STATISTICAL ANALYSIS PLAN Sec 12.1.3

Protocol No.:	SHP643-101
Protocol Title:	A Phase 1, Open-label Study to Evaluate the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of a Single Dose of Lanadelumab Administered Subcutaneously in Healthy Adult Japanese Subjects and Matched Healthy Adult Caucasian Subjects
Drug:	SHP643, lanadelumab (formerly DX-2930)
Sponsor:	Dyax Corp. (an indirect and wholly-owned subsidiary of Shire plc) 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Version 1.0, Date 21 Jun 2018

Version No:	Document History Description of Update	Author(s)	Effective Date
0.1	Draft	PPD, MS PPD PPD PPD PPD BSc (Hons) PPD, PPD	12Feb2018
0.2	Draft	PPD, MS PPD PPD PPD PPD, BSc (Hons) PPD, PPD	05Mar2018
0.3	Stable Draft	PPD, MS PPD PPD PPD PPD, BSc (Hons) PPD, PPD	30Mar2018

1.0	Final	PPD MS PPD PPD PPD , BSc (Hons) PPD , PPD	21Jun2018

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ABBREVIATIONS

λ_Z	first order rate constant associated with the terminal (log-linear) phase of elimination
%CV	percent coefficient of variation
ADA	anti-drug antibody
AE	adverse event
ANOVA	analysis of variance
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
$AUC_{0\text{-last}}$	area under the concentration-time curve from time zero to the last quantifiable concentration in plasma
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from time zero extrapolated to infinity
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
HMWK	intact high molecular weight Kininogen
cHMWK	cleaved high molecular weight Kininogen
CI	confidence interval
C_{max}	maximum observed plasma drug concentration
CL/F	apparent clearance following extravascular administration divided by the fraction of dose absorbed
CSR	Clinical Study Report
DMC	data monitoring committee
eCRF	electronic case report form
ECG	electrocardiogram
FXII(a)	factor XII (activated)
GGT	gamma glutamyl transferase
ISR	injection site reactions
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
N	number of subjects
PCI	potentially clinically important
PD	pharmacodynamic
PK	pharmacokinetic

pKal	plasma kallikrein
PT	preferred term
RBC	red blood cells
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t½	terminal half-life
T3	tri-iodothyronine
T4	Thyroxine
t_{max}	time of maximum observed concentration sampled during a dosing interval
TSH	thyroid-stimulating hormone
V_z/F	apparent volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic (PK), safety and tolerability, and pharmacodynamic (PD) data described in the approved study protocol dated 27 Nov 2017, the Protocol Administrative Change Memo #1 dated 05 Dec 2017, and the Protocol Administrative Change Memo #2 dated 26 Jan 2018. Specifications for tables, figures, and listings (TFLs) are contained in a separate document (SHP643-101 TFL Shells).

No formal statistical hypothesis will be tested. The following summaries will be provided for all PK, safety and tolerability, and PD analysis endpoints, unless otherwise specified in this SAP: For continuous variables (e.g., age): number of subjects (n), mean, standard deviation (SD), median, minimum and maximum value; for categorical variables (e.g., sex): number and percentage of subjects. Summaries will be presented by ethnic group (Japanese, Caucasian) and for all groups combined (overall), as appropriate. For the PK parameters/endpoints, appropriate point estimates and confidence intervals (CIs) will be provided, but no formal between-ethnic group comparisons will be performed.

2. STUDY DESIGN

2.1 General Study Design

This study is a Phase 1, open-label, matched-control, single-dose, single-center study to evaluate the PK, safety and tolerability, and PD of lanadelumab administered to healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy adult volunteer subjects.

A total of 32 subjects between the ages of 18-55, inclusive, will be enrolled:

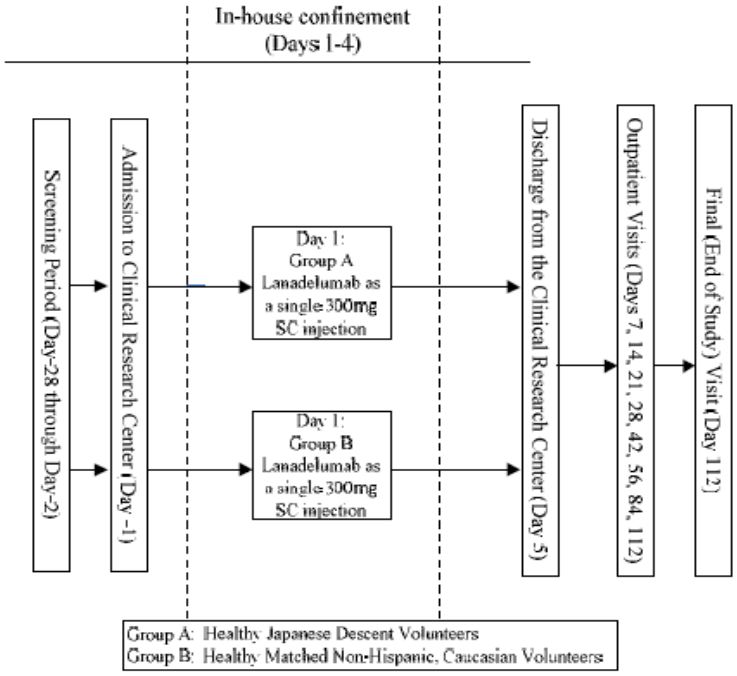
- 16 subjects of Japanese descent born in Japan, who have resided outside of Japan for no longer than 5 years and are of Japanese parentage, defined as having 2 Japanese parents and 4 Japanese grandparents, all born in Japan, and
- 16 non-Hispanic Caucasian subjects, each of whom has 2 non-Hispanic, Caucasian parents and 4 non-Hispanic, Caucasian grandparents.

Assuming a 25% dropout rate (based on previous clinical experience), approximately 24 subjects (12 subjects from each ethnic group) are expected to complete the study. Study subjects who withdraw or discontinue early may be replaced at the discretion of the sponsor.

Non-Hispanic Caucasian subjects will be matched in a 1:1 ratio to Japanese subjects based on sex (1:1 male: male, female: female), age (±5 years), and body mass index (BMI) (±15%). For example, a Japanese male, age 40 years, and BMI of 22 kg/m^2 will be matched with a Caucasian male, age 40 ± 5 years (35-45 years [inclusive]), and BMI of 22 ±15% (18.7-25.3 kg/m^2, inclusive). Matching is intended to ensure that the ethnic groups are comparable at baseline with respect to sex, age, and BMI. All subjects will receive a single dose of 300 mg of lanadelumab administered by subcutaneous (SC) injection into the abdomen on Day 1.

The study duration will be comprised of a 28-day screening period, one 5-day in-house treatment period, and multiple out-patient visits (Day 7 [± 1 day], Day 14 [± 1 day], Day 21 [± 1 day], Day 28 [± 1 day], Day 42 [± 2 days], Day 56 [± 2 days], Day 84 [± 3 days] and Day 112 [± 3 days]) after the single dose of investigational product is administered. The maximal total duration of study participation for a subject is approximately 140 days if the maximal screening, treatment, and out-patient durations are used.

Figure 1: Study Design Flow Chart



2.2 Randomization

Not applicable.

2.3 Blinding

Not applicable. This study is open-label.

2.4 Schedule of Assessments

Table 1: Schedule of Assessments

Visit	Screening	In-House Treatment Period						Out-Patient Visits[a]/ Early Discontinuation[b]
Study Day	–28 to -02	-1	1	2	3	4	5	
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demography and medical/medication history	X	X [c]						
Physical examination	X	X					X	X
Vital signs (blood pressure, pulse) supine [d]	X	X	X	X	X	X	X	X
Body temperature (oral)	X		X					X
Height, Weight and BMI [e,f]	X	X					X	X
Electrocardiogram (12-lead) [d]	X [g]	X [g]	X	X	X	X	X	X
Biochemistry[h], hematology, and urinalysis	X	X		X			X	X
PT, aPTT, INR	X	X					X	X
HIV, HBsAg, and HCV antibodies	X							
Serum Pregnancy test (all females) [d]	X	X					X	X
FSH (females only)	X							
Urine drug and alcohol (breath test) screening [i]	X	X						X [j]
Investigational Product administration			X					
Pharmacokinetic blood sampling [d]			X	X	X	X	X	X [j]
Anti-drug antibody testing [d]			X					X
Pharmacodynamic blood sampling [d]			X	X	X	X	X	X [j]
Check-in to the CRC		X						
Discharge from the CRC							X	
In-house confinement		X	X	X	X	X		
Out-patient visits	X							X
Adverse events/serious adverse events	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X

HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

a. There will be multiple out-patient visits on: Day 7 (± 1 day), Day 14 (± 1 day), Day 21 (± 1 day), Day 28 (± 1 day), Day 42 (± 2 days), Day 56 (± 2 days), Day 84 (± 3 days) and End of Study Day 112 (± 3 days), after the dose of investigational product is administered on Day 1. Refer to Table 2 for complete details.

b. In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

c. Medical history and medication history review only

d. See Table 2 for detailed collection time points

e. Height will be recorded at the Screening Visit only

f. BMI criteria for eligibility will be calculated at the Screening Visit.

g. ECGs will be performed in triplicate at Screening and Day -1 only. Thereafter, all subsequent ECGs will be single recordings

h. Thyroid function tests (TSH, T3, T4) will be collected as part of the biochemistry panel at Screening only.
i. Drugs of abuse at screening, and drugs of abuse and alcohol (breath test) on Day -1 and at all out-patient visits.
j. No PK or PD sample, or urine drug or alcohol screen should be collected for early discontinuation.

Table 2: Detailed Schedule of Assessments

	In-House Treatment Period												Out-Patient Visits							
Study Day	**Day 1**								**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7±1**	**Day 14±1**	**Day 21±1**	**Day 28±2**	**Day 42±2**	**Day 56±2**	**Day 84± 3**	**Day 112±3 End of Study (or Early Term.[a])**
Hour (relative to dosing time)	**Pre dose**	**0**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**	**48h**	**72h**	**96h**								
Physical examination												X	X	X	X	X	X	X	X	X
Vital signs (blood pressure, pulse) supine	X[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body temperature (oral)	X												X	X	X	X	X	X	X	X
Weight												X	X	X	X	X	X	X	X	X
Electrocardiogram (12-lead) [c]	X[b]		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry, hematology, and urinalysis									X			X	X	X	X	X	X	X	X	X
PT, aPTT, INR												X	X	X	X	X	X	X	X	X
Serum Pregnancy (all women)												X	X	X	X	X	X	X	X	X
Urine drug and alcohol (breath test) screen													X	X	X	X	X	X	X	X[d]
Investigational Product administration		X																		
Pharmacokinetic blood sampling	X[b]						X		X	X	X	X	X	X	X	X	X	X	X	X[d]
Pharmacodynamic blood sampling	X[b]						X		X	X	X	X	X	X	X	X	X	X	X	X[d]
Anti-drug antibody sampling	X[b]													X		X		X		X
Adverse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	In-House Treatment Period												Out-Patient Visits							
Study Day	**Day 1**								**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7±1**	**Day 14±1**	**Day 21±1**	**Day 28±2**	**Day 42±2**	**Day 56±2**	**Day 84± 3**	**Day 112±3 End of Study (or Early Term.[a])**
Hour (relative to dosing time)	**Pre dose**	**0**	**1h**	**2h**	**4h**	**6h**	**8h**	**12h**	**24h**	**48h**	**72h**	**96h**								
events/serious adverse events																				
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments.

b. These assessments should be performed within 60 minutes prior to dose administration.

c. ECG's will be performed as single records at each timepoint.

d. No PK or PD sample, or urine drug or alcohol screen should be collected for early discontinuation.

2.5 Determination of Sample Size

The planned sample size for this study is 32 subjects: 16 subjects of Japanese descent and 16 matched non-Hispanic Caucasian subjects.

Assuming a 25% dropout rate (based on previous clinical experience), the sample size ensures approximately 24 subjects (12 Japanese and 12 matched non-Hispanic Caucasians) complete the study, and 24 subjects are evaluable for PK analysis purposes. The sample size is considered adequate for the primary objective of the study (defined in Section 3) and therefore adequate for providing reliable estimates of PK parameters, and similarly for the secondary objective.

No formal statistical hypothesis will be tested. The sample size was based on clinical judgment, precedent PK studies of similar design, and similar subject population, not on statistical considerations such as study power. Any subject who prematurely discontinues the study, whether part of a matched pair or is not yet matched, may be replaced at the discretion of the study sponsor to ensure there are approximately 12 evaluable subjects in each ethnic group for PK analysis purposes.

3. OBJECTIVES

3.1 Primary Objective

To evaluate the PK properties of lanadelumab administered as a single SC dose of 300 mg in healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects.

3.2 Secondary Objective

To assess the safety and tolerability of lanadelumab administered as a single SC dose of 300 mg to healthy adult volunteer subjects of Japanese descent and matched, non-Hispanic Caucasian healthy volunteer subjects.

3.3 Exploratory Objectives

To explore the PD properties of lanadelumab including plasma kallikrein (pKal) activity and cleaved high molecular weight kininogen (cHMWK) plasma levels after a single SC dose of 300 mg of lanadelumab administered to healthy adult volunteer subjects of Japanese descent and matched non-Hispanic, Caucasian healthy volunteer subjects.

4. ANALYSIS POPULATIONS/ANALYSIS SETS

4.1 Enrolled Set

The Enrolled Set will consist of all subjects for whom an enrollment number has been assigned. Background summaries (e.g., subject disposition) will be based on the Enrolled Set, unless otherwise specified in this SAP.

4.2 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who received at least 1 dose of lanadelumab (investigational product). All safety analyses will be based on the Safety Analysis Set.

4.3 Pharmacokinetic Set

The PK Set will consist of all subjects in the Safety Analysis Set who have at least 1 evaluable postdose PK concentration value. All PK analyses will be based on the PK Set.

4.4 Pharmacodynamic Set

The PD Set will consist of all subjects in the Safety Analysis Set who have at least 1 evaluable postdose PD value. All PD analyses will be based on the PD Set.

5. SUBJECT DISPOSITION

The number and percentage of subjects included in each analysis set (Enrolled, Safety, PK and PD) will be summarized as appropriate.

The number and percentage of subjects who completed the study or prematurely discontinued will be presented, along with primary reasons for discontinuation, as recorded on the study completion page of the electronic case report form (eCRF). All enrolled subjects who prematurely discontinued the study will be listed in the subject disposition listing along with reasons for discontinuation.

Subject disposition summary and listing will be based on the Enrolled Set, and the summary will be presented by ethnic group and for all groups combined.

6. PROTOCOL DEVIATIONS

Protocol deviations will be classified as major or minor in accordance with applicable Shire standard operating procedures and based on the following definitions:

- **Major protocol deviation** is a subset of protocol deviations that may significantly impact subject's rights, safety or well-being, the statistical analysis, and/or the interpretation of product safety / efficacy

- **Minor protocol deviation** is a subset of protocol deviations, which include changes or alterations in the conduct of the study that do not have a significant impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

All protocol deviations will be presented in the protocol deviation listing and based on the Enrolled Set. No summaries are planned.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

7.1 Demographic and other Baseline Characteristics

The following demographic and other baseline characteristics will be summarized by ethnic group and overall. Demographics include: age (years), sex (male, female), ethnicity (not Hispanic or Latino), and race (White, Asian). Other baseline characteristics include: weight (kg), height (cm), and BMI (kg/m^2). Note: sex, age and BMI are the matching factors.

Age will be calculated as the integer part of: (date of screening – date of birth + 1)/365.25, and BMI will be calculated as: weight (kg) / (height [m])^2. Height and weight at screening assessment will be used to calculate BMI.

Continuous variables, such as age, weight, height, and BMI will be summarized using descriptive statistics including n, mean, SD, median, minimum, and maximum. Categorical variables such as sex, ethnicity, and race will be summarized by reporting the number and percentage of subjects in each category.

All demographic and other baseline characteristics variables that will be summarized will be taken from the Screening Visit. Summaries will be based on the Safety Analysis Set, PK Set and PD Set, as appropriate. Demographics and other baseline characteristics data will be listed, and the listing will be based on the Safety Analysis Set. Subject matching will be listed only, and the listing will be based on the Enrolled Set.

7.2 Medical History

A complete medical and medication history will be collected at the Screening Visit including recent use of medication (30 days prior to entering the screening period) and history of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.1 or higher).

Medical history will be listed and summarized by system organ class (SOC) and preferred term (PT), and based on the Safety Analysis Set. The summary will include number and percentage of subjects who experienced the event, and number of events experienced. SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the table Total column (i.e., the Total column will be sorted in descending order after sorting by SOC and PT).

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

Exposure in this single-dose (300 mg, single-administration) study will be summarized in terms of the total dose (mg) administered and summarized by ethnic group and overall.

Total dose administered (mg) will be calculated as follows:

$$\text{Total dose administered (mg)} = \text{Planned dose (mg)} \times \frac{\text{Total volume administered (mL)}}{\text{Planned volume (mL)}}$$

where the planned dose is 300 mg; the planned volume is 2 mL; and the total volume administered will be collected in the eCRF.

Summary will include: n, mean, SD, median, minimum, and maximum, and based on the Safety Analysis Set. An exposure data listing, based on the Safety Analysis Set, will be provided and include date and time of dose administration and other exposure data, e.g. planned dose/volume, total dose/volume and location of dose.

8.2 Measurement of Treatment Compliance

This is a single-dose (single-administration) study in which the investigational product will be administered on Day 1 to all subjects and at the study site only (in-house confinement treatment period). All compliance-related data will be included in the exposure data listing. No separate treatment compliance summary or data listing will be provided.

9. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version September 2017 or higher.

For statistical analysis purposes, prior and concomitant medications are defined as follow ("time" implies date and time):

- **Prior medication:** Any medication with start time **prior to** time of investigational product administration.
- **Concomitant medication:** Any medication with start time **at or after** time of investigational product administration, OR medications with start time **prior to** investigational product administration but continuing at or after investigational product administration. Any medication with a start date after the end of the follow-up period (Day 112/ End of Study Visit) will be considered post-treatment medication and not concomitant medication.

For medications with partial onset times, non-missing date parts will be used to determine if the medication is concomitant or prior medication. If a determination cannot be made using the non-missing date parts as to when the medication occurred relative to investigational product administration then the medication will be classified as concomitant medication. Additional information is provided in Section 18.5.

Both prior and concomitant medication usage will be summarized by therapeutic class and preferred term, and based on the Safety Analysis Set. The summary will include number and percentage of subjects who took the medication. Therapeutic class will be sorted alphabetically, and PT will be sorted within each therapeutic class in descending frequency in the table Total column (i.e., the Total column will be sorted in descending order after sorting by therapeutic class and PT). Medications can be counted both as prior and concomitant medications. Multiple medication usage by a subject in the same PT will be counted only once for that PT. All prior and concomitant medications will be listed, and the listings will be based on the Safety Analysis Set.

10. EFFICACY ANALYSES

Not applicable.

11. SAFETY ANALYSES

Safety endpoints include the occurrence and number of treatment-emergent adverse events (TEAEs), vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), electrocardiogram (ECG) results, body weight, clinical laboratory test results (hematology, clinical chemistry, coagulation and urinalysis), and immunogenicity response (development of anti-drug antibodies [ADAs]). For each safety endpoint, unless otherwise specified, the last non-missing value before the administration of investigational product will be used as **baseline** for all analyses of that safety endpoint.

All safety analyses will be descriptive and based on the Safety Analysis Set. Continuous variable summaries will include: number of subjects (n), mean, SD, median, minimum and maximum values, and categorical variable summaries will include: number and percentage of subjects.

11.1 Adverse Events

Adverse events (AEs) will be coded using the MedDRA (Version 20.1 or higher).

Treatment-emergent AEs are AEs with onset at the time of or following the first exposure to investigational product, or medical conditions present prior to the start of investigational product but increased in severity or relationship at the time of or following the start of treatment, up to the last follow-up visit. **Note**: In this study, all AEs will be collected from the time the informed consent is signed through the last follow-up visit (Day 112/End of Study).

An overall summary of the number of subjects with TEAEs will be presented, including, but not limited to: the number and percentage of subjects with any TEAEs, severe TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation from the study, TEAEs resulting in hospitalization, and TEAEs leading to death. An overall summary of the number of TEAEs will be summarized also.

In addition, the number of TEAEs and number and percentage of subjects reporting TEAEs will be tabulated by SOC and PT. The number and percentage of subjects reporting TEAEs will be summarized by SOC, PT, and maximum severity, as appropriate, based on applicable Shire TFL standards. (Note: all severity levels will be presented in the summary). SOC will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the table Total column (i.e., the Total column will be sorted in descending order after the sorting by SOC and PT). Also, all TEAEs and related TEAEs will each be summarized by PT only and in decreasing frequency in the table Total column, and separately non-SAEs will be summarized by SOC and PT and sorted as planned for the other summaries. TEAEs considered related to investigational product will also be summarized by SOC and PT. If more than 1 TEAE occurs within the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. For example, if a subject experienced a mild headache not related to investigational product, and a moderate headache related to investigational product, then the subject will be counted once for headache using the moderate headache related to investigational product.

Serious TEAEs, TEAEs related to investigational product, TEAEs leading to discontinuation from the study, and TEAEs leading to death will be summarized by SOC and PT. Injection site reactions (ISRs) are not predefined in the study protocol. Any ISRs, if reported as AEs, will be summarized along with all other TEAEs as appropriate.

All AE data will be listed. Listings will be presented for all AEs (TEAEs and non-TEAEs), serious AEs, severity of AEs, AEs related to investigational product, AEs leading to discontinuation from the study, and AEs leading to death.

All TEAE summaries will be based on the Safety Analysis Set. Listings will be based on all enrolled subjects.

11.2 Clinical Laboratory Variables

Raw (actual) clinical laboratory values (in SI units) and changes in raw values from baseline at each post-baseline assessment time point will be summarized as continuous variables. Shift tables from baseline to each assessment time point will be provided for categorical variables. The following laboratory variables/parameters will be summarized:

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell (WBC) count – total and differential, total neutrophils (absolute), eosinophils (absolute), monocytes (absolute), basophils (absolute), and lymphocytes (absolute).

Coagulation Prothrombin Time, activated partial thromboplastin time, and international normalized ratio

Biochemistry Sodium, potassium, glucose, blood urea nitrogen (BUN), creatinine, calcium, chloride, phosphorus, total protein, total CO_2 (bicarbonate), albumin, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, and uric acid.

Urinalysis pH, glucose, protein, blood, ketones, bilirubin, nitrites, leukocyte esterase, and specific gravity.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 3 and Table 4. The number and percentage of subjects with post-baseline PCI values at each scheduled time point will be tabulated for each set of PCI criteria. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 post-baseline PCI value. A supportive listing of subjects with post-baseline PCI values will be provided for each set of PCI criteria including the subject number, baseline, and post-baseline values.

All clinical laboratory data will be listed, and listings will be based on the Safety Analysis Set.

Table 3: Primary Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Classification	Criteria
Biochemistry		
Sodium	HIGH	> 5 mmol/L (5 mEq/L) above ULN
	LOW	> 5 mmol/L (5 mEq/L) below LLN
Potassium	HIGH + INCREASE	Above ULN and increase of > 0.5 mmol/L (0.5 mEq/L) from baseline value
	LOW + DECREASE	Below LLN and decrease of > 0.5 mmol/L (0.5 mEq/L) from baseline value
Creatinine	HIGH + INCREASE	> 150µmol/L and increase > 30% from baseline value
BUN	HIGH	> 1.5 x ULN
Glucose (fasting)	HIGH	≥ 6.7 mmol/L
	LOW	≤ 4.2 mmol/L
Calcium	HIGH and INCREASE	Above ULN and Increase of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 0.25 mmol/L (1.0 mg/dL) from baseline value
Phosphorus	HIGH	> 0.162 mmol/L (0.5 mg/dL) above ULN
	LOW	> 0.162 mmol/L (0.5 mg/dL) below LLN
Total protein	HIGH and INCREASE	Above ULN and Increase of ≥ 20 g/L (2.0 g/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 20 g/L (2.0 g/dL) from baseline value
Albumin	HIGH and INCREASE	Above ULN and Increase of ≥ 10 g/L (1.0 g/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of ≥ 10 g/L (1.0 g/dL) from baseline value
Uric acid (with normal diet)	HIGH and INCREASE	Above ULN and Increase of > 0.119 mmol/L (2.0 mg/dL) from baseline value
	LOW and DECREASE	Below LLN and Decrease of > 0.119 mmol/L (2.0 mg/dL) from baseline value
ALT	HIGH	> 2 x ULN
AST	HIGH	> 2 x ULN
ALP	HIGH	> 1.5 x ULN
GGT	HIGH	> 1.5 x ULN
Total bilirubin	HIGH	> 1.5 x ULN
T4	HIGH	> 140.28 nmol/L
	LOW	< 57.92 nmol/L
T3	HIGH	> 2.765 nmol/L
	LOW	< 0.922 nmol/L
TSH	HIGH	>5.0 µU/mL
	LOW	<0.5 µU/mL

Parameter	Classification	Criteria
Hematology		
RBC count	HIGH	>7.5 x10^{12}/L
	LOW	<3 x10^{12}/L
Hematocrit	HIGH	>1.3 x ULN
	LOW and DECREASE	≤0.6 x LLN and Decrease of ≥ 0.06 L/L (6.0%) from baseline value
Hemoglobin	HIGH	>200 g/L (20g/dL)
	LOW and DECREASE	< 100g/L (10g/dL) and Decrease of ≥ 20g/L (2.0 g/dL) from baseline value
WBC count	HIGH	>2 x ULN OR >16.0 x 10^9/L (16 x 10^3/μL)
	LOW	< 0.5 x LLN OR < 3.0 x 10^9/L (3 x 10^3/μL)
Neutrophils	HIGH	> 6.2 x 10^9/L (6.2 x 10^3/μL) OR > 70 %
	LOW	< 1.5 x 10^9/L (1.5 x 10^3/μL) OR < 40%
Lymphocytes	HIGH	> 4.0 x 10^9/L (1.5 x 10^3/μL) OR > 44 %
	LOW	< 0.8 x 10^9/L (0.8 x 10^3/μL) OR < 22 %
Monocytes	HIGH	> 1.1 x 10^9/L (1.1 x 10^3/μL) or > 11%
Eosinophils	HIGH	> 0.5 x 10^9/L (> 500/μL) and > 10.0%
	LOW	NA
Basophils	HIGH	> 0.2 x 10^9/L (0.2 x 10^3/μL) or > 2%
	LOW	NA
Platelet count (thrombocytes)	HIGH	>1.5 x ULN OR > 500 x 10^9/L (100 x 10^3/μL)
	LOW	<0.6 x LLN OR < 100 x 10^9/L (100 x 10^3/μL)
Urinalysis		
Glucose	HIGH	≥ 1+
Blood	HIGH	≥ 2+
Bilirubin		Positive
Protein	HIGH	≥ 2+
Nitrite		Positive
Ketones	HIGH	≥ 2+
Leukocyte Esterase		Positive

BUN: blood urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma glutamyl transferase, T3: triiodothyronine, T4: thyroxine, TSH: thyroid-stimulating hormone, RBC: red blood cell, WBC: white blood cell, NA: not available.

Table 4: Secondary Criteria for Potentially Clinically Important Laboratory Tests

Parameter	Classification	Criteria
Biochemistry		
Sodium	HIGH	≥ 148 mEq/L
	LOW	≤ 129 mEq/L
Potassium	HIGH	≥ 5.5 mEq/L
	LOW	≤ 3.2 mEq/L
Creatinine	HIGH	≥ 2.1 mg/dL
BUN	HIGH	> 31 mg/dL
Glucose (fasting)	HIGH	> 125 mg/dL
	LOW	≤ 54 mg/dL
Calcium	HIGH	≥ 11.6 mg/dL
	LOW	≤ 7.4 mg/dL
Phosphorus	HIGH	NA
	LOW	≤ 1.9 mg/dL
Total protein	HIGH	NA
	LOW	< 5.0 g/dL
Albumin	HIGH	NA
	LOW	< 2.5 g/dL
ALT	HIGH	≥ 5.1 x ULN
AST	HIGH	≥ 5.1 x ULN
ALP	HIGH	≥ 3.1 x ULN
Total bilirubin	HIGH	≥ 1.51 x ULN
Hematology		
Hemoglobin (Female)	HIGH	NA
	LOW and DECREASE	≤ 9.4 gm/dL and Decrease of ≥ 2.1 gm/dL from baseline value
Hemoglobin (Male)	HIGH	NA
	LOW and DECREASE	≤ 10.4 gm/dL and Decrease of ≥ 2.1 gm/dL from baseline value
WBC count	INCREASE	≥ 20,001 cell/mm^3
	DECREASE	≤ 1,499 cell/mm^3
Neutrophils	HIGH	NA
	DECREASE	≤ 999 cell/mm^3
Lymphocytes	HIGH	NA
	DECREASE	≤ 499 cell/mm^3
Eosinophils	HIGH	> 5000 cell/mm^3
	LOW	NA

Parameter	Classification	Criteria
Platelet count (thrombocytes)	HIGH	NA
	LOW	≤ 99,000 cell/mm^3
Urinalysis		
Glucose	HIGH	≥ 2+
Protein	HIGH	≥ 2+
BUN: blood urea nitrogen, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, WBC: white blood cell, NA: not available. Based on Grade 3 or Grade 4 criteria from Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA Guidance for Industry, September 2007).		

11.3 Vital Signs (Including Height and Weight)

Raw (actual) values for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, and body temperature) and their changes from baseline at each post-baseline assessment time point will be summarized.

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 5. The number and percentage of subjects with PCI post-baseline values at each scheduled time point will be tabulated. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline vital sign value. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline PCI values.

All vital signs data (including height and weight) will be listed, and listing(s) will be based on the Safety Analysis Set.

Table 5: Criteria for Potentially Clinically Significant Vital Signs

Parameter	Classification	Criteria
Systolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 140 and increase of ≥ 20 from baseline value
	LOW and DECREASE	≤ 90 and decrease of ≥ 20 from baseline value
Diastolic blood pressure (mm Hg)	HIGH and INCREASE	≥ 90 and increase of ≥ 15 from baseline value
	LOW and DECREASE	≤ 50 and decrease of ≥ 15 from baseline value
Pulse rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	≤ 45 and decrease of > 15 from baseline value
Temperature	HIGH	> 38.3°C or > 100.9°F
	LOW	< 35°C or < 95°F

11.4 Electrocardiogram (ECG)

Raw (actual) values for ECG variables (e.g., heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each post-baseline assessment time point will be presented. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections; and if RR is not available, then 60/heart rate will be used in the correction formula. Electrocardiogram interpretation, per the investigator, will be summarized by assessment time point for all scheduled assessments. In addition, a shift table from baseline to each post-baseline assessment time point for categorical ECG results will be provided.

Subject's baseline ECG is defined as the single ECG collected predose on Day 1 (or unscheduled ECG collected after the scheduled predose timepoint but prior to the administration of investigational product).

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 6. The number and percentage of subjects with post-baseline PCI values at each scheduled time point will be tabulated. The percentages will be calculated relative to the number of subjects with available non-PCI baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCI post-baseline ECG value. A listing of all subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline PCI values.

All ECG data will be listed, and listing will be based on the Safety Analysis Set. Listings of ECG data, including interpretation by individual subject, will also be produced.

Table 6: Criteria for Potentially Clinically Important ECG Values

Parameter	Classification	Criteria
Overall Evaluation	ABNORMAL	Overall Evaluation is ABNORMAL
Heart rate (bpm)	HIGH and INCREASE	≥ 100 and increase of > 15 from baseline value
	LOW and DECREASE	≤ 45 and decrease of > 15 from baseline value
PR interval (msec)	HIGH and INCREASE	≥ 200 and increase of ≥ 20 from baseline value
QRS interval (msec)	HIGH	≥ 120
QTc interval (men) (msec)	HIGH	> 430 and increase from baseline value > 30
QTc interval (women) (msec)	HIGH	> 450 and increase from baseline value > 30

11.5 Other Safety Variables

11.5.1 Immunogenicity Testing for Anti-Drug Antibodies

For immunogenicity, the number and percentage of subjects with ADA prevalence, ADA incidence, pre-existing ADA, treatment-induced ADA, treatment-boosted ADA, transient ADA, persistent ADA, non-neutralizing ADA, and neutralizing ADA will be summarized by ethnic group. The ADA titer and reactivity, as well as the neutralizing antibody responses will be listed.

Pre-existing ADA: a laboratory reported confirmatory positive ADA prior to treatment.

Treatment-induced ADA: ADA developed *de novo* (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA).

Treatment-boosted ADA: Pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by 4-fold increase or more), where the fold increase will be calculated as: $\log_2$(post-dose ADA titer/pre-existing ADA titer).

ADA prevalence: The proportion of all individuals having drug-reactive antibodies (including pre-existing antibodies) at any point in time. This term is distinct from ADA incidence (see below).

ADA incidence: The proportion of the study population found to have seroconverted or boosted their pre-existing ADA during the study period. Synonymous with “treatment-emergent ADA”, ADA incidence is the sum of both treatment-induced and treatment-boosted ADA-positive subjects as a proportion of the evaluable subject population.

Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which ought to be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject’s last sampling time point is ADA-negative.

Persistent ADA response:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or

- Treatment-induced ADA incidence only in the last sampling time point of the treatment study period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

All immunogenicity summaries and data listing(s) will be based on the Safety Analysis Set. The overall ADA status (positive or negative) of each subject will be presented in the listing. Subjects meeting the criteria for ADA incidence will be considered positive for overall ADA status, and all other subjects will be considered negative for overall ADA status.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

12.1 Pharmacokinetic Methods

Individual PK data will be listed, and listing(s) will be based on the Safety Analysis Set; all summaries and analyses of the PK data will be based on the PK Set.

12.1.1 Concentration Data

Blood samples will be drawn from each subject during this study for the determination of plasma concentrations of lanadelumab. Serial blood samples will be collected during the in-house treatment period on Days 1 to 5 for PK analysis at predose, and at 8, 24, 48, 72, and 96 hours after administration of the investigational product. One postdose blood sample will be also drawn from each subject on Days 7, 14, 21, 28, 42, 56, 84 and 112 for the determination of lanadelumab concentrations. Actual sampling times post-dose will be considered protocol deviations where the sample deviated from nominal collection time by more than ±5 minutes within the first 4 hours, ±15 minutes between 4 and 96 hours, ±1 day between Days 7 and 21, ±2 days between Days 28 and 56, and ±3 days on Days 84 and 112. Samples collected outside these windows will be flagged in data listings. Plasma concentrations of lanadelumab will be measured using a validated analytical method.

Individual lanadelumab plasma concentrations will be listed by ethnic group, subject, overall ADA status, day, and time based on the Safety Analysis Set and summarized by ethnic group and time, and separately by ethnic group, overall ADA status and nominal time, all based on the PK Set. Summaries will include: number of subjects (n), arithmetic mean, SD, percent coefficient of variation (%CV), median, minimum, maximum, geometric mean, and %CV of geometric mean. In addition, the mean and individual lanadelumab plasma concentration versus time profiles by ethnic group and overall ADA status will be presented in figures on both linear and semi-logarithmic scales. Mean (±SD) lanadelumab plasma concentration versus nominal time profiles will be presented for the PK Set using nominal time. All sampling times considered to be protocol deviations will be excluded from summaries and mean plots. Individual lanadelumab plasma concentration versus time profiles will be presented using nominal time based on the Safety Analysis Set.

12.1.2 Handling BLQ Values

The following procedures will be used for lanadelumab plasma PK concentrations below the lower limit of quantification (LLOQ):

- Samples that are below limit of quantification (BLQ) will be reported as <LLOQ in the data listings, where LLOQ is replaced by the actual value for LLOQ for specific PK assay.

- Samples that are BLQ are treated as zero in the calculation of summary statistics (e.g. mean, SD, etc.) for the plasma PK concentrations at individual time points. Geometric mean and %CV of geometric mean will be set to missing where zero values exist.

- Mean concentrations are reported as zero if all values are BLQ or zero, and no other descriptive statistics are reported. If the calculated mean (±SD) concentration is less than the LLOQ, the value will be reported as calculated. The mean values derived using these concentrations will be used to create the mean plasma concentration versus time plots.

- For calculation of area under the plasma concentration curve (AUC), BLQ values are set equal to zero in the dataset loaded into Phoenix® WinNonlin® (Certara USA, Inc, Princeton, NJ) for PK analysis. WinNonlin® uses the zero values that occur before the first time point with a concentration greater than LLOQ. Values that are BLQ after the first measurable concentration will be set to "missing" in the dataset loaded into WinNonlin®.

- Missing values will not be imputed.

12.1.3 Pharmacokinetic Parameters

The PK analysis will be conducted using Phoenix® WinNonlin® (Certara USA, Inc, Princeton, NJ) Version 6.4 or higher. Pharmacokinetic parameters will be determined from the lanadelumab plasma concentration-time data using non-compartmental analysis based on actual sampling times. All samples will be used in the PK analysis regardless of whether they are considered protocol deviations or not.

The PK parameters for lanadelumab will include, but may not be limited to:

- C_{max} Maximum observed lanadelumab plasma concentration

- t_{max} Time of maximum observed lanadelumab plasma concentration

- $AUC_{0\text{-last}}$ Area under the lanadelumab plasma concentration-time curve from time zero to the last quantifiable plasma concentration, calculated using the linear-up/log-down trapezoidal rule

  In this method, the linear trapezoidal method of calculation is used for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid

- $AUC_{0\text{-}\infty}$ Area under the lanadelumab plasma concentration-time curve from time zero extrapolated to infinity

- λ_z First order rate constant associated with the terminal (log-linear) portion of the lanadelumab plasma concentration curve

- $t_{½}$ Terminal half-life
- CL/F Apparent clearance
- V_z/F Apparent volume of distribution

Body weight-adjusted $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, C_{max}, CL/F, and V_z/F PK parameters will also be determined.

12.2 Statistical Analysis of Pharmacokinetic Parameters

Descriptive statistical analysis of PK parameters will be based on the PK Set. The plasma PK parameters of lanadelumab will be summarized by ethnic group, and separately by ethnic group and overall ADA status. Summaries will include: n, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean, and %CV of geometric mean. In addition, 95% confidence intervals (CIs) for PK parameters will be provided. Listing of individual plasma PK parameters of lanadelumab will be provided based on the Safety Analysis Set. Individual (observed) and body weight-adjusted PK parameters (y-axis) versus body weight (x-axis) by ethnic group and overall ADA status will be presented in figures on both linear and semi-logarithmic scales for $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, C_{max}, CL/F, and V_z/F.

Following ln-transformation, the PK parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$, will be analyzed using an analysis of variance (ANOVA) model, for estimation purposes. No formal hypothesis testing will be performed. The model will include ethnic group as a fixed effect. Point estimates and their associated 90% CIs will be constructed for the differences in the ln-transformed parameters. The point estimates and their associated 90% CIs will be then back-transformed to provide point estimates for the ratio (Japanese Subjects/Caucasian Subjects) of geometric least squares means and associated 90% CIs on the original scale.

To assess the impact of overall ADA status on the ethnic group comparison, if data permits, a sensitivity analysis will be performed by repeating the above ANOVA analyses by overall ADA status.

12.3 Pharmacodynamic Methods

Individual PD data will be listed, and listing(s) will be based on the Safety Analysis Set; all summaries and analyses of the PD data will be based on the PD Set.

12.3.1 Pharmacodynamic Data

Blood samples will be drawn from each subject during this study for the determination of inhibition of pKal activity and plasma cHMWK levels. Serial blood samples will be collected during the in-house treatment period on Days 1 to 5 for PD analysis at predose, and at 8, 24, 48, 72, and 96 hours after administration of the investigational product. Post-dose blood samples will be also drawn from each subject on Days 7, 14, 21, 28, 42, 56, 84 and 112 for the determination of inhibition of pKal activity and plasma cHMWK levels. Actual sampling times post-dose will be considered protocol deviations where the sample deviated from nominal collection time by

more than ±5 minutes within the first 4 hours, ±15 minutes between 4 and 96 hours, ±1 day between Days 7 and 21, ±2 days between Days 28 and 56, and ±3 days on Days 84 and 112. Samples collected outside these windows will be flagged in data listings. The pKal activity and plasma cHMWK levels will be measured using validated analytical methods.

Individual pKal activity, inhibition of pKal, and plasma cHMWK levels (from both untreated and treated samples (including intact 110 kDa, 56 kDa, 46 kDa and %cHMWK) will be listed by subject, ethnic group, day, and time based on the Safety Analysis Set and summarized by ethnic group and nominal time based on the PD set. Summaries will include: n, arithmetic mean, SD, %CV, median, minimum, maximum, geometric mean, and %CV of geometric mean. In addition, the mean and individual inhibition of pKal activity and plasma cHMWK levels (%cHMWK from treated samples only) versus nominal time by ethnic group will be presented in figures on a linear scale. Mean (±SD) inhibition of pKal activity and mean (+SD) plasma cHMWK levels (treated samples only) versus nominal time will be presented for the PD Set using nominal time. All sampling times considered to be major protocol deviations will be excluded from summaries and mean plots. Individual inhibition of pKal activity and plasma cHMWK levels versus time will be presented using nominal time based on the Safety Analysis Set.

12.3.2 Baseline-adjusted Pharmacodynamic Data

Individual plasma cHMWK levels (treated samples only) will be baseline-adjusted at each time point. Baseline is defined as the predose cHMWK level on Day 1. Baseline-adjusted levels of cHMWK will be calculated by subtracting the appropriate baseline values from the reported laboratory levels for that particular subject. If the baseline-adjusted cHMWK level gives a negative value then the negative level will be used as is for analysis.

Individual baseline-adjusted cHMWK levels (from both untreated and treated samples including intact 110 kDa, 56 kDa, 46 kDa and %cHMWK) will be listed by subject, ethnic group, day, and time based on the Safety Analysis Set and summarized by ethnic group and time based on the PD Set separately for original and baseline-adjusted cHMWK. Summaries will include: n, arithmetic mean, SD, %CV, median, minimum, and maximum. In addition, the mean and individual baseline-adjusted plasma cHMWK levels (treated samples only) versus time by ethnic group will be presented in figures on a linear scale. Mean (SD) baseline-adjusted plasma cHMWK levels (treated samples only) versus time will be presented for the PD Set using nominal time. All sampling times considered to be protocol deviations will be excluded from summaries and mean plots. Individual baseline-adjusted plasma cHMWK levels versus time will be presented using nominal time based on the Safety Analysis Set.

12.3.3 Pharmacodynamic Parameters

Not applicable.

12.4 Statistical Analysis of Pharmacodynamic Parameters

Not applicable.

13. OTHER ANALYSES

No other analyses are planned for this study.

14. INTERIM ANALYSIS

No interim analysis is planned for this study.

15. DATA MONITORING/REVIEW COMMITTEE

No Data Monitoring Committee (DMC) is planned for this study.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.3 of SAS® or higher on a suitably qualified environment. Phoenix® WinNonlin® (Certara USA, Inc, Princeton, NJ) Version 6.4 or higher will be used for calculating PK parameters.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

The following changes have been made to the PK analyses specified in the protocol (dated 27 Nov 2017):

- Inclusion of overall ADA status in PK concentration and parameter listings. Additionally, PK concentrations and parameters will be summarized by overall ADA status.
- Addition of the body weight-adjusted PK parameter $AUC_{0-\infty}$.
- Addition of ANOVA statistical analysis model to evaluate the PK of lanadelumab between ethnic groups.
- Removal of the word 'concentration' from the PD population definition, which is not applicable for the PD markers in this study.

No other changes to the analyses specified in the protocol (dated 27 Nov 2017) have been made.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, median, SD, minimum, maximum. Unless specified otherwise, summary statistics will be presented to 1 more significant digit than the raw data. The minimum and maximum values will be presented to the same number of decimal places as the raw data; the mean and median will be presented to 1 more decimal place than the raw data; and the SD and standard error will be presented to 2 more decimal places than the raw data. BMI, averaged laboratory results e.g. diastolic/systolic blood pressure and pulse (when taken in triplicate), and derived questionnaire scores will be rounded to 1 decimal place for reporting.

Categorical and count variables will be summarized by the number of subjects and the percent of subjects in each category, as appropriate. Percentages will be presented as whole numbers.

18.2 Derived Efficacy Endpoints

Not applicable.

18.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated or unscheduled assessments before the start of investigational product, then the results from the most recent assessment made prior to the start of investigational product will be used as baseline.

If post-baseline assessments are repeated, these will be captured as unscheduled visits, and the value recorded at the scheduled visit will be used for generating descriptive statistics.

All assessments, including unscheduled and repeated assessments, will be presented in the data listings.

18.4 Missing Date of Investigational Product

Since this is a Phase 1 single-dose study in which the investigational product will be administered on Day 1, missing dates of investigational product are not expected.

18.5 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date will be imputed first.

18.5.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Note: This is a single-dose study, and thus the use of "first dose" below equates to "dose."

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

18.5.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then it will be replaced with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

18.6 Missing Date Information for Adverse Events

For AEs, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 18.5.1. Incomplete stop dates will not be imputed.

18.7 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

18.8 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18.9 Character Values of Clinical Laboratory Variables

The actual values of clinical laboratory variables as reported in the database will be presented in data listings. No coded values (e.g., when a character string is reported for a numerical variable) are necessary.

19. REFERENCES

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA Guidance for Industry, September 2007)

20. TABLE OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

This summary lists the planned TFLs. The list may differ from TFLs actually produced for the Clinical Study Report (CSR). If changes to the list are made after the SAP sign-off, the SAP will not be modified to reflect the changes. Refer to the CSR for TFLs actually produced.

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