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PAREXEL International

Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

D3250C00030

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

Version: Final 2.0

Date: 04/Aug/2017

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	17/Nov/2016	PPD	New Document
Draft 2.0	02/Dec/2016	PPD	Updated as per comments in Draft 1.0
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Draft 4.0	15/Dec/2016	PPD	Updated per comments on Draft 3.0
Draft 5.0	16/Dec/2016	PPD	Updated per comments on Draft 2.0
Final 1.0	16/Dec/2016	PPD	Updated per comments on Draft 5.0 and finalization of document
Draft 6.0	26/Jun/2017	PPD	Updated for study changes per protocol amendment 1.0 and after the Final 1.0 SAP
Draft 7.0	24/Jul/2017	PPD	Updated per comments on Draft 6.0

Version	Version Date	Author	Summary of Changes Made
Draft 8.0	01/Aug/2017	PPD	Final draft version for approval
Final 2.0	04/Aug/2017	PPD	Finalization of document

SIGNATURE PAGE - ASTRAZENECA

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

PPD

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4 Aug 2017

Date (DD Mmm YY)

Global Product Statistician

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07 Aug 2017

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Vice President R&D, Clinical Pharmacology, Pharmacometrics, and DMPK (CPD)

SIGNATURE PAGE - PAREXEL

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

PPD

PPD

10 Aug 17

Date (DD Mmm YY)

Biostatistician

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
ADA	Anti-drug antibody
AE	Adverse event
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
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last observed time point
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
CI	Confidence interval
CL/F	Apparent extravascular clearance
C_{max}	Maximum observed concentration
CRF	Case Report Form
CRP	C-reactive protein
CSP	Clinical Study Protocol
CV	Coefficient of variation
DRM	Data review meeting
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GGT	Gamma glutamyl transpeptidase
Hb	Hemoglobin
IMP	Investigational Medical Product

Abbreviation / Acronym	Definition / Expansion
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NC	Not calculated
NCA	Non-compartmental analysis
ND	Not determined
NR	No result
PDS	protocol deviation specification
PK	Pharmacokinetic
Q1	25^{th} percentile
Q3	75^{th} percentile
QCD	Quantitative Clinical Development
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System Organ Class
t½	Terminal half-life
TEAE	Treatment-emergent adverse event
TLFs	Tables, Listings and Figures
T_{max}	Time when the maximum concentration is observed
TOST	Two one-sided tests
TSH	Thyroid-stimulating hormone
V_z/F	Apparent volume of distribution based on the terminal phase
WBC	White blood cell
λ_z, Lamda Z	First order rate constant associated with the terminal (log-linear) elimination phase
%AUCextra	Percentage of AUC obtained by extrapolation

AMENDMENT HISTORY

Date	Version change	Brief description of change
26 June 2017	Final 1.0 to Draft 6.0	• Remove Physical Examination appendix based on protocol amendment 1. Abnormal results at baseline will be included as part of Medical History and abnormal results post baseline will be included as AEs. As a result, physical examination will not be listed by body system for each subject and each time point. • PK vendor change from MedImmune to PXL QCD • Add summary tables for both PK concentration and PK parameters by injection site and weight category

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final 1.0 CSP, dated, 19/Oct/2016 and the protocol amendment 1.0, dated 07/Jul/2017. 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. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum. The SAP describes the statistical analysis as it is foreseen when the study is being planned.

1. STUDY OBJECTIVES

1.1 Primary Objective

- To compare the pharmacokinetic (PK) exposure following single subcutaneous (SC) administration of benralizumab by using Accessorized pre-filled syringe (APFS) or Autoinjector (AI) devices

1.2 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

2. STUDY DESIGN

This study will be a 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 AI. Eligible subjects will be healthy subjects aged 18 to 55 years, with a body weight of 55.0 to 100.0 kg and a body mass index (BMI) of 18 to 29.9 kg/m^2 inclusive. A total of 180 subjects will be randomized. Randomization will be stratified by weight group (55.0 to 69.9 kg, 70.0 to 84.9 kg and 85.0 to 100.0 kg), and 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), shown 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:

- A screening period, maximum of 28 days,
- On 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 enrolment, eligible subjects will enter a screening period of maximally 28 days. Subjects will return 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).

A schedule of assessments is given in Section 7.2, Table 2 of the CSP.

3. STUDY POPULATION

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.

Detailed lists of inclusion and exclusion criteria are shown in Sections 7.5.1 Inclusion Criteria and 7.5.2 Exclusion Criteria of the CSP.

4. STATISTICAL BASIS FOR SAMPLE SIZE

While this study is not a formal bioequivalence study, a total of 162 subjects (81 subjects per group) are required for this study to achieve with 80% power and a 90% two-sided confidence interval (CI) for geometric mean ratios of area under the concentration-time curve (AUC) and maximum observed concentration (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% coefficient of variation (CV) PK variability for primary endpoints of benralizumab AUC and C_{max}. Assuming 10% dropout rate, approximately 180 subjects will be enrolled to provide adequate numbers of subjects to assess the primary and secondary objectives of the study. This approximation is deemed sufficient for this study.

5. RANDOMIZATION

A total of 180 subjects will be randomized. Subjects will be stratified by body weight category (55.0-69.9 kg/70.0-84.9 kg/85.0-100.0 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 lists will be prepared for each study site separately. Randomization numbers 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.

Day -1 body weight assessment will be used to categorize the body weight groups.

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Analysis Variables

6.1.1 Demographic and Background Variables

The following demographic and anthropometric information will be recorded at Screening unless otherwise stated:

- Date of informed consent

- Medical history (including start and stop dates [or ongoing if applicable], medical history term)
- Age (years)
- Sex
- Ethnic origin (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White or Other)
- Height (cm) at Screening
- Body weight (kg) at Screening and Day -1
- Body mass index BMI calculated as [weight/height^2] (kg/m^2), obtained at Screening

Age and BMI will obtained from the Case Report Form (CRF) and not re-calculated outside the study database.

6.1.2 Prior and concomitant medication

The following information will be given:

- Medication or therapy, indication
- Start and end date and time, ongoing, prior
- Dose frequency, route, units

6.1.3 Drug administration

Benralizumab administration dates and times will be recorded for each subject. The location of administration (arm, thigh or abdominal wall), the device type (APFS or AI), dose and dose unit will also be recorded.

6.1.4 Pharmacokinetic Variables

Blood samples for determination of serum benralizumab concentration will be collected at the following time points: Day 1 Pre-dose, Days 2, 4, 5, 6, 8, 15, 29, 43 and 57.

Where possible, the following PK parameters will be assessed for benralizumab on serum concentrations. Additional PK parameters may be determined and reported as appropriate.

Table 2 Pharmacokinetic Parameters after Single Dose Administration

Parameter	Definition
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	Area under the concentration-time curve from time zero to the last observed time point
CL/F	Apparent extravascular clearance
C_{max}	Maximum observed concentration
$t_{1/2}$	Terminal half-life
T_{max}	Time when the maximum concentration is observed
V_z/F	Apparent volume of distribution based on the terminal phase
λ_z	First order rate constant associated with the terminal (log-linear) elimination phase
$\%AUC_{extra}$	Percentage of AUC obtained by extrapolation

6.1.4.1 Pharmacokinetic Parameter Calculation Methods

The PK analyses of the serum concentration data for benralizumab will be performed by PXL Quantitative Clinical Development (QCD).

Non-compartmental PK analysis (NCA) will be performed using Phoenix WinNonlin (version 6.3, or higher, Certara, Princeton, New Jersey), in accordance with PXL SOPs.

PK analysis will, where possible, be carried out using actual sampling times recorded in the raw data. If actual times are missing, nominal times will be used. A non-compartmental approach consistent with the route of administration will be used for parameter estimation.

PK parameters will be estimated according to the following guidelines:

- C_{max} and T_{max} will be obtained directly from the concentration-time data.
- AUC_{last} will be estimated using the linear/log trapezoidal method.
- AUC_{inf} will be estimated as the sum of corresponding AUC_{last} and $C_{last}/\lambda z$ values:

$$AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

- CL/F will be calculated as: $CL/F = \frac{\text{Dose}}{AUC_{inf}}$
- V_z/F will be calculated as: $Vz/F = \frac{CL/F}{\lambda_z}$

- Terminal half-life ($t_{1/2}$) will be calculated as: $t_{1/2}=\frac{\ln(2)}{\lambda_z}$, where λ_z is the first-order terminal rate constant estimated via linear regression of the terminal log-linear decay phase.

6.1.5 Immunogenicity Variables

Anti-drug Antibody (ADA) sampling will be collected at the following time points: Day 1 pre-dose, Day 29 and 57. A sample is defined as positive if the reported titer is 50 or above.

For each subject, the following responses variables will be evaluated:

- ADA positive at any visit (at baseline and/or post-baseline)
- ADA positive at both baseline and post-baseline
- ADA positive at post-baseline only
- ADA positive at baseline only

At the study level, a subject's ADA status will be defined as being ADA positive if a positive ADA result is available at any time (including baseline or any post-baseline measurements); otherwise a subject's ADA status will be defined as ADA negative.

6.1.6 Safety Variables

6.1.6.1 Adverse Events

An adverse event 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.

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

Serious adverse events (SAEs) will be recorded from the time of informed consent.

The following variables will be collected for each Adverse Event (AE):

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity as measure of severity (Mild, Moderate, Severe)
- Whether the AE is serious or not

- Causality to IMP (Investigational Medical Product)
- Action taken with regard to investigational product (Dose Not Changed, Dose Increased, Dose Reduced, Drug Interruption, Drug Permanently Discontinued, Not Applicable)
- AE caused subject's withdrawal from study (yes or no)
- Outcome (Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Fatal)
- Whether the AE was associated with device malfunction

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

6.1.6.2 Clinical Laboratory Tests

Hematology, Serum Clinical Chemistry and Urinalysis

Safety laboratory parameters as shown in Table 3 will be measured at the following visits: Screening, Day -1, 8, 29 and 57.

Table 3 Clinical Laboratory Tests

Hematology	
White blood cell (WBC) count	Lymphocytes absolute count
Hemoglobin (Hb)	Monocytes absolute count
Platelets	Eosinophils absolute count
Neutrophils absolute count	Basophils absolute count
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[1]	
Thyroid-stimulating hormone (TSH)[1]	Follicle-stimulating hormone (FSH) (post-menopausal women only)[1]

Table 3 Clinical Laboratory Tests
Urinalysis
Glucose
Protein
Blood
Microscopy (if positive for protein or blood): Red blood cell (RBC), WBC, Casts (Cellular, Granular, Hyaline)

[1] At Screening only.

6.1.6.3 Vital Signs

Vital signs will be measured at the following time points: Screening, Day -1, Day 1 Pre-dose and 2 h post-dose, Days 2, 4, 5, 6, 8, 15, 29, 43 and 57.

The following vital signs measurements will be obtained:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats per minute [bpm])
- Oral body temperature (degree Celsius)

6.1.6.4 Electrocardiograms

An Electrocardiogram (ECG) will be performed at the following visits: Screening, Day 1, 29 and 57.

The ECG will be evaluated by the Investigator as normal or abnormal. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the Investigator. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented.

6.1.6.5 Physical Examination

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. The complete exam will be performed at visit: Screening, Days 8, 29 and 57.

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory. The brief exam will be performed on Day -1.

6.1.7 Eligibility Variables

Viral serology and drugs of abuse, alcohol will be assessed for eligibility. These results will not be listed in the CSR.

Follicle-stimulating hormone (females only) and serum pregnancy testing (females only) will be assessed and reported at screening.

Urine pregnancy testing will be performed at the following time points: Day -1 and Day 57

Table 4 Pregnancy Testing (Female Subjects Only)

Beta human chorionic gonadotropin (beta-hCG)
Human chorionic gonadotropin (hCG) urine test (dipstick)

6.2 Analysis Populations

6.2.1 Randomized subjects

Randomized subjects include all subjects who pass screening and are randomized to a treatment (device) and an injection site.

6.2.2 Safety Analysis Set

The safety analysis set is a subset of the randomized subjects consisting of all subjects in the randomized set who received benralizumab.

Unless otherwise stated all listings except for PK concentration listing will be presented on the safety analysis set. Presentation of all data tabulations and figures except for PK data will also be on the safety analysis set, unless otherwise stated.

6.2.3 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 or incomplete dose administration) and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK tabulations and figures will be based on the PK analysis set.

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All listings will include stratification factors (weight group and injection site). All summary tables will be presented by treatment (device), unless stated otherwise.

Demographic (Age, Sex, Race and Ethnicity) and baseline characteristics data will be summarized separately by treatment (device) and overall.

Pharmacokinetic data will be summarized separately by treatment (device) only and by treatment (device), body weight and injection site.

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) Version 19.1.

Medical and surgical history will listed for each subject by System Organ Class and Preferred Term assigned to the event or history by MedDRA.

Prior and concomitant medication will listed for each subject by preferred drug name and medication as reported coded to preferred drug name using the World Health Organization Drug Dictionary Enhanced Plus Herbal (September 2016).

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, Mean, Standard Deviation [SD], Median, Minimum and Maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$. For PK data, geometric mean, geometric mean +/- SD and coefficient of variation (CV%) based on log-transformed data will be presented.

Unless otherwise stated rules for decimal places are as follows:

- n and N the population total are always given as whole numbers,
- Ratios 2 decimal places,
- All measured data will be listed with the same number of decimal places or significant figures (with same precision) as the original raw data, with the exception of data for which the original number of decimals exceeds four decimal places; in these cases the data will be presented to three significant figures,
- An extra digit of precision will be added (typically four significant digits in total) for reporting of the geometric least-squares (LS) means and bounds of all confidence intervals within inferential analyses,

- A maximum of three decimal places will apply to all summary statistics.

The following rules will apply to any repeated safety assessments occurring within the treatment period:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;

- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing relative to the scheduled time-point will be used in descriptive statistics and in the calculation of changes from baseline.

For safety assessments performed at Screening, if the repeated assessment occurs at Screening the last available value will be used in the summary statistics.

6.3.2 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later [1]. The PK analysis will be performed using Phoenix WinNonlin (version 6.3, or higher, Certara, Princeton, New Jersey) in accordance with PXL SOPs.

6.3.3 Missing Data

Missing dates and times in the AE data will be handled as described in Section 6.3.11.1. Concentrations that are BLQ in the PK data will be handled as described in Section 6.3.9.2.

There will be no imputations of other missing data. All subjects will be included into the safety analysis set as far as the data permit.

6.3.4 Baseline Definition

Baseline will be the last available non-missing value prior to IMP. Scheduled or unscheduled measurements can be used as the baseline value. Measurement specific baseline time points based on planned time points in the protocol are presented in Table 5.

Table 5 Definition of Baseline

Category	Measurement	Definition of Baseline
Safety	Vital signs Clinical laboratory	Pre-dose Day 1; if missing, Day -1; if missing, Screening Day -1, if missing Screening
Immunogenicity	ADA	Pre-dose Day 1

ADA=Anti-drug antibody.

6.3.5 Interim Analysis

No interim analyses will be performed in this study.

6.3.6 Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Subjects who developed IP discontinuation criteria during the study but were not discontinued
- Dosing deviations (e.g., incorrect treatment (device) received, subject was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the clinical unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) document. All protocol deviations will be discussed at the data review meeting (DRM) prior to database hard lock in order to define the analysis sets for the study. All disallowed medications will be reviewed before the DRM by the PK Scientist and Biostatistician, noted in the DRM Report and included in the DRM Minutes for any medications that lead to discontinuations.

Important deviations will be those which are considered to potentially impact upon the interpretation of the primary PK endpoint in the study. Only important protocol deviations will be listed and tabulated in the Clinical Study Report (CSR) [Appendix 16.2.2.1]. Subjects excluded from the PK analysis set will be listed [Appendix 16.2.3.1]. Data excluded from the PK analysis set will be listed in [Appendix 16.2.3.2] if applicable.

6.3.7 Demographic and Baseline Data

All demographic and baseline data will be presented using the Safety analysis set. All summary statistics for age (years) and height will be given as whole numbers. The weight and BMI will be presented to one decimal place. For categorical parameters percentages are presented with one decimal place.

Disposition

Subject disposition of study completion and withdrawal will be summarized by treatment (device) group and overall [Table 14.1.1]. Subject population disposition will be summarized overall [Table 14.1.2].

A listing of informed consent response [Appendix 16.2.1.2.1-16.2.1.2.2] and a randomization listing, to include body weight category and injection site will also be presented for each site (Germany and United Kingdom) separately [Appendix 16.2.1.3.1-16.2.1.3.2]. Subjects discontinuing from the study will be listed [Appendix 16.2.1.1], this will include duration of study and reason for discontinuation.

Demographic data

Demographic variables (Age, Sex, Race, Ethnicity, Height, Weight and BMI) will be listed by randomized subjects [Appendix 16.2.4.1]. Weight is measured at Screening at Day -1, height only at Screening, both will be listed [Appendix 16.2.9.4].

The summary statistics of weight, height and BMI will be based on the measurements at Day -1. If either weight or height is missing in a subject, the Screening measurement will be summarized.

Demographic characteristics (Age, Sex, Race and Ethnicity) will be summarized by treatment (device) and overall [Table 14.1.3]. The denominator for percentages will be the number of subjects in the Safety analysis set per treatment (device).

Subject characteristics (Height, Weight and BMI) will be summarized separately by treatment (device) and overall [Table 14.1.4].

Medical history

Medical history data will be listed by randomized subjects including visit, description of the disease/procedure, MedDRA SOC, MedDRA Preferred Term (PT), start date, and stop date (or ongoing if applicable) [Appendix 16.2.4.2].

Pregnancy test results (including FSH) will be listed [Appendix 16.2.8.11].

6.3.8 Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of Investigational Medical Product (IMP); all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed [Appendix 16.2.4.3] by randomized subjects and will include the following information: reported name, preferred term, the route of

administration, dose, frequency, start date/time, duration and indication. The duration will be calculated as:

Duration = end date/time – start date/time

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated. Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

6.3.9 Pharmacokinetic Concentrations and Variables

All tables and figures in this section will be based on the PK analysis set; all listings in this section will be based on the Safety analysis set unless otherwise specified.

6.3.9.1 Data presentation

Descriptive statistics and listings of concentration data and parameters

PK concentration data will be listed to the same number of significant figures as the data received from the bioanalytical laboratory. All descriptive statistics of PK concentration will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameters data, the listings will be presented according to the following rules:

- C_{max} – will be presented to the same number of significant figures as received from the bioanalytical laboratory
- T_{max} – will be presented as received in the data, usually to 2 decimal places
- AUC_{inf}, AUC_{last}, $t_{1/2}$, CL/F and V_z/F will be presented to 3 significant figures
- λ_z – will be presented to 5 significant figures
- $\%AUC_{extra}$ – will be presented to 2 decimal places

For PK parameters data the descriptive statistics of the PK parameters will be presented according to the following rules:

- C_{max}, AUC_{inf}, AUC_{last}, $t_{1/2}$, CL/F and V_z/F – all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

- T_{max} – all descriptive statistics will be presented as received in the data, usually to 2 decimal places

ADA status will be evaluated as a potential exclusion criterion for subject data included in the PK analysis. Serum concentration data associated with positive ADA status will be flagged in the PK concentration listings and may be excluded from the NCA, summary statistics and/or mean profiles, as determined based on emerging data and the formal DRM.

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided [Appendix 16.2.5.1], based on the safety analysis set. A listing of serum concentrations, based on nominal times only, will be presented [Appendix 16.2.6.1], based on the PK analysis set.

Serum concentrations and PK parameters will be summarized separately by treatment (device) only [Table 14.2.1.1] and by treatment (device), weight category [Table 14.2.1.2], injection site [Table 14.2.1.3] and injection site and weight category [Table 14.2.1.4]. In addition to the standard descriptive statistics the following will be presented: geometric mean, geometric CV% and geometric mean +/-SD. For T_{max}, only median, min, max and 95% CI will be presented.

All PK parameters will be listed [Appendix 16.2.6.2] (based on the PK analysis set) by treatment (device) and subject, and summarized by treatment (device) [Table 14.2.2.1].

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where *s* is the SD of the log-transformed data.

Figures of concentration data

Combined individual serum concentration versus actual times will be plotted in linear and semi logarithmic scale shown on one page [Figure 14.2.1]. Separate plot panels will be presented for each treatment (device) by weight category and injection site.

Geometric mean serum concentration (±SD) versus nominal sampling time will be plotted in linear and semi logarithmic scale (no SD presented for the semi logarithmic scale) with both scales on one page [Figure 14.2.2]. Separate plot panels will be presented for each treatment (device) by weight category and injection site.

For mean plots, BLQ values will be handled as described for the summary tabulations Section 6.3.9.2. For individual plots serum concentrations which are BLQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any BLQ serum concentrations will be regarded as missing.

Likewise, concentrations Not Determined (ND) and Not Applicable (NA) will be set to missing.

Figures of PK parameters

Box plots of AUC_{inf}, AUC_{last}, C_{max} and $t_{1/2}$ will be provided by body weight group, separately for each parameter and with results from both devices displayed on the same plot side by side. A box plot will be superimposed on individual PK parameter values for each weight group. The top whisker will extend to the maximum value and the bottom whisker will extend to the minimum value; the middle bar will represent the median value; the mean value will also be displayed on the figures [Figure 14.2.3].

Results from the secondary analysis in Section 6.3.9.3 will be plotted: the geometric mean ratios of abdomen/arm, thigh/arm and thigh/abdomen and corresponding 90% CIs from the statistical pair-wise comparisons for AUC_{inf}, AUC_{last} and C_{max} will be presented in a forest plot for each treatment (device) [Figure 14.2.4].

All plots will be based on the PK analysis set.

6.3.9.2 Handling of Values Below the Limit of Quantification (BLQ) in Concentration Summaries and Listings

Serum concentrations that are BLQ or if there are missing values (e.g., no result [NR]) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean and CV% will be set to Not Determined. The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not Applicable (NA) will be written in the field for standard deviation and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

Three observations > LLOQ are required as a minimum for a serum concentration to be summarized. Two values are presented as a minimum and maximum with the other summary statistics as Not Calculated (NC).

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

6.3.9.3 Statistical Analysis of Pharmacokinetic Data

Primary PK analysis

The primary objective is to compare AUC_{inf}, AUC_{last} and C_{max} between APFS and AI devices following single SC administration of benralizumab. The analysis of variance (ANOVA) model will be employed on the log-transformed AUC_{inf}, AUC_{last} and C_{max}, 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. The tables will also include the geometric least square means with 95% CI [Table 14.2.3.1]. Supporting statistical output for the analysis of PK parameters documented in Appendix 16.1.9.2.1.

The following SAS code will be applied, with AI sorted before APFS:

```
proc mixed data = <data>;

    class <treatment_device> <weight category> <injection site>;

    model <log_var> = <treatment_device>  <weight category>  <injection site>;

    lsmeans <treatment_device> / cl alpha = 0.05;

   estimate "AI versus APFS"    <treatment_device>   1  -1 / cl alpha = 0.10 ;

run;

quit;
```

Secondary PK analysis

For T_{max}, a nonparametric analysis may be performed, based on evaluation during the blind data review.

To evaluate the PK of benralizumab administered to various anatomical injection sites and weight category, the PK parameters will be summarized by treatment (device) and injection sites [Table 14.2.2.3], and body weight categories [Table 14.2.2.2].

Furthermore, the ANOVA model of the primary analysis with the addition of the interaction term treatment (device)-by-injection site will be presented [Table 14.2.3.2]. The estimated differences of pairwise comparison between injection site within each treatment (device) and the corresponding 90% CI (2-sided) on the log scale will be back-transformed to obtain the geometric mean ratios of abdomen/arm, thigh/arm and thigh/abdomen and their corresponding 90% CIs.

Supporting statistical output for the analysis of PK parameters documented in Appendix 16.1.9.2.2.

The following SAS code will be applied:

```
proc mixed data = <data>;

    class <treatment_device> <weight category> <injection site>;

    model <log_var> = <treatment_device>  <weight category>  <injection site>
       <treatment_device>  *  <injection site>;

       estimate "estimate details"    <treatment_device>   <injection site>

 <treatment_device>  *  <injection site>  specify 1s and 0s as applicable   / cl alpha = 0.10 ;

run;

quit;
```

6.3.10 Immunogenicity Analysis

ADA results will be listed by treatment (device), subjects study ADA status with positive study status first and then subjects with negative study status, subject identifier, and visit including ADA titer and eosinophil count [Appendix 16.2.6.3].

ADA responses observed during the study, as specified in Section 6.1.5, will be summarized by treatment (device) and overall [Table 14.2.4.2]. ADA positive and negative status will be summarized by visit, treatment (device) and overall [Table 14.2.4.1].

The hypersensitivity reported on treatment period will be presented by preferred term for ADA status [Table 14.2.4.3].

6.3.11 Safety Analysis

Safety and tolerability data will be summarized by treatment (device) only.

6.3.11.1 Adverse Events

All AEs will be coded using MedDRA vocabulary, and will be listed by treatment (device) for each subject. A Treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) after dosing.

AEs will be assigned to the treatment period or pre-treatment as follows:

- Pre-treatment: All AEs with start date/time prior to dosing.
- Treatment period: AEs with start date/time at the time of or after dosing until the final visit.

The following listings will be included:

- MedDRA coding, including MedDRA lowest level term; PT and SOC [Appendix 16.2.7.1].
- Onset and resolution, including pre-treatment AE, PT, verbatim term, date of onset and resolution and time from IMP [Appendix 16.2.7.2].
- Relationship and causality, including PT, verbatim term, severity, action taken, outcome, causality, SAE and withdrawn [Appendix 16.2.7.3].
- Table of Key Information listing AEs leading to death [Table 14.3.2.1].
- Table of Key Information listing SAE [Table 14.3.2.2].
- Table of Key Information listing AEs that led to discontinuation from study (DAE) [Table 14.3.2.3].
- Table of Key Information listing for AEs associated with device malfunction [Table 14.3.2.4].
- Table of Key Information listing for AEs associated with injection site reactions [Table 14.3.2.5].

All key information listings for AEs will display the baseline eosinophil count and the subject ADA status.

Tabulation of subject counts

A summary (n and percentage) of subjects with at least one AE per category, including AEs with outcome death or discontinuation and SAEs will be presented by treatment (device) and overall [Table 14.3.1.1].

Adverse events subject based, will be summarized by treatment (device) and overall, by SOC and PT. The overall summary will additionally be by pre-treatment and treatment period respectively [Tables 14.3.1.2.1 - 14.3.1.2.2].

Causality of AE will be summarized by treatment (device) and overall, by PT [Table 14.3.1.3]. Maximum intensity of AE will be summarized by treatment (device) and overall by PT [Table 14.3.1.4].

Adverse events associated with injection site reactions will be summarized by subject counts and percentages, by treatment (device), administration site and PT [Table 14.3.1.5].

Tabulation by episode count

A summary of the number of episodes by categories, including AEs with outcome death or discontinuation and SAEs will be presented by treatment (device) and total [Table 14.3.1.6].

Tabulations will be presented showing the number of episodes by treatment (device) and overall, by PT.

- Separately, in total [Table 14.3.1.7].

Missing start dates/times

No partial/missing date/time are allowed in the eCRF. However if it occurs, adverse events with missing start dates/times will be handled as follows:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing.

- If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01. If the end date is non-informative (i.e., is missing or does not contain enough

information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01.

- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

6.3.11.2 Clinical Safety Laboratory Tests (hematology, biochemistry and urinalysis)

Laboratory values hematology (Erythrocytes and Platelets, Leukocytes) [Appendix 16.2.8.2-16.2.8.3], clinical chemistry (Liver Function, Electrolytes/Minerals, Lipids/Proteins, Other chemistry, Thyroid panel) [Appendix 16.2.8.4-16.2.8.8] and Hormones [Appendix 16.2.8.9] will be listed by treatment (device) and subject and study time point and will include changes from baseline. Urinalysis Macroscopic, [Appendix 16.2.8.10.1] and Microscopic [Appendix 16.2.8.10.2] if necessary, will be listed by treatment (device), subject and study time point.

A listing of the clinical laboratory normal ranges will be provided [Appendix 16.2.8.1]. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

A listing for pregnancy testing [Appendix 16.2.8.11] will be provided.

The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

Descriptive statistics for non-categorical clinical laboratory data including hematology and clinical chemistry will be presented by treatment (device) and time-point for both individual values and changes from baseline [Table 14.3.4.1].

Shift tables for maximum and minimum post–baseline change in hematology and clinical chemistry will also be presented [Table 14.3.4.2.1-14.3.4.2.2].

In summaries, listings and figures, lab results and normal ranges will be presented in the International System (SI) unit. Eosinophils data will be presented in both SI and conventional units (cells/μL) in summaries.

Combined individual blood eosinophil count (in SI and conventional units) versus actual times will be plotted in linear scale for each treatment (device) by weight category and injection site [Figure 14.2.5. and Figure 14.2.6].

6.3.11.3 Vital Signs

The results of the vital signs measurements will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements

[Appendix 16.2.9.1]. Absolute values will be compared to the relevant reference ranges and classified as low (below range), normal (within range or on limits) or high (above range). All values falling outside the reference ranges (Table 6) will be flagged and listed.

Table 6 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure	mmHg	60	120
Systolic Blood Pressure	mmHg	100	160
Pulse Rate	Beats/min	40	120
Body Temperature	Celsius	36.5	38

Descriptive statistics will be presented by treatment (device) and time point for both observed values and changes from baseline [Table 14.3.5.1].

6.3.11.4 Twelve-Lead Electrocardiogram

A listing of the Investigator's judgment of the overall ECG as normal or abnormal will be displayed for each time point [Appendix 16.2.9.2]. If abnormal, it will be further documented as to whether the abnormality is clinically significant by the Investigator.

A shift table will be generated to display normal, abnormal – not clinically significant, abnormal – clinically significant, and not done. The table will be presented for baseline to each post baseline observation [Table 14.3.5.2].

6.3.12 Changes of analysis from protocol

- The only results to be captured in DataLabs for physical examination are abnormal results as described in the protocol amendment 1. Abnormal results at baseline will be included as part of Medical History and abnormal results post baseline will be included as AEs. As a result, physical examination will not be listed by body system for each subject and each time point.

7. REFERENCES

1. SAS® Version 9.2 or later (SAS Institute, Cary, North Carolina, United States of America).

2. Phoenix® WinNonlin® 6.3 (or higher) (Certara, L.P., Princeton, New Jersey, USA).

8. TABLES TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Subject Disposition and Demographic Data

Table 14.1.1 Subject disposition (Randomized subjects set)

Table 14.1.2 Subject population disposition (Randomized subjects set)

Table 14.1.3 Demographic characteristics (Safety analysis set)

Table 14.1.4 Subject characteristics (Safety analysis set)

Pharmacokinetic Data

Table 14.2.1.1 Summary of serum benralizumab concentrations (<Unit>) for each treatment (device) (Pharmacokinetic analysis set)

Table 14.2.1.2 Summary of serum benralizumab concentrations (<Unit>) for each treatment (device) by weight category (Pharmacokinetic analysis set)

Table 14.2.1.3 Summary of serum benralizumab concentrations (<Unit>) for each treatment (device) by injection site (Pharmacokinetic analysis set)

Table 14.2.1.4 Summary of serum benralizumab concentrations (<Unit>) for each treatment (device) by injection site and weight category (Pharmacokinetic analysis set)

Table 14.2.2.1 Summary of benralizumab pharmacokinetic parameters for each treatment (device) (Pharmacokinetic analysis set)

Table 14.2.2.2 Summary of benralizumab pharmacokinetic parameters for each treatment (device) by weight category (Pharmacokinetic analysis set)

Table 14.2.2.3 Summary of benralizumab pharmacokinetic parameters for each treatment (device) by injection site (Pharmacokinetic analysis set)

Table 14.2.2.4 Summary of benralizumab pharmacokinetic parameters for each treatment (device) by injection site and weight category (Pharmacokinetic analysis set)

Table 14.2.3.1 Statistical comparison of key pharmacokinetic parameters between treatment (device) (Pharmacokinetic analysis set)

Table 14.2.3.2	Statistical comparison of key pharmacokinetic parameters between injection site within treatment (device) (Pharmacokinetic analysis set)
Table 14.2.4.1	Anti-drug antibody status by visit (Safety analysis set)
Table 14.2.4.2	Anti-drug antibody response (Safety analysis set)
Table 14.2.4.3	Hypersensitivity reported during the on-treatment period by preferred term by ADA Status (Safety analysis set)

Adverse Events

Table 14.3.1.1	Number (%) of subjects who had at least one on-treatment adverse event in any category (Safety analysis set)
Table 14.3.1.2.1	Number (%) of subjects who had at least one adverse event, by preferred term, arranged by system organ class, pre-treatment (Safety analysis set)
Table 14.3.1.2.2	Number (%) of subjects who had at least one adverse event, by preferred term, arranged by system organ class, on-treatment period (Safety analysis set)
Table 14.3.1.3	Number (%) of subjects who had at least one on-treatment adverse event by preferred term presented by investigator's causality assessment (Safety analysis set)
Table 14.3.1.4	Number (%) of subjects who had at least one on-treatment adverse event by preferred term presented by maximum reported intensity (Safety analysis set)
Table 14.3.1.5	Number (%) of subjects who had at least one injection site adverse event by preferred term (Safety analysis set)
Table 14.3.1.6	On-treatment Adverse events in any category – episode level (Safety analysis set)
Table 14.3.1.7	On-treatment Adverse events, by preferred term – event counts (Safety analysis set)

Adverse Events - Key Information Listings

Table 14.3.2.1	Key information for on-treatment adverse events with outcome equals death (Safety analysis set)
Table 14.3.2.2	Key information for on-treatment serious adverse events (Safety analysis set)
Table 14.3.2.3	Key information for adverse events leading to discontinuation from study (Safety analysis set)
Table 14.3.2.4	Key information for adverse events related to device malfunction (Safety analysis set)
Table 14.3.2.5	Key information for adverse events related to injection site reactions (Safety analysis set)

Laboratory Assessments

Table 14.3.4.1	Descriptive statistics for clinical laboratory results and change from baseline results (SI units) (Safety analysis set)
Table 14.3.4.2.1	Maximum post-baseline shift from baseline in clinical laboratory results (Safety analysis set)
Table 14.3.4.2.2	Minimum post-baseline shift from baseline in clinical laboratory results (Safety analysis set)

Other Safety Assessments

Table 14.3.5.1	Descriptive statistics for vital signs and change from baseline results (Safety analysis set)
Table 14.3.5.2	Post-baseline shift from baseline in twelve lead electrocardiogram results (Safety analysis set)

9. FIGURES TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Figure 14.2.1 Combined individual serum benralizumab concentrations by weight category and injection site (Linear Scale and Semi logarithmic scale) (Pharmacokinetic analysis set)

Figure 14.2.2 Geometric mean serum concentrations of benralizumab versus time by injection site for each treatment (device) and weight category (Linear Scale and Semi logarithmic scale) (Pharmacokinetic analysis set)

Figure 14.2.3 Box plots of selected PK parameters versus body weight category by treatment (device) (Pharmacokinetic analysis set)

Figure 14.2.4 Forest plot of pairwise comparison AUC_{inf}, AUC_{last} and C_{max} across injection site, within each treatment (device) (Pharmacokinetic analysis set)

Figure 14.2.5 Combined individual blood eosinophil count in SI units (<unit>) by weight category and injection site (Linear Scale) (Safety analysis set)

Figure 14.2.6 Combined individual blood eosinophil count in conventional units (<unit>) by weight category and injection site (Linear Scale) (Safety analysis set)

10. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Disposition

Appendix 16.2.1.1 Discontinued subjects (Safety analysis set)

Appendix 16.2.1.2.1 Informed consent center Germany

Appendix 16.2.1.2.2 Informed consent center United Kingdom

Appendix 16.2.1.3.1 Randomization scheme and codes center Germany

Appendix 16.2.1.3.2 Randomization scheme and codes center United Kingdom

Protocol Deviations

Appendix 16.2.2.1 Subjects with important protocol deviations (Safety analysis set)

Analysis Populations

Appendix 16.2.3.1 Subjects excluded from the Pharmacokinetic analysis set (Safety analysis set)

Appendix 16.2.3.2 Data excluded from the Pharmacokinetic analysis set (Safety analysis set)

Demographics and Baseline Characteristics

Appendix 16.2.4.1 Demographic and baseline characteristics, randomized subject

Appendix 16.2.4.2 Medical/surgical history, randomized subjects

Appendix 16.2.4.3 Medication on entry and during the study, randomized subjects

Exposure/Compliance/Drug Concentration

Appendix 16.2.5.1	Individual serum benralizumab pharmacokinetic sample collection times and concentrations (Safety analysis set)

Pharmacokinetic Data

Appendix 16.2.6.1	Individual serum benralizumab concentrations for each treatment (device) (PK analysis set)
Appendix 16.2.6.2	Individual serum benralizumab pharmacokinetic parameters for each treatment (device) (PK analysis set)

Immunogenicity Data

Appendix 16.2.6.3	Anti-drug antibodies (Safety analysis set)

Adverse Events

Appendix 16.2.7.1	Adverse events, MedDRA coding safety analysis set
Appendix 16.2.7.2	Adverse events, safety analysis set – onset and resolution
Appendix 16.2.7.3	Adverse events, safety analysis set – relationship and causality

Laboratory Assessments

Appendix 16.2.8.1	Clinical laboratory normal ranges in SI units and laboratory outlier criteria
Appendix 16.2.8.2	Hematology parameters, safety analysis set: Erythrocytes and Platelets
Appendix 16.2.8.3	Hematology parameters, safety analysis set: Leukocytes
Appendix 16.2.8.4	Clinical laboratory values, safety analysis set: Liver Function
Appendix 16.2.8.5	Clinical laboratory values, safety analysis set: Electrolytes/Minerals
Appendix 16.2.8.6	Clinical laboratory values, safety analysis set: Lipids/Proteins
Appendix 16.2.8.7	Clinical laboratory values, safety analysis set: Other chemistry
Appendix 16.2.8.8	Clinical laboratory values, safety analysis set: Thyroid panel

Appendix 16.2.8.9	Clinical laboratory values, safety analysis set: Hormones
Appendix 16.2.8.10.1	Urinalysis, safety analysis set: Macroscopic
Appendix 16.2.8.10.2	Urinalysis, safety analysis set: Microscopic
Appendix 16.2.8.11	Pregnancy test results

Other Safety Assessments

Appendix 16.2.9.1	Individual vital sign data, safety analysis set
Appendix 16.2.9.2	Electrocardiogram data overall evaluation, safety analysis set results
Appendix 16.2.9.3	Individual weight values, safety analysis set

Any changes to the TFL numbering and/or titles will only be updated in the TFL Shells. Any analysis changes that would result in a change of adding or removing TFLs would need to be updated in the SAP and TFL Shells.

11. DOCUMENTATION OF STATISTICAL METHODS

Appendix 16.1.9.2.1 Supporting output for Table 14.2.3.1 Statistical comparison of key pharmacokinetic parameters between treatment (device) (Pharmacokinetic analysis set)

Appendix 16.1.9.2.2 Supporting output for Table 14.2.3.2 Statistical comparison of key pharmacokinetic parameters between injection site within treatment (device) (Pharmacokinetic analysis set)