a humanized anti-eosinophil mAb and depletes eosinophils via a mechanism of enhanced ADCC. Benralizumab's unique mechanism of action induces direct, rapid and nearly complete depletion of eosinophils in the lung tissue, sputum, blood and bone marrow. Benralizumab has demonstrated pharmacodynamic activity and clinical efficacy in asthma control in Phase 1, 2 and 3 studies.

In global pivotal trials, benralizumab has been administered by health care providers using accessorized pre-filled syringe (APFS) device. The APFS combination product is a single-use, disposable system that is designed to administer the labeled dose into the subcutaneous (SC) space as 1 injection and automatically provides a safety mechanism to reduce the occurrence of accidental needle-sticks during disposal of the system. The functionality and reliability of APFS for home administration were evaluated in another study (GREGALE). The Autoinjector (AI) combination product is an automated, single-use, disposable system that is designed to administer the labeled dose into the SC space as 1 injection in a two-step operation and has a locking needle shield to reduce the occurrence of accidental needle-sticks during disposal of the system.

An open-label, single dose PK comparability study is required to demonstrate comparable drug exposure (AUC and C<sub>max</sub>) following SC benralizumab administration by using APFS or AI devices. As for other therapeutic immunoglobulin G (IgG) monoclonal antibodies, body weight was previously identified as a relevant PK covariate for benralizumab. In addition, the use of different anatomical regions for SC injections may influence the absorption of protein drugs. In this study, descriptive comparison of benralizumab PK by weight and injection site will be provided.

## 5.3. Dose Rationale

The efficacy and safety of a fixed 30 mg SC dose of benralizumab has been evaluated in 2 large Phase 3 studies in severe asthma patients with an eosinophilic phenotype [3, 9].

## 5.4. Adverse Events

### Possible Risks (Potential Risks)

- Serious infections (defined as infections that are life-threatening, requiring intravenous (IV) antibiotics or hospitalization)
- Helminth parasitic infections
- Hypersensitivity/allergic reactions
- Immune complex disease (type III hypersensitivity reactions)
- Malignancies

### Adverse Events (Observed)

In the recent Phase 3 SIROCCO study [3], the most common (observed in > 3% of the patients) adverse events (AEs) were asthma, nasopharyngitis, upper respiratory tract infection, headache, bronchitis, sinusitis, influenza, acute sinusitis, back pain, cough, hypertension, pyrexia, nausea, rhinitis, pharyngitis, arthralgia, rhinitis allergic, viral infection, pain in extremity, dyspnea, gastro esophageal reflux disease, asthenia, dizziness and gastroenteritis.

In the recent Phase 3 CALIMA study [9], the most common (observed in > 3% of the patients) AEs were nasopharyngitis, asthma, upper respiratory tract infection, bronchitis, headache, sinusitis, hypertension, influenza, rhinitis, rhinitis allergic, nasal congestion, diarrhea, arthralgia, back pain, gastroenteritis, contusion, cough, pharyngitis, pyrexia, oropharyngeal pain, oral candidiasis, pneumonia bacterial and viral upper respiratory tract infection.

In both studies, the AEs showed a largely similar distribution between treatment and placebo arms.

## 5.5. Risk-benefit and Ethical Assessment

Benralizumab is primarily being studied in severe asthma where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and oral corticosteroids [10]. In adult patients whose asthma was poorly controlled on medium-to-high dose ICS/LABA therapy, benralizumab at doses of  $\geq 20$  mg produced improvements in multiple metrics of asthma control including the annual rate of asthma exacerbations, lung function, ACQ-6 scores, and symptoms [6]. These findings have subsequently been confirmed in 2 large Phase 3 studies [3, 9] where a fixed dose of 30 mg was given either Q4W or Q8W.

Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (e.g., anaphylaxis or immune complex disease). 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 tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumors. Risk minimization measures herein include exclusion of subjects with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The efficacy and safety data obtained to date support the continued clinical development of benralizumab in patients with asthma.

A detailed assessment of the overall risk/benefit of benralizumab is provided in the Investigator's Brochure.

## **6. STUDY OBJECTIVES**

### **6.1. Primary Objective**

- To compare the PK exposure following single SC administration of benralizumab by using APFS or AI devices

### **6.2. Secondary Objectives**

- To evaluate the PK of benralizumab administered to various anatomical injection sites and in subjects with different body weight ranges
- To evaluate the safety and tolerability of benralizumab
- To evaluate the immunogenicity of benralizumab

Refer to [Section 11.9.1](#) for PK parameters, [Section 9.3](#) for safety variables and [Section 9.4](#) for immunogenicity assessments.

## 7. OVERALL DESIGN AND PLAN OF THE STUDY

### 7.1. Overall Study Design

This study will be a multicenter, randomized, open-label, parallel group Phase 1 study designed to compare benralizumab PK exposure in healthy subjects following single SC administration of fixed 30 mg dose of benralizumab by using APFS and single-use AI. Eligible subjects will be healthy subjects aged 18 to 55 years, with a body weight of 55 to 100 kg and a body mass index (BMI) of 18 to 29.9 kg/m<sup>2</sup>. A total of 180 subjects will be randomized. Randomization will be stratified by weight group (55 to 69.9 kg, 70 to 84.9 kg and 85 to 100 kg), and within each of the 3 weight groups, subjects will be randomized 1:1:1:1:1:1 to 1 of the 6 combinations of treatment (APFS or AI) with injection site (upper arm, abdomen or thigh), presented in [Table 1](#). This study will be performed at 2 study centers.

**Table 1 Design of a Pharmacokinetic Comparability Study in Healthy Subjects for Benralizumab Accessorized Pre-Filled Syringe and Autoinjector Devices**

Number of Subjects		APFS			AI			Total
		Upper Arm	Abdomen	Thigh	Upper Arm	Abdomen	Thigh	
Body Weight	55.0 to 69.9 kg	10	10	10	10	10	10	60
	70.0 to 84.9 kg	10	10	10	10	10	10	60
	85.0 to 100.0 kg	10	10	10	10	10	10	60
Total		90			90			180

AI: Autoinjector; APFS: Accessorized pre-filled syringe device

The study will comprise of:

- A screening period of maximum of 28 days,
- One treatment period during which subjects will be resident from the day before dosing (Day -1) until 2 hours after dosing on Day 1. The subjects will then return to the center for ambulant visits on Days 2, 4, 5, 6, 8, 15, 29 and 43, and
- An End-of-Treatment visit on Day 57 (Week 8).

After a screening period of up to 28 days, eligible subjects will be admitted to the unit on Day -1 (1 day before dosing) to reassess their eligibility. Subjects who meet eligibility criteria will be randomized on Day 1 to receive a single dose of 30 mg benralizumab by either APFS or AI device. The study will be completed after the End-of-treatment visit on Day 57 (Week 8).

#### 7.1.1. End of Study

The end of study is defined as the last subject's last visit to the clinical unit.

### 7.1.2. Interim Analyses

No interim analyses will be performed in this study.

### 7.1.3. Expected Duration of the Study

Each subject will be involved in the study for 12 to 13 weeks (8 to 9 weeks active participation) and 28 days screening period.

## 7.2. Schedule of Assessments

The schedule of assessments displaying assessments/tasks and time points is presented in [Table 2](#).

**Table 2 Schedule of Assessments**

	Screening Day -28 to -2	Day -1	Days 1 to 57
Informed consent	X		
Inclusion/exclusion criteria	X	X	
Height	X		
Weight	X	X	
Other demographic data	X		
Medical history	X		
Urinary drug and alcohol screen	X	X	
Serum pregnancy and FSH test	X		
Urine pregnancy test (dipstick)		X	Day 57
Serology	X		
Randomization			Day 1
<b>Study residency:</b>			
Check-in		X	
Check-out			Day 1 (2 h post-dose)
Non-residential visit	X		Days 2, 4, 5, 6, 8, 15, 29, 43 and 57
<b>IMP (Benralizumab) administration:</b>			Day 1 (0 h)
<b>Safety and tolerability:</b>			
Adverse event questioning			Pre-dose and 2 h post-dose (Day 1), Days 2, 4, 5, 6, 8, 15, 29, 43 and 57
Vital signs	X	X	Pre-dose and 2 h post-dose (Day 1), Days 2, 4, 5, 6, 8, 15, 29, 43 and 57
12-lead electrocardiogram	X		Days 1, 29 and 57
Clinical laboratory evaluations	X	X	Days 8, 29 and 57
Physical examination	X	X(brief)	Days 8, 29 and 57 (2 h post dose (brief))
<b>Pharmacokinetics</b>			
Serum benralizumab concentration <sup>a</sup>			Pre-dose (Day 1), Days 2, 4, 5, 6, 8, 15, 29, 43 and 57
<b>Immunogenicity</b>			
ADA			Pre-dose (Day 1), Days 29 and 57

ADA: anti-drug antibody; FSH: follicle-stimulating hormone; IMP: investigational medicinal product

a Samples to determine serum Benralizumab concentrations will be collected at consistent times across the different study days.

### 7.3. Order of Assessments

It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point.

The sequence at a particular time point is:

1. Electrocardiograms (ECGs), if applicable
2. Vital signs (systolic and diastolic blood pressure [BP], pulse rate and oral temperature)
3. Pharmacokinetic blood sampling (will be drawn at the specified time points)
4. Anti-drug antibody and safety laboratory blood sampling.

### 7.4. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1. On Day 1 of the treatment period, subjects will be fasted (except for water) for 10 hours prior to dosing until 2 hours after dosing. Subjects will receive a meal before they are discharged from the clinical unit.
2. Subjects should abstain from alcohol for 72 hours prior to check-in on Day -1, until after their Day 15 PK sampling visit.
3. Subjects should abstain from caffeine-containing foods and beverages for 24 hour prior to check-in on Day -1, until discharge from the clinical unit.
4. During admission period, subjects will receive a standard diet, which excludes alcohol-containing products. No additional food or beverages must be consumed while in the clinical unit.
5. During the subjects' outpatient periods, subjects should abstain from consuming high-energy drinks (e.g., red bull), food containing poppy seeds and any over-the-counter (OTC) medication or herbal preparations until after their End-of-Treatment Visit has been completed. Subjects should also limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup = 250 mL soda, 180 mL coffee or 240 mL tea). Subjects should consume no more than 2 units of alcohol per day (1 unit = 10 mL or 8 g of pure alcohol) and completely abstain from 72 hours prior next visit.
6. Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the study End-of-Treatment visit.
7. Medication restrictions. Refer to [Section 8.7](#).

## **7.4.1. Reproductive Restrictions**

### **7.4.1.1. *Women of Non-Child-Bearing Potential***

Women of non-child-bearing potential are defined as female subjects who are permanently surgically sterilized or post-menopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation.

Females are considered post-menopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels are in the post-menopausal range.

### **Pregnancy Testing**

Women of non-child-bearing potential can be included only after a negative highly sensitive serum pregnancy test. Additionally urine pregnancy testing will be done as per the schedule of assessments.

### **7.4.1.2. *Male Subjects***

#### **Restrictions for Male Subjects**

There is no information about effects that benralizumab could have on the development of the fetus in humans. Therefore, it is important that women of child-bearing potential, who are the partners of male subjects, do not become pregnant during the study and for a total period of 16 weeks after the male subject has attended the study End-of-Treatment visit.

As a precaution, all male subjects should avoid fathering a child by either true abstinence\* or use together, with their female partner/spouse, a highly effective contraception form of birth control in combination with a barrier method, starting from the time of investigational medicinal product (IMP) administration until 16 weeks after the study End-of-Treatment visit.

\* True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception).

Highly effective contraception is defined as having a low failure rate, i.e., less than 1% per year when used consistently and correctly. Highly effective contraception forms of birth control include:

- Hormonal contraception, i.e., oral, injectable or implantable hormonal contraceptives for the female partner/spouse (Note: Not all oral contraception methods have a low failure rate.);
- Hormonal or non-hormonal intrauterine device, established intrauterine device (IUD, loop) or intrauterine system for the female partner/spouse;
- The subject has undergone effective surgical sterilization before he entered the clinical study;
- The subject's female partner/spouse that has undergone effective surgical sterilization before the subject entered the clinical study and she is the sole sexual partner of the subject during the clinical study.

Barrier methods of contraception include:

- Condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants);
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for the female partner/spouse

Male subjects who have been sterilized are required to use one barrier method of contraception (condom) from the time of IMP administration until after the End-of-Treatment visit.

### **Sperm Donation**

Male subjects should not donate sperm for the duration of the study and for at least 16 weeks after the study End-of-Treatment visit.

### **Pregnancy**

Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the Investigator. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

## **7.5. Selection of Study Population**

The Investigator should keep a subject-screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

This study will be conducted in male and female subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

### **7.5.1. Inclusion Criteria**

For inclusion in the study, subjects should fulfill the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures.
2. Healthy male and/or female subjects of non-child-bearing potential aged 18 to 55 years (inclusive) with suitable veins for cannulation or repeated venipuncture.
3. Females must have a negative pregnancy test at screening and on admission to the unit, must not be lactating and must be of non-child-bearing potential, confirmed at screening by fulfilling one of the following criteria:
  - 3.1. Post-menopausal defined as amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels in the post-menopausal range.
  - 3.2. Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
4. All male subjects who are sexually active must agree to use a highly effective contraception form of birth control in combination with a barrier method from the first dose of IMP until 16 weeks after the study End-of-Treatment visit.
5. Have a BMI between 18 and 29.9 kg/m<sup>2</sup> inclusive and weigh at least 55 kg and no more than 100 kg inclusive.
6. Only applicable to the PAREXEL Early Phase Clinical Unit Berlin: Able to understand, read and speak the German language.

### 7.5.2. Exclusion Criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or known history of allergy or reaction to any component of the investigational product formulation.
3. History of anaphylaxis to any biologic therapy.
4. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to standard of care therapy.
5. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained or during the screening period.
6. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
  - 6.1. Affect the safety of the subject throughout the study.
  - 6.2. Influence the findings of the studies or their interpretations.
  - 6.3. Impede the subject's ability to complete the entire duration of study.
7. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.
8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level  $\geq 1.5$  times the upper limit of normal (ULN) confirmed during screening period.
9. White blood cell count and neutrophils  $<$  lower limit of normal.
10. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.

11. Any positive result on screening for serum hepatitis B surface antigen or anti-HBc antibody, hepatitis C antibody, and human immunodeficiency virus (HIV) antibody. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll.
12. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the Investigator.
13. Has received another new chemical entity (defined as a compound which has not been approved for marketing) within 3 months of the first administration of investigational product in this study. The period of exclusion begins 3 months after the final dose or 1 month after the last visit whichever is the longest.  
*Note: subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.*
14. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.
15. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.
16. Receipt of any marketed (e.g., omalizumab, mepolizumab etc.) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer.
17. Receipt of live attenuated vaccines 30 days prior to randomization on Day 1.
18. History of Guillain-Barré syndrome.
19. Current smokers or those who have smoked or used nicotine products including e-cigarettes within the 3 months prior to screening, as judge by the Investigator.
20. Current malignancy, or history of malignancy except for:
  - Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
  - Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.
21. Positive screen for drugs of abuse, of alcohol at screening or on admission to the study unit.
22. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

23. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, mega-dose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life  
*Note: Hormonal replacement therapy is not allowed for females.*
24. Involvement of any AstraZeneca, PAREXEL or study site employee or their close relatives.
25. Subjects who have previously received benralizumab.
26. Judgment by the Investigator that the subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.
27. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

### **7.5.3. Discontinuation Individual Stopping Criteria and Withdrawal from the Study**

Subjects will be discontinued from the study in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe noncompliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (e.g., ECG, BP, pulse rate, laboratory assessments and AEs).
- Study specific withdrawal criteria: If a subject reports symptoms, which are considered unacceptable by the subject or the Investigator, he/she will be withdrawn from the study. In particular:
  - Any other severe or serious adverse event (SAE) that is judged as possibly related to the IMP by the Investigator
  - Any case of Potential Hy's Law (PHL) according to [Appendix 15.3](#)

The appropriate AE form in the case report form (CRF) is to be completed.

### **7.5.4. Premature Termination of the Study and Stopping Criteria**

The study may be terminated prematurely if:

- The PI and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance, when there is at least 1 case of 1 SAE considered related to the IMP by the PI and the Sponsor.
- The Sponsor considers the applied doses of the study drug to be no longer relevant.

- The Sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the PI and the Sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

#### 7.5.5. Total Blood Volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarized in [Table 3](#).

**Table 3 Total Blood Volume**

Test	Sample volume (mL)	Number of samples	Total blood volume (mL)
Hematology	2.7	5	13.5
Clinical chemistry	7.5	5	37.5
Pharmacokinetics	3.5	10	35
Immunogenicity	3.5	3	10.5
<b>Total</b>			<b>96.5</b>

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

## 8. TREATMENTS

### 8.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in [Table 4](#) and [Table 5](#).

**Table 4 Identity of the Investigational Medicinal Product (Accessorized Pre-Filled Syringe)**

<b>IMP:</b>	<b>Benralizumab</b>
Formulation:	30 mg/mL solution for injection in accessorized pre-filled syringe
Strength/concentration:	30 mg/mL
Dose:	30 mg
Route of administration:	SC
Specific device for drug administration, if applicable:	Accessorized pre-filled syringe
Regimen:	Single Dose
Special handling requirements:	Store between 2-8°C (36- 46°F), protected from the light
Availability of the IMP:	01 Nov 2016

**Table 5 Identity of the Investigational Medicinal Product (Autoinjector)**

<b>IMP:</b>	<b>Benralizumab</b>
Formulation:	30 mg/mL solution for injection in Autoinjector
Strength/concentration:	30 mg/mL
Dose:	30 mg
Route of administration:	SC
Specific device for drug administration, if applicable:	Autoinjector
Regimen:	Single Dose
Special handling requirements:	Store between 2-8°C (36- 46°F), protected from the light
Availability of the IMP:	01 Nov 2016

AstraZeneca will provide detailed preparation, storage and handling instructions for each product and treatment. Details of the batch numbers will be included in the Trial Master File and the final CSR, as applicable.

### 8.2. Supply of Investigational Medicinal Product

The IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) and will be supplied by AstraZeneca.

A technical agreement between PAREXEL and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMP at the clinical unit.

### **8.3. Storage and Handling Procedures**

The IMP will be stored in a secure facility under appropriate storage conditions. Details of storage conditions will be provided on the label of the IMP.

AstraZeneca will be permitted, upon request, to audit the supplies, storage, dispensing procedures and records.

### **8.4. Labeling**

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements and Annex 1 of medical device directive for labeling.

### **8.5. Drug Accountability, Dispensing and Destruction**

The IMP provided for this clinical study will be used only as directed in the clinical study protocol.

In accordance with GCP, the clinical unit will account for all supplies of the IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of the IMP will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

In the case of a malfunctioning APFS or AI, the center should contact the study monitor to initiate a product complaint process according to applicable guidelines.

### **8.6. Dose and Treatment Regimens**

Subjects will be randomized to receive a single SC dose of 30 mg benralizumab by either APFS or AI device under fasted conditions. Within each SC injection group, subjects will be stratified to 3 weight categories: 55 to 69.9 kg, 70 to 84.9 kg or 85 to 100 kg. Within each weight category, subjects will be randomized 1:1:1:1:1 to receive the injection (APFS or AI device) at 1 of 3 anatomical sites: Upper arm, Abdomen and Thigh.

Other restrictions are described in [Section 7.4](#). Data of subjects may be excluded from the PK analysis set as described in [Section 11.3.2](#).

## **8.7. Concomitant and Post-study Treatment(s)**

Apart from paracetamol/acetaminophen (up to 2000 mg per day), no concomitant medication or therapy will be allowed.

The subjects should be instructed that no other medication will be allowed, including herbal remedies, vitamin supplements and over-the-counter products, without the consent of the PI.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the PI during the residential period.

When any medication is required, it should be prescribed by the PI or General Practitioner (GP) in case of a medical emergency. Following consultation with AstraZeneca Lead Physician, the PI should determine whether or not the subject should continue in the study. Administration of concomitant medications that may influence the measurement of the PK endpoints may be documented as a protocol deviation after consultation of the PI with AstraZeneca Lead Physician.

## **8.8. Treatment Compliance**

Dosing will take place at the PAREXEL Early Phase Clinical Units (Berlin and London). Compliance will be assured by direct supervision and witnessing of study drug administration.

Administration of IMP will be recorded in ClinBase™.

## **8.9. Randomization**

### **8.9.1. Subject Enrolment and Randomization**

The PI will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.
- Each potential subject is assigned a unique enrolment number at screening upon signing the Informed Consent.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomization code.

Randomization will done prior to dosing on the day of dosing.

Randomization codes will be assigned as subjects become eligible for randomization at the 2 geographical sites (codes to be used without leading zero(s)).

When using unique enrolment number, the specific format must be followed (i.e., reduced enrolment number “01001” in ClinBase™ and on labels, full enrolment number “E0001001” for outputs).

If a subject withdraws his/her participation in the study, then his/her enrolment/randomization code cannot be reused.

### **8.9.2. Procedures for Randomization**

Upon completion of the randomization requirements specifications form, the randomization will be produced by PAREXEL according to the AZRand process.

A total of 180 subjects will be randomized. Subjects will be stratified by body weight category (55 to 69.9 kg/70 to 84.9 kg/85 to 100 kg). Within each of the 3 weight groups, subjects will be randomized 1:1:1:1:1:1 to one of the 6 combinations of treatment (APFS or AI) with injection site (upper arm, abdomen or thigh). As a result, 10 subjects will be allocated to each of the 18 randomization combinations for 2 device groups (Table 1). Randomization list will be prepared for each study site separately. Randomization number will be assigned to subjects sequentially within each weight category at each site. To keep the balance, each site must ensure they randomize subjects in complete blocks.

Once a randomization number has been allocated to a subject, it should not be assigned to another subject.

### **8.9.3. Procedures for Handling Incorrectly Randomized Subjects**

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is randomized in error and this is identified before dosing, the subject should be withdrawn from the study.

If a subject, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety.

### **8.10. Blinding**

This is an open-label study.

## **9. MEASUREMENTS AND METHODS OF ASSESSMENTS**

### **9.1. Appropriateness of Measurements**

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of benralizumab planned to be given during this study, no safety issues are expected.

For timing of assessments, refer to [Table 2](#).

### **9.2. Pharmacokinetics**

#### **9.2.1. Sample Collection and Handling**

Blood samples for the determination of serum concentrations of benralizumab will be collected for the treatment period as specified in the schedule of assessments ([Table 2](#)).

For the PK analysis, it is important that the date and time of each SC injection is recorded for each subject.

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual. Serum samples will be analyzed for benralizumab using a validated assay.

#### **9.2.2. Pharmacokinetic Drug Assays**

Blood samples for determination of benralizumab concentrations in serum will be analyzed by PPD on behalf of AstraZeneca Research and Development (R&D), using a validated assay. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Full details of the analytical method and analyses performed used will be described in a separate bioanalytical report.

#### **9.2.3. Disposal of Pharmacokinetic Samples**

Pharmacokinetic samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from RAs.

A summary of PK analysis results will be reported in the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

### **9.3. Safety and Eligibility Measurements**

Safety and tolerability variables will include:

- Adverse events
- Vital signs (systolic and diastolic BP, pulse rate and body temperature)
- Electrocardiograms
- Physical examination
- Laboratory assessments (hematology, clinical chemistry and urinalysis).

Viral serology and drugs of abuse and alcohol will be assessed for eligibility. Follicle-stimulating hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

#### **9.3.1. Adverse Events**

Refer to [Section 12.2.3](#).

#### **9.3.2. Vital Signs**

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse rate (beats per minute [bpm])
- Oral body temperature (degrees Celsius)

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

#### **9.3.3. Resting 12-lead Electrocardiogram**

A 12-lead ECG will be obtained after the subject has rested in the supine position for at least 10 minutes at each of the time points specified in the schedule of assessments ([Table 2](#)) using the sites own ECG machines.

At each time point, the PI or study physician will judge the overall ECG as normal or abnormal and this evaluation will be reported in ClinBase. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the PI. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented in ClinBase. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

The PI or study physician may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the PI 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.

### 9.3.4. Physical Examination

#### Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

#### Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular and respiratory systems.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

### 9.3.5. Laboratory Assessments

#### 9.3.5.1. Hematology

White blood cell (WBC) count	Lymphocytes absolute count
Hemoglobin (Hb)	Monocytes absolute count
Platelets	Eosinophils absolute count
Neutrophils absolute count	Basophils absolute count

#### 9.3.5.2. Serum Clinical Chemistry

Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)*
Urea	Aspartate aminotransferase (AST)*
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total bilirubin*
Calcium	
Glucose(fasting)	
C-reactive protein (CRP)	
T4 (screening only)	
Thyroid-stimulating hormone (TSH) (screening only)	Follicle-stimulating hormone (FSH) (post-menopausal women only)

\* In case a subject shows an AST or ALT  $\geq 3$  x upper limit of normal (ULN) or total bilirubin  $\geq 2$  x ULN please refer to [Appendix 15.3](#) 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

### **9.3.5.3. Urinalysis**

Glucose

Protein

Blood

Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)

### **9.3.5.4. Pregnancy Testing (Female Subjects Only)**

Beta human chorionic gonadotropin (beta-hCG) (at screening)

Human chorionic gonadotropin (hCG) urine test (dipstick) (at admission and Day 57)

### **9.3.5.5. Viral Serology**

Human immunodeficiency virus (HIV) I and II

Hepatitis B core antibody

Hepatitis B surface antigen (HBsAg)

Hepatitis C virus antibody

### **9.3.5.6. Drugs of Abuse and Alcohol**

Testing for the following drugs of abuse and alcohol will be conducted to determine eligibility at screening and prior to dosing ([Table 2](#)).

Amphetamine

Benzodiazepines

Alcohol

Methadone

Tetrahydrocannabinol (THC)

Barbiturates

Cocaine

Phencyclidine

Opiates

Urine creatinine

Tricyclic anti-depressants (TCA)

## **9.3.6. Concomitant Medication**

Refer to [Section 8.7](#).

## **9.4. Immunogenicity**

### **9.4.1. Sample Collection and Handling**

Serum samples for immunogenicity assessments (ADA) will be collected according to the schedule of study procedures (see [Table 2](#)).

Instructions for immunogenicity (ADA) sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual.

### **9.4.2. Immunogenicity Assays**

Blood samples for the determination of serum concentrations of ADA will be analyzed by PPD on behalf of AstraZeneca R&D, using a validated assay.

A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

### **9.4.3. Disposal of Immunogenicity Samples**

The immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from RAs.

## **9.5. Procedures for Handling of Biological Samples**

### **9.5.1. Storage And Destruction of Biological Samples**

The PK and immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from RAs.

#### **9.5.1.1. Pharmacokinetic and Immunogenicity Samples**

For disposal of PK samples, see [Section 9.2.3](#). For disposal of immunogenicity samples, please see [Section 9.4.3](#).

### **9.5.2. Labeling and Shipment of Biohazard Samples**

Samples will be labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (for International Airline Transportation Association [IATA] guidance, see [Appendix 15.2](#) of this clinical study protocol).

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

### **9.5.3. Chain of Custody Of Biological Samples**

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the clinical unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca bio-bank system during the entire life cycle.

#### **9.5.4. Withdrawal of Informed Consent for Donated Biological Samples**

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analyzed and the action documented. As collection of donated biological samples is an integral part of the study, consent withdrawal implies that the subject is withdrawn from further study participation.

AstraZeneca ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented and the signed document returned to the clinical unit.

## **10. DATA QUALITY ASSURANCE AND DATA MANAGEMENT**

### **10.1. Quality Control and Source Data Verification**

Source data verification will be conducted with due regard to subject confidentiality.

The clinical unit will allow the study monitor and Sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, while maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the clinical unit.

### **10.2. Audit/Inspections**

The clinical unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of RAs. The PI must allow the applicable persons access to all relevant facilities and data/documents. The PI must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

### **10.3. Study Monitoring**

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

### **10.4. Data Collection**

The ClinBase system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the clinical unit. The PI will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase.

#### **10.4.1. Case Report Forms and Source Documents**

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase. All source documents from which ClinBase entries are derived should be placed in the subject's personal records.

The original ClinBase entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the PI for resolution.

#### **10.4.2. Access to Source Documents**

During the course of the clinical study, a study monitor will make clinical unit visits to review protocol compliance, compare ClinBase entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, RAs of certain countries, IECs may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The PI assures the Sponsor of the necessary support at all times.

#### **10.5. Data Management**

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with Food and Drug Administration (FDA) 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, Sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the PI for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

## **11. STATISTICAL METHODS**

### **11.1. Overview**

The statistical methodology below describes the high-level statistical analysis principles as it is foreseen when the study is being planned.

The statistical analysis plan (SAP) will be prepared prior to first subject enter treatment period and any subsequent amendments will be documented, with final amendments completed prior to database lock.

### **11.2. General Statistical Methodology**

The analysis of all endpoints will include all data captured during the study, unless the subject withdraws consent from study participation, regardless of whether study treatment is prematurely discontinued or delayed, and/or irrespective of protocol adherence.

Summary data will be presented in tabular format by treatment groups. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including n, mean, standard deviation, median, minimum value and maximum value (unless stated otherwise) for non-PK data. For PK data, in addition, geometric mean and coefficient of variation (CV%) based on log-transformed data will be presented.

### **11.3. Study Populations**

#### **11.3.1. Safety Analysis Set**

The safety analysis set will include all subjects who received benralizumab.

Unless otherwise stated the safety analysis set will be used for the presentation of all data except for PK data.

#### **11.3.2. Pharmacokinetic Analysis Set**

All subjects who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (e.g., disallowed medications) and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset.

### **11.4. Determination of Sample Size**

While this study is not a formal bioequivalence study, a total of 162 subjects (81 subjects per treatment group) are required for this study to achieve with 80% power and a 90% two-sided confidence interval (CI) for geometric mean ratios of AUC and  $C_{max}$  being within a limit of

0.8 to 1.25 inclusive. The calculation is based on two one-sided tests (TOST) at 5% alpha level under an assumption of maximum 50% CV PK variability for primary endpoints of benralizumab AUC and  $C_{max}$ . Assuming 10% dropout rate, 180 subjects will be enrolled to provide adequate numbers of subjects to assess the primary and secondary objectives of the study.

### 11.5. Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject. All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study and all important protocol deviations will be listed by subject.

### 11.6. Subject Disposition

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Summary tabulation of subject disposition will be provided. A listing of informed consent response and a randomization listing will also be presented.

### 11.7. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject and summarized. Listing of medical history will also be provided.

### 11.8. Prior and Concomitant Medication and Drug Administration

Prior and concomitant medication will be listed and drug administration dates and times will be listed for each subject.

### 11.9. Pharmacokinetic Analysis

#### 11.9.1. Pharmacokinetic Parameters

Where possible, the following PK parameters will be assessed for benralizumab on serum concentrations.

#### Primary Pharmacokinetic Parameters

AUC	Area under the concentration-time curve
$C_{max}$	Maximum observed concentration

## Secondary Pharmacokinetic Parameters

$T_{max}$	Time when the maximum concentration is observed
$t_{1/2}$	Terminal half-life
CL/F	Apparent extravascular clearance
$V_z/F$	Apparent volume of distribution based on the terminal phase

Additional PK parameters may be determined where appropriate.

### 11.9.2. Derivation of Pharmacokinetic Parameters

The non-compartmental analysis (NCA) of the serum concentration data for benralizumab will be performed by PAREXEL Quantitative Clinical Development (QCD) using Phoenix WinNonlin (version 6.3 or higher) in accordance to PAREXEL SOPs.

Pharmacokinetic analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used. Serum concentration data associated with positive ADA status may be excluded from the NCA.

### 11.9.3. Presentation of Pharmacokinetic Data

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 summarized 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.

### 11.9.4. Statistical Analysis of Pharmacokinetic Data

#### 11.9.4.1. Primary PK Analysis Method

The study primary objective is to compare AUC and  $C_{max}$  between APFS and AI devices following a single SC administration of benralizumab.

The analysis of variance (ANOVA) model will be employed on the log-transformed  $C_{max}$  and AUC separately, with fixed effects of treatment (device), body weight group and injection site in order to provide a descriptive comparison of the PK exposure between the 2 devices. The estimated treatment (device) differences and the 90% CI (2-sided) on the log scale will be back-transformed to obtain the geometric mean ratios of AI to APFS and its corresponding 90% CI.

#### **11.9.4.2. Secondary PK Analysis Method**

For  $T_{max}$ , a nonparametric analysis may be performed. Secondary PK parameters will be summarized.

To evaluate the PK of benralizumab administered to various anatomical injection sites, the PK parameters will be summarized by injection sites, body weight ranges and treatment (device). Furthermore, a similar ANOVA model for primary analysis may be used to include the interaction of treatment (device)-by-injection site.

### **11.10. Analysis of Safety Data**

#### **11.10.1. Adverse Events**

Adverse events will be summarized by means of counts summaries by study period (pre-treatment and treatment period). Adverse events will be listed for each subject and summarized by System Organ Class (SOC) and Preferred Term assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA).

Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

#### **11.10.2. Vital Signs**

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

#### **11.10.3. Resting 12-Lead Electrocardiogram**

Twelve-Lead ECG results will be listed for each subject.

#### **11.10.4. Physical Examination**

Abnormal baseline/screening results of the physical examination will be documented in medical history for each subject.

#### **11.10.5. Laboratory Assessments**

Laboratory safety variables (hematology and clinical chemistry) and change from baseline will be summarized 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 be summarized. The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

### **11.11. Analysis of Immunogenicity Data**

For the analysis of immunogenicity data, ADA to benralizumab will be summarized using descriptive statistics at each visit. Anti-drug antibody titers-time profiles of benralizumab by treatment 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. The hypersensitivity reported during the on-study period will be evaluated for ADA status.

## 12. ADVERSE EVENTS

### 12.1. Definitions

#### 12.1.1. Definition of Adverse Events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, ECG).

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the subject has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

#### 12.1.2. Definitions of Serious Adverse Event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see [Appendix 15.1](#) of this clinical study protocol.

#### 12.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the

CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

## **12.2. Recording of Adverse Events**

### **12.2.1. Time Period for Collection of Adverse Events**

Adverse Events will be collected from randomization throughout the treatment period up to and including the End-of-Treatment visit.

SAEs will be recorded from the time of informed consent.

### **12.2.2. Follow-up of Unresolved Adverse Events**

Any AEs that are unresolved at the subject's last visit in the study are followed up by the PI or study physician for as long as medically indicated, but without further recording in ClinBase.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **12.2.3. Variables**

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Principle Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

Additional variables will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)

### 3. Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in [Section 12.1.2](#).

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

#### **12.2.4. Causality Collection**

The PI or study physician will assess causal relationship between investigational product 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 investigational product?”

For SAEs, causal relationship will also be assessed for other medication, any additional drug 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 15.1](#) of this clinical study protocol.

#### **12.2.5. Adverse Events Based on Symptoms and Signs**

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: “*Have you had any health problems since you were last asked?*”, or revealed by observation will be collected and recorded in ClinBase.

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.

#### **12.2.6. Adverse Events Based on Examinations and Tests**

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the CSR.

Deterioration as compared to baseline in protocol mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria.

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

Wherever possible the reporting PI or study physician should use the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin 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.

#### **12.2.7. Hy's Law**

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3$  x ULN together with total bilirubin  $\geq 2$  x ULN may need to be reported as SAEs. Please refer to [Appendix 15.3](#) for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

### **12.3. Reporting of Serious Adverse Events**

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

If any SAE occurs in the course of the study, then the PI, study physician or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the PI 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 will be undertaken immediately.

Principle Investigators, study physicians or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

## **13. LEGAL AND ADMINISTRATIVE ASPECTS**

### **13.1. Archiving of Study Documents**

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

Investigator specific essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents could be retained for a longer period however, if required by the regulatory requirements or by an agreement with AstraZeneca. It is the responsibility of AstraZeneca to inform the Investigator as to when these documents no longer need to be retained.

Study documentation will be archived by the contract research organization (CRO) for 15 years.

### **13.2. Publication of Study Results**

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, the Investigator may prepare a joint publication with AstraZeneca. The Investigator must undertake not to submit any part of the individual data from this clinical study protocol for publication without prior consent of AstraZeneca at a mutually agreed time.

### **13.3. Clinical Study Report**

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IEC and the national RA in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

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## **15. APPENDICES**

### **15.1. Additional Safety Information**

#### **FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT**

##### **Life-threatening**

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

##### **Hospitalization**

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

##### **Important Medical Event or Medical Intervention**

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

## A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a “reasonable possibility” that an AE may have been caused by the IMP.

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

A “reasonable possibility” could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship, unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## 15.2. International Airline Transportation Association 6.2 Guidance Document

### LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association classifies bio hazardous agents into 3 categories

([http://www.iata.org/whatwedo/cargo/dangerous\\_goods/infectious\\_substances.htm](http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

#### CATEGORY A

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are for example, Ebola and Lassa Fever viruses. Category A pathogens:

- Are to be packed and shipped in accordance with IATA Instruction 602.

#### CATEGORY B

**Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D and E viruses, and HIV types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

Category B pathogens:

- Are to be packed in accordance with UN3373 and IATA Instruction 650.

#### EXEMPT

**Exempt** refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.  
([http://www.iata.org/whatwedo/cargo/dangerous\\_goods/infectious\\_substances.htm](http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm))
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

### **15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law**

Guidance used: FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

#### **Introduction**

During the course of the study, the PI will remain vigilant for increases in liver clinical chemistry. The PI is responsible for determining whether a subject meets PHL criteria at any point during the study.

The PI participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug-Induced Liver Injury (DILI) caused by the IMP.

The PI is responsible for recording data pertaining to PHL/HL cases and for reporting AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

#### **Definitions**

##### Potential Hy's Law

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 3 \times$  ULN and total bilirubin (TBL)  $\geq 2 \times$  ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP).
- The elevations do not have to occur at the same time or within a specified time frame.

##### Hy's Law (HL)

- AST or ALT  $\geq 3 \times$  ULN and TBL  $\geq 2 \times$  ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.
- The elevations do not have to occur at the same time or within a specified time frame.

#### **Identification of Potential Hy's Law Cases**

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT  $\geq 3 \times$  ULN

- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

The PI will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see definition above) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

### **Follow-Up**

#### ***Potential Hy's Law Criteria not met***

If the subject does not meet PHL criteria the PI will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol.

#### ***Potential Hy's Law Criteria met***

If the subject does meet PHL criteria the PI will:

- Notify the AstraZeneca representative who will then inform the central study team.

The study physician contacts the PI, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data.

Subsequent to this contact, the PI will:

- Monitor the subject until liver clinical chemistry variables and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- Complete the 3 Liver CRF Modules as information becomes available.

If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

### **Review and Assessment of Potential Hy's Law Cases**

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the clinical chemistry abnormality was initially detected, the study physician contacts the PI in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The

AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the PI will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is no explanation that would clarify the ALT or AST and TBL elevations other than IMP causality:

- Report an SAE (report term ‘Hy’s Law’) according to AstraZeneca standard processes.
  - The ‘Medically Important’ serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of ‘related’ should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

## 16. SIGNATURES

### 16.1. Declaration of Sponsor or Responsible Medical Expert (Physician)

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

#### Sponsor Signatory/Responsible Medical Expert

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**Signature**

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**Date of signature**

PPD

AstraZeneca

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## 16.2. Declaration of Sponsor or Responsible Medical Expert (Global Statistician)

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

### Sponsor Signatory/Global Statistician

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**Signature**

**Date of signature**

PPD

AstraZeneca

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### **16.3. Declaration of Sponsor or Responsible Medical Expert (Lead Clinical Pharmacologist)**

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

#### **Sponsor Signatory/Global Statistician**

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**Signature**

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**Date of signature**

PPD

MedImmune

#### 16.4. Declaration of the Principal Investigator

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

#### Principal/Coordinating Investigator

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**Signature**

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**Date of signature**

PPD

PAREXEL Early Phase Clinical Unit London

## 16.5. Declaration of the Principal Investigator

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administered using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

### Principal/Coordinating Investigator

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**Signature**

**Date of signature**

PPD

PAREXEL Early Phase Clinical Unit Berlin

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## 16.6. Declaration of the Deputy Principal Investigator

**Protocol Title:** A Multicenter, Randomized, Open-Label, Parallel Group Phase 1 Pharmacokinetic Comparability Study of Benralizumab Administrated using Accessorized Pre-Filled Syringe (APFS) or Autoinjector (AI) in Healthy Volunteers

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the IMP, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on GCP applicable to this clinical study.

### Deputy Principal/Coordinating Investigator

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**Signature**

PPD

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**Date of signature**

PAREXEL Early Phase Clinical Unit Berlin