Statistical Analysis Plan

Protocol Number: CD-RI-CAT-354-1054

A Phase 1, Open-label Study to Evaluate the Pharmacokinetics of Tralokinumab in Adolescents with Asthma

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List of Abbreviations:

Abbreviation or Specialised Term	**Definition**
ADA	anti-drug antibodies
AE	adverse event
AHR	airway hyperresponsiveness
ALT	alanine transaminase
ATS	American Thoracic Society
AST	aspartate transaminase
AUC	area under the concentration-time curve
βHCG	beta-human chorionic gonadotrophin
BLQ	Below Limit of Quantification
BMI	body mass index
CI	confidence interval
CL/F	apparent systemic clearance
C_{max}	maximum concentration
CRF	case report form
ECG	Electrocardiogram
ERS	European Respiratory Society
EU	European Union
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG4	immunoglobulin G4
IL-13	interleukin-13
IM	immunogenicity

Abbreviation or Specialised Term	**Definition**
IV	Intravenous
IXRS	interactive voice/web response system
LABA	long-acting beta agonist
MAb	monoclonal antibody
OCS	oral corticosteroids
PEF	peak expiratory flow
PK	pharmacokinetics
SABA	short-acting beta agonist
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of mean
SID	subject identification number
SMC	Safety Monitoring Committee
SUSAR	suspected unexpected serious adverse reactions
Th2	T-helper type 2
$t_{1/2}$	terminal phase elimination half-life
t_{max}	time of occurrence for maximum drug concentration
ULN	upper limit of normal
Vss/F	apparent volume of distribution at steady-state

1 Introduction

This document describes the statistical methodology for CD-RI-CAT-354-1054, a Phase 1, Open-label Study to Evaluate the Pharmacokinetics of Tralokinumab in Adolescents with Asthma. Some background information and an overview of the study design are provided in Section 2. Section 3 and onwards of the document details the statistical summaries relating to each study objective as well as describing general conventions and definitions. A separate statistical programming plan (SPP), containing table templates and specifications, has also been created to be used in conjunction with this document.

2 Background

Asthma is a chronic inflammatory disease in the airways characterized by bronchial hyperactivity and reversible limitation of airflow that causes wheezing, shortness of breath, cough, and chest tightness.

Uncontrolled asthma in childhood is associated with increased healthcare utilization and adverse impact on quality of life, and can have long-term effects on lung function, with impairment frequently persisting into adulthood (National Heart, Lung, and Blood Institute, 2007). In the Children and Asthma in America survey of children and adolescents aged 4-18 years with asthma, more than half of the subjects (54%) had at least one sudden, severe asthma attack within the previous 12 months and 19% had a severe attack at least twice within the past year. A total of 42% of children had some form of urgent or emergency care visit for their asthma in the past year. In addition limitations on daily activities were reported in 62% and children in the survey missed an average of 3.7 days of school in the past year with 9% missing more than 2 weeks (Massanari et al, 2009).

There is therefore a clear medical need for therapies to treat childhood asthma, particularly those with severe asthma unable to gain complete asthma control using currently available therapies.

Interleukin-13 (IL-13) is a member of the interleukin family of cytokines and is secreted predominantly by CD4+ T-helper-2 (Th2) cells. Interleukin-13 receptors are expressed on a number of cell types including key cells involved in asthma (Hershey, 2003). There is considerable evidence that IL-13 is a key mediator in the pathogenesis of established asthmatic disease and may have a number of effects (Hershey, 2003; Saha et al, 2008).

Clinical data have been reported that show an improvement in lung function in adult subjects with moderate to severe asthma following blockade of IL-13 (Corren et al, 2011), supporting the hypothesis that IL-13 is an important mediator in asthma.

Tralokinumab is a human recombinant monoclonal antibody (MAb) of the immunoglobulin G4 (IgG4) subclass that specifically binds human IL-13, blocking interactions with IL-13 receptors. Studies with tralokinumab to date have exclusively enrolled adult subjects; however, future efficacy and safety studies are expected to enroll both adults and adolescents since IL-13 is expected to be an important mediator in both age groups. The current study will explore the PK profile of 300 mg SC tralokinumab in adolescent subjects and the resulting data will be compared with PK data from completed studies in adults.

2.1 Study Overview

This is a Phase 1, open-label, single-dose study to evaluate the PK profile of tralokinumab in adolescent subjects (12-17 years) with asthma requiring the daily use of controller medications described at Step 2-5 of the GINA guidelines (GINA 2010). A total of 20 subjects will be entered into the study at approximately 4 sites in Europe. Ten subjects will be aged between 12-14 years and 10 subjects will be aged between 15-17 years. All subjects entered into the study will receive a single SC 300 mg dose of tralokinumab.

Subjects will attend the clinic and informed consent will be obtained from the legal representative and informed assent will be obtained from the subject. If the screening assessments are initiated at this consent visit, they must be completed within 14 days. If the screening assessments are not initiated at the consent visit, the subject will return to the clinic within 30 days of this consent visit and will complete their screening assessments within 14 days (Days -14 to -1) before investigational product administration. Subjects will receive a single 300 mg SC dose of tralokinumab on Day 1 and will then return to the clinic up to Day 57 for safety follow-up as outlined in Figure 2.1-1.

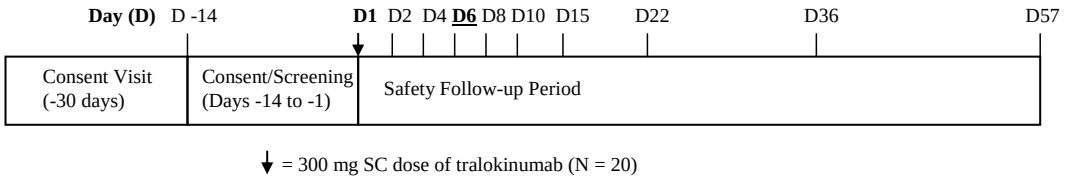

Figure 2.1-1 Study Flow Diagram

Subjects will be in the study for up to 101 days; including up to 30 days for consent, 14 days for screening and 57 days for safety follow-up.

2.2 Randomization and Blinding

The study is neither randomized nor blinded. It consists of a single-dose open-label 300 mg SC administration of tralokinumab.

2.2.1 Subject Randomization Procedures and Treatment Allocation

As earlier indicated, this is not a randomized study. All subjects receive open-label tralokinumab.

An IXRS will be used to assign investigational product kit numbers and to ensure equal distribution between age groups; 10 subjects will be between 12-14 years old and 10 subjects will be between 15-17 years old. A subject is considered entered into the study when the investigator or designee notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of investigational product kit numbers to the subject.

Each subject who meets the eligibility criteria will be assigned open-label investigational product.

The procedure for using IXRS is as follows:

- The investigator or designee confirms that written informed consent and subject assent has been obtained and that the subject has met all eligibility criteria.
- The investigator or designee calls or logs onto the IXRS and provides the subject identification number (SID) and subject's baseline characteristic(s) used to verify that it is the same subject.
- The IXRS assigns an investigational product kit number to the subject.

- Confirmation of this information is sent to the investigational product manager at the site who dispenses the investigational product member to the team member who will administer investigational product to the subject, and records the appropriate information in the pharmacy record and investigational product accountability log.

Investigational product should be administered on the same day the investigational product is dispensed. If there is a delay in the administration of investigational product such that it will not be administered within the specific timeframe, the monitor should be notified immediately.

2.2.2 Blinding

This study is not blinded.

2.3 Sample Size Considerations

The number of subjects has been based on the desire to obtain adequate PK and safety data while exposing as few subjects as possible to tralokinumab and procedures. A total of 20 subjects are considered sufficient to provide adequate information and to ensure that the study includes subjects across the adolescent age range.

3 Statistical Methods

3.1 General Considerations

Data will be provided in data listings sorted by subject number and cohort when applicable. Tabular summaries will be presented. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum.

Data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to MedImmune SAS® programming standards and MedImmune SAS® validation procedures.

Non-compartmental pharmacokinetic analyses will be performed using WinNonlin® Professional software (Pharsight Corporation, Mountain View, CA), version 5.1 or higher. Additionally, population PK analyses will be performed using NONMEM® software (ICON Development Solutions, Ellicott City, MD, USA), version 7.0 or higher, but results will be reported separately. All PK analyses will be performed by MedImmune's Global PK-PD & Bioanalysis group.

3.2 Subject Populations

Two populations have been defined in this study, the PK population and the Safety Population.

3.2.1 PK Population

The PK population includes all subjects who receive the investigational product and who have at least one detectable post dosing tralokinumab serum concentration.

3.2.2 Safety Population

The safety population includes all subjects who receive the investigational product.

3.3 Baseline Characteristics

Several summaries, which include Subject Population for Evaluation, Number of Subject Enrolled by Site, and Status of Enrolled Subjects, will be provided to describe the study population. These summaries will aid in interpretation of the assessment of the primary, secondary and exploratory objectives and provide an overview of study conduct.

The summary of the number of subjects enrolled by site will be sorted by site number and will contain the primary investigator's name/location.

The summary of enrolled subject status at end of study will include an enumeration of the number of subjects who completed the study and the number who did not complete the study due to the following reasons: adverse event, death, lost to follow-up, withdrawal of consent, and other.

All the baseline characteristics (demographics, baseline disease characteristics, medical history and asthma history), concomitant asthma and non-asthma medications taken prior to study entry, and concomitant asthma and non-asthma medications taken during the study, will be summarized for the PK population since the primary objective of this study is PK assessment.

Demographics and baseline disease characteristics will be summarized for the overall population and by age cohort

The following demographic characteristics will be summarized: age in years, gender, race, ethnicity, weight, height, and Body Mass Index (BMI). BMI is calculated as follows:

$$BMI = \text{weight (kg)} / [\text{height (m)}]^2$$

The summary of baseline disease characteristics will include descriptive statistics for whole blood eosinophil count, and spirometry [pre- and post-bronchodilator FEV_1, pre-bronchodilator FEV_1 % predicted, % reversibility in FEV_1, FVC, FVC % predicted, and FEV1/FVC ratio].

Prior and concomitant medications will be coded using the latest available version of AstraZeneca Drug Dictionary (AZ DD). All prior and concomitant medications will be summarized.

Summary	**Population**
Study Populations for Evaluation	NA
Number of Subjects Enrolled by Site	Safety
Status of Enrolled Subjects at End of Study	Safety
Demographics	PK (overall population and by age cohort)
Baseline Disease Characteristics	PK (overall population and by age cohort)
Summary of Medical History	PK
Summary of Asthma History	PK
Summary of Asthma Medications at Study Entry	PK
Summary of Asthma Medications After Enrollment	PK
Summary of Non-Asthma Concomitant Medications at Study Entry	PK
Summary of Non-Asthma Concomitant Medications After Enrollment	PK

3.4 Study Drug Exposure

The following summary will be provided:

Summary	Population
Total Amount of Study Drug Exposure in mg	Safety
Total Amount of Study Drug Exposure in mg/kg	Safety

The summary of study drug exposure will include descriptive statistics for total amount of study drug (in both mg and mg/kg) administered to each subject. The total amount of study drug (in mg and mg/kg) administered to the subject is defined as:

Total actual volume administered (ml) × drug concentration (mg/ml) and

Total actual volume administered (ml) × drug concentration (mg/ml) /weight.

For this trial, the drug concentration administered is 150 mg/ml.

3.5 Summaries to Support the Primary Objective

The primary objective of this study is to evaluate the PK profile of a single-dose 300 mg SC administration of tralokinumab in adolescent subjects with asthma.

Individual tralokinumab serum concentrations will be listed. Descriptive statistics summarizing serum concentration data by time point, will be provided; these will include N, geometric mean, arithmetic mean, standard deviation (SD), percent coefficient of variation, median, minimum, and maximum. Semilog plots of the individual serum concentrations of tralokinumab over nominal time will be provided labeled by cohort. Semilog plots of the mean +/- standard error of the mean (SEM) of serum concentrations over time of tralokinumab for the overall PK population and stratified by cohort will also be produced.

Non-compartmental PK analysis will be performed using the software package WinNonlin® according to MedImmune SOP CT-030103.

The following PK parameters will be estimated by non-compartmental analysis:

- $AUC_{(0\text{-infinity})}$: the area under the serum concentration-time profile from time zero to infinity (units: μg.day/mL);
- $AUC_{(0\text{-t})}$: the area under the serum concentration-time profile from time zero to the last measurable time point (units: μg.day/mL);
- C_{max}: the maximum observed serum concentration of tralokinumab following SC administration (units: μg /mL);
- t_{max}: the time to C_{max} (units: days);
- $t_{1/2}$: the terminal-phase elimination half-life (units: days);
- CL/F: the apparent systemic clearance (units: mL/day);
- Vss/F: the apparent steady-state volume of distribution (units: mL).

PK parameters will be tabulated along with descriptive statistics for each cohort and overall. Descriptive statistics for PK parameters (apart from t_{max}) will include N, geometric mean, arithmetic mean, standard deviation (SD), percent coefficient of variation, median, minimum, and maximum. For t_{max}, only median, minimum and maximum will be reported.

Two other PK parameters will be incorporated along with descriptive statistics for each cohort and overall: normalized body weight apparent systemic clearance (CL/F, in mL/day/Kg) and apparent steady-state volume of distribution (Vss/F, in mL/Kg). The normalization by total body weight at baseline of CL/F and Vss/F will be performed for each individual subject as defined respectively by:

(CL/F)/weight and

(Vss/F)/weight.

The PK data gathered in this study will be added to a population PK model to assess any PK differences between adolescents and adults and guide dosing for future studies that include adolescents. This analysis will be reported separately.

Summary	**Population**
Summary of Serum Tralokinumab Concentrations	PK (overall and by age cohort)
Summary of PK Parameters	PK (overall and by age cohort)

Semilog plot of Individual Serum Tralokinumab Concentration Over Nominal Time labeled by cohort	PK
Semilog plots of Mean Serum Tralokinumab Concentration (±SEM) Over Nominal Time	PK (overall and by age cohort)

3.6 Summaries to Support the Secondary Objectives

The secondary objectives of this study are:

1) To evaluate the safety and tolerability of tralokinumab.
2) To evaluate the immunogenicity (IM) of tralokinumab.

3.6.1 Safety and Tolerability of Tralokinumab

3.6.1.1 Adverse Events

An adverse event (AE) is defined in the protocol as any medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, was considered an AE.

A serious adverse event (SAE) is any AE that may be one or more of the following: results in death; is immediately life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect in offspring of the subject; is an important medical event that may require medical intervention to prevent one of the outcomes listed above.

The reporting period for AEs and SAEs is the period immediately following the time that written informed consent is obtained through the end of study (Study Day 57).

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product. A treatment emergent event is defined as a new sign, symptom, disease, or other untoward medical condition occurring after receipt of investigational product, or a worsening of a subject's pre-existing condition.

Adverse events will be coded using a Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA used will be indicated in the tables/listings.

Per protocol, (sections 6.1.3.1 and 6.3.2), hepatic function abnormality was defined as an adverse event of special interest (AESI): i.e., any increase in ALT or AST greater than 3 x ULN, and concurrent increase in bilirubin to greater than 2 x ULN. [Concurrent findings are those that derive from the same blood draw, or from separate blood draws taken within 8 days of each other.]

Adverse events (AE) and serious adverse events (SAE) will be summarized by MedDRA system organ class, preferred term, severity, and relationship to investigational product. Summary tabulations to be provided for adverse events include the following:

Summary	**Population**
Number of Subjects with Non-Treatment Emergent Adverse Events	Safety
Rate Summary of Non-Treatment Emergent Adverse Events	Safety
Number of Subjects with Treatment Emergent Adverse Events	Safety
Rate Summary of All Treatment Emergent Adverse Events	Safety
Number of Subjects with Treatment Emergent Adverse Events by Highest Severity	Safety
Number of Subjects with Treatment Emergent Adverse Events Sorted by Frequency	Safety
Number of Subjects with Related Treatment Emergent Adverse Events	Safety
Number of Subjects with Related Treatment Emergent Adverse Events by Highest Severity	Safety

Summary	Population
Number of Subjects with Non-Treatment Emergent Serious Adverse Events	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events by SAE Criteria	Safety
Number of Subjects with Related Treatment Emergent Serious Adverse Events	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events by Highest Severity	Safety
Non-Treatment Emergent Adverse Events Resulting in Death	Safety
Treatment Emergent Adverse Events Resulting in Death	Safety
Number of Subjects with Treatment Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug	Safety

3.6.1.2 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24-48 hours). These repeat tests may either be performed by the central clinical laboratory or by a laboratory local to the site as clinically indicated.

Laboratory measurements will be evaluated with descriptive statistics (N, mean, median, standard deviation, minimum and maximum) for lab results and changes from baseline at each collection time point. Unless otherwise indicated, baseline will be defined as the last valid measurement prior to dosing. The geometric mean may be used to summarize the data if it is thought that the numbers are too small for the usual summary statistics to provide value meaning to interpretation of the data.

All laboratory values will be included in the listings and values outside of the normal range will be flagged. For laboratory values reported as lower than the limit of quantification (LLOQ), a value equal to half of the limit of quantification will be imputed in the summaries.

However, all laboratory measurements will be included in the data listings as reported without any imputation.

Summary	Population
Hematology Results	Safety
Serum Chemistry Results	Safety
Change from Baseline in Hematology Results	Safety
Change from Baseline in Serum Chemistry Results	Safety
Shift Table for Hematology Results	Safety
Shift Table for Serum Chemistry Results	Safety
Summary of Urinalysis Results	Safety

3.6.1.3 Vital Signs

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained at all visits. On Day 1 vital signs will be obtained before investigational product administration. The values thus obtained will be defined as the baseline values. Changes from baseline in the quantitative measurements will be derived from these.

After investigational product administration, subjects will be monitored for immediate drug reactions; vital signs will be taken at 15, 30, 45 minutes, and 1, 4, and 8 hours after dosing. Discharge from site will be determined by the investigator.

Vital signs (blood pressure, temperature, pulse rate, and respiration rate) will be obtained at visits 3, 4, 7, 9, and 12 after the subject has been resting for at least 5 minutes.

Vital sign (blood pressure, temperature, pulse rate, and respiration rate) results and change from baseline for vital sign results will be summarized using descriptive statistics. In addition, a listing of vital signs data will be generated.

Summary	Population
Summary of Vital Sign Results	Safety
Change from Baseline for Vital Sign Results	Safety

3.6.1.4 ECG

Computerized 12-lead ECG recordings will be obtained after the subject has been supine for at least 10 minutes. Each lead will be recorded for at least 3-5 beats at a speed of 25 mm/sec paper speed and 10 mm/mV amplitude. Heart rate, PR, QRS, QT and QTc intervals (msec) will be recorded from the 12-lead ECG. The principal investigator or a designated sub-investigator will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings..

For ECGs, baseline is defined as the value obtained from the screening visit. The number of subjects with qualitative ECG results or findings will be produced. In addition, the observed values for quantitative assessments (heart rate, PR, QRS, QT, and QTc intervals) and the change from screening in quantitative assessments will be summarized with descriptive statistics. All ECG data will be listed.

Summary	**Population**
Summary of Qualitative ECG Findings/Results	Safety
Summary of Quantitative ECG Test Results	Safety
Change from Screening in Quantitative ECG Test Results	Safety

3.6.1.5 Physical Examination

All abnormal physical exam findings (pre and post-dose assessments) will be listed.

3.6.2 Immunogenicity of Tralokinumab

The incidence rate of positive serum antibodies to Tralokinumab will be reported.

Summary	**Population**
Summary of Subjects with Anti-Tralokinumab Antibodies	PK`

3.7 Summaries to Support the Exploratory Objectives

An exploratory objective of this study is to evaluate the effect of tralokinumab on pulmonary function.

Spirometry will be performed by the investigator or qualified designee on equipment provided by a central vendor according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al, 2005). Pre-bronchodilator FEV_1 and FVC will be captured at visits 2, 3, 7, 9 and 12, post-bronchodilator FEV_1 will only be captured at screening (visit 2).

Spirometry testing must be performed in the morning between 6:00 and 11:00 AM according to the schedule of study procedures. On Day 1 (visit 3), spirometry testing will be performed before administration of tralokinumab. This will be the baseline measure.

All morning spirometry testing must be completed between 6.00 and 11.00 AM and within ± 1 hour of the time the screening spirometry was completed. For example, if the screening spirometry is at 8:00 AM, then all spirometry testing at subsequent visits need to be completed between 7:00 and 9:00 AM.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each clinic spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The maximum FEV_1 of the 2 best efforts will be used for the analysis. The percentage of predicted normal value for FEV_1 will be recorded using appropriate reference values. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest $FEV_{1)}$.

Reversibility is calculated as follows:

$$\% \text{ Reversibility} = \frac{(\text{post-bronchodilator } FEV_1 - \text{ pre- bronchodilator } FEV_1) \times 100}{\text{pre-bronchodilator } FEV_1}$$

Spirometric parameters (FEV_1, FEV_1 % predicted, FVC, FVC % predicted and FEV1/FVC ratio at baseline and reversibility at screening) as well as the change from baseline and percent change from baseline in spirometric parameters will be summarized with descriptive statistics. A plot of mean (+/- SEM) pre-bronchodilator FEV1 over time and the mean (+/- SEM) change from baseline in pre-bronchodilator FEV1 over time will also be produced.

Summary	Population
Summary of Spirometry Results	PK
Change from Baseline in Spirometry Results	PK
Percent Change from Baseline in Spirometry Results	PK

4 Missing Data

Missing data will not be imputed unless otherwise specified in the Statistical Programming Plan. For all PK summary tables, listings and figures, serum concentrations that are below the assay's lower limit of quantitation (LLOQ) will be set to zero prior to deriving the summary statistics or plotting the concentration values. For the PK data analyses, post-dose values of "no sample" (NS), "insufficient same for analysis" (IS), or "not reported" (NR) will be omitted. Missing PK observations will not be imputed.

5 General Statistical Conventions

- For PK data, the following conventions will be used:

  The Below Limit of Quantification (BLQ) observations will be changed to zero for mean concentration calculation. However, if the calculated mean is less than the assay low limit of quantification (0.5 μg/mL), the mean value will be reported as <0.5.
- Laboratory data reported as ND (not done) will be counted as missing when calculating summary statistics.
- In general, all calculations will be performed prior to rounding.
- All percentages will be formatted as (xx.x%) with the exception of 100% which will be displayed as (100%). For 100% and percentages less than 10, a space will be included between the "(" and the first digit, for example, (6.3%) rather than (6.3%). For 0%, the percentage will be displayed as (0.0%).

- No formal testing is currently planned since all subjects receive the same treatment. However, should the cohorts be compared and P-values generated, these P-values will be rounded to three decimal digits. P-values that are less than 0.001 will be reported as "< 0.001" on the tables.
- For analyses of pre-dose laboratory data, if the time of the pre-dose laboratory collection actually occurs after dosing, the data will be excluded from analyses.
- If N = 1, then the standard deviation and/or standard error should be displayed as "NA". If N= 0, then all summary statistics (other than N) will be displayed as "NA".

6 References

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