STATISTICAL ANALYSIS PLAN

SHP643, lanadelumab (formerly DX-2930)
PHASE 1

A Randomized, Open-label, Single-dose, Parallel-arm, Single-center, Phase 1 Study to Determine the Bioavailability of Lanadelumab Administered Subcutaneously with the Prefilled Syringe and the Autoinjector in Healthy Adult Volunteer Subjects

PROTOCOL IDENTIFIER: SHP643-102

Study Sponsor(s): Dyax Corp., a Takeda company

300 Shire Way, Lexington, MA 02421 USA

Author: [redacted]

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	19 November 2019	Initial final version

TABLE OF CONTENTS

ABBREVIATIONS

λ_z	Terminal elimination rate constant
ADA	anti-drug antibody
AE	adverse event
AI	auto injector
ANCOVA	analysis of covariance
AUC	Area under the concentration-time curve
$AUC_{0\text{-last}}$	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
BMI	body mass index
BW	body weight
C_{max}	maximum observed plasma drug concentration
CL/F	Apparent body clearance
eCRF	electronic case report form
ECG	electrocardiogram
FDA	Food and Drug Administration
HAE	hereditary angioedema
IP	investigational product
LLOQ	lower limit of quantification
LS	least-squares
N	number of subjects
PCI	potentially clinically important
PFS	prefilled syringe
PK	pharmacokinetic
PT	preferred term
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{½}$	Terminal half-life
t_{max}	Time to reach C_{max} in plasma

Vd_z/F	Apparent volume of distribution associated with the terminal slope following extravascular administration

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of pharmacokinetic (PK), safety and tolerability data as described in the original protocol dated 29 Jan 2019. Specifications for tables, figures, and listings are contained in a separate document.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

The currently approved presentation for lanadelumab is a vial configuration with the patients using ancillary components to withdraw and administer liquid drug product from the vial. Lanadelumab has been prepared and administered via vial and syringe throughout the clinical development of the drug for treatment of hereditary angioedema (HAE). The Food and Drug Administration (FDA) agreed that no dedicated PK study would be required for the transition from a vial to a prefilled syringe (PFS); (FDA correspondence on IND 116647 dated 13 January 2017). A clinical bioequivalence study, however, is necessary to bridge between the PFS and the auto injector (AI), which is also currently under development at Takeda. Takeda considers that the AI will be more convenient for use by the patient (fewer preparation steps and easier administration) in comparison with other potential delivery methods (eg, vial / syringe or PFS). Extensive in vitro device design verifications will be performed to demonstrate the accuracy and consistency of dose delivery using the AI device, according to full ISO11608:2014 standards.

This study is being conducted to assess the bioavailability of lanadelumab administered as a single subcutaneous (SC) dose of 300 mg delivered by a 2 mL PFS or a 2 mL AI in healthy adult volunteer subjects and to evaluate the safety and tolerability of a single SC 300 mg dose of lanadelumab administered via PFS or AI. This study may be used to support the use of an AI based injection system in patients with HAE.

2.1.1 Primary Objective

To evaluate bioavailability of lanadelumab following a single, 2 mL SC dose of 300 mg delivered by PFS or AI in healthy adult subjects.

2.1.2 Secondary Objective(s)

To assess the safety and tolerability of a single 2 mL 300 mg SC injection of lanadelumab administered by a PFS or AI in healthy adult subjects.

2.1.3 Exploratory Objective(s)

[redacted]

2.2 Endpoints

2.2.1 Safety Endpoints

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory results (hematology, clinical chemistry, coagulation and urinalysis)
- Vital signs (including blood pressure (BP), pulse rate, body temperature)
- 12-lead electrocardiogram (ECG)
- Antidrug antibodies (ADA)

2.2.2 Pharmacokinetic Endpoint(s)

- $AUC_{0\text{-last}}$: Area under the concentration-time curve from time zero to the last quantifiable concentration in plasma, calculated using the linear up/log down trapezoidal rule.
- $AUC_{0\text{-}\infty}$: Area under the concentration-time curve from time zero extrapolated to infinity, calculated using the linear up/ log down trapezoidal rule
- C_{max}: Maximum observed plasma drug concentration
- t_{max}: Time to reach C_{max} in plasma
- $t_{1/2}$: Terminal half-life, calculated as $\ln(2)/\lambda_z$
- CL/F: Apparent clearance, calculated as: $Dose/AUC_{0\text{-}\infty}$
- Vd_z/F: Apparent volume of distribution associated with the terminal slope following extravascular administration, calculated as: CL/F / λz
- λ_z: Terminal elimination rate constant

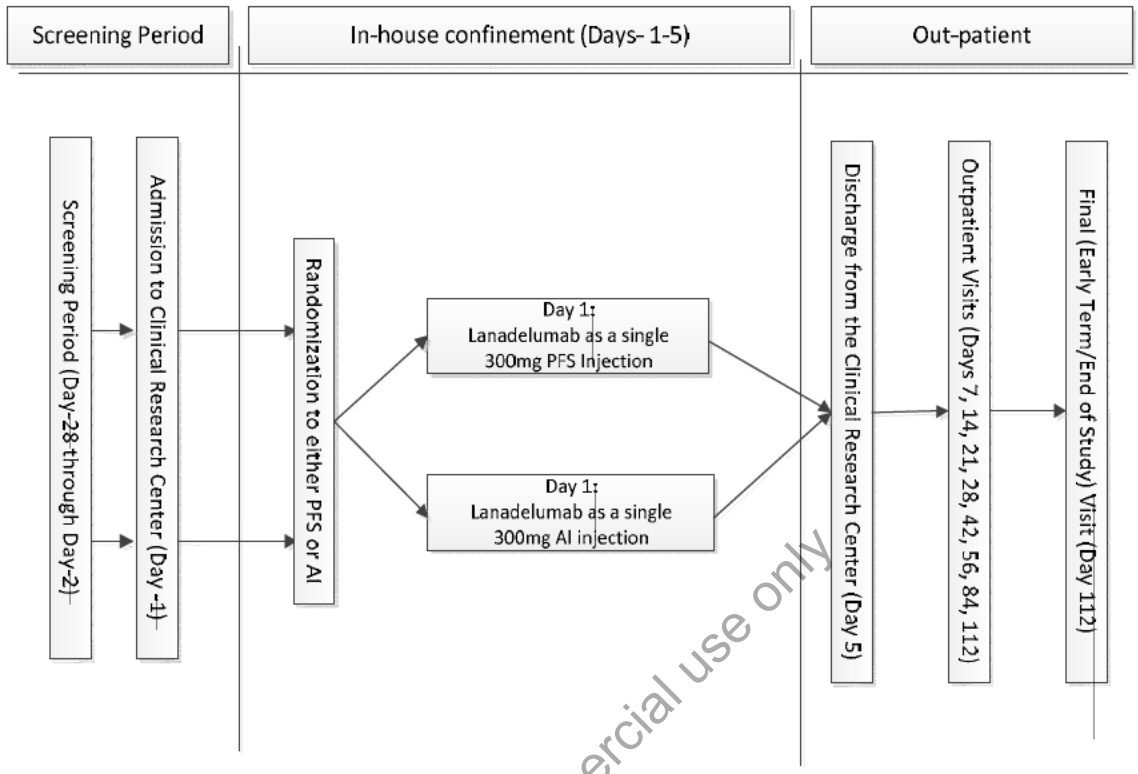
3. STUDY DESIGN

3.1 General Description

This is a Phase 1, randomized, open-label, single dose, parallel-arm single-center study to evaluate the PK, safety and tolerability of lanadelumab administered via PFS or AI to healthy adult volunteer subjects. A total of approximately 176 subjects between the ages of 18-55, inclusive, will be enrolled. All subjects will be randomized 1:1 to receive a single 2 mL SC dose 300 mg of lanadelumab by either PFS or AI in the abdomen on study day 1 administered by designated study site personnel. Fifty-percent of the randomized subjects will receive the lanadelumab injection via a PFS, and the other 50% will receive the lanadelumab injection via an AI. This study is a parallel group design rather than a crossover design, as a crossover design was not feasible due to the long half-life of lanadelumab (approximately 17-21 days). Randomization will be stratified by body weight (2 strata: 45 to <80 kg and ≥80 kg) to balance the two study arms more closely.

The study duration will comprise of a 28-day screening period, one 5-day in-house treatment period, and 8 out-patient visits. The maximal total duration of study participation for a subject is approximately 140 days if the maximal screening, treatment, and out-patient visit durations are used.

Figure 1: Study Design Flow Chart



3.2 Randomization

Subject screening numbers are assigned to all subjects as they consent to take part in the study. The subject screening number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting with 0001.

The actual treatment given to individual subjects is determined by a randomization schedule. Randomization will be stratified by body weight (2 strata: 45 to <80 kg and ≥80 kg) to balance the two study arms more closely

The randomization number represents a unique number corresponding to investigational product (IP) allocated to the subject and will be allocated prior to dosing after eligibility has been determined.

A 4-digit randomization number, starting at 1001, will be allocated immediately prior to dosing after eligibility has been determined. If a randomization number is allocated incorrectly the study monitor must be notified as soon as the error is discovered. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. For randomized subjects, the

randomization number will be the identifying number used throughout the electronic case report form (eCRF).

3.3 Blinding

This is an open-label study. However, the access to randomized treatment codes will be limited during the conduct of the study to avoid unnecessary bias. The PK scientist will not have access to the randomized treatment codes when reviewing the PK data before the database lock. The accessibility to treatment codes for each individual study team member is specified in the clinical trial integrity document.

3.4 Sample Size and Power Considerations

The planned sample size for this study is approximately 176 subjects; 88 subjects in the PFS arm and 88 subjects in the AI arm. The sample size was calculated using SAS (SAS Institute, Cary, NC; version 9.3) based on the two one-sided tests procedure of Schuirmann on the log-transformed data.

Considering a parallel group design and assuming a total variability of 40% for Cmax (expected to be larger than the total variability for AUC) and a true ratio of test/reference of 100%, equivalence between test and reference in their bioavailability based on the acceptance interval of 80.00 to 125.00% can be demonstrated with a power of 90% and a type I error of 5% based on 66 subjects per group (132 subjects in total). To account for up to 25% potential drop outs and/or non-reliable concentration time-profiles, approximately 88 subjects per group (176 in total) need to be randomized to ensure that at least 66 subjects complete the study in each administration type group.

4. STATISTICAL ANALYSIS SETS

4.1 Randomized Set

The Randomized Set consists of all subjects randomized to an administration type group. Background summaries (e.g., subject disposition) will be based on the Randomized Set, unless otherwise specified in this SAP.

4.2 Safety Set

The Safety Set will consist of all randomized subjects who received the dose of lanadelumab. Analysis will be performed according to the treatment actually received

regardless of the randomized treatment. All safety analyses will be based on the Safety set.

4.3 Pharmacokinetic Set

The PK Set is defined as all randomized subjects who received the complete dose of lanadelumab (as determined by the investigator or site staff) and have sufficient data to calculate at least 1 primary PK endpoint ($AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ or C_{max}). Subjects must not have protocol deviations that would impact data analysis. The PK Set will be used for the analysis of PK endpoints.

The protocol deviation log will be reviewed on a case-by-case basis. Subjects' inclusion/exclusion from the PK Set will be determined at the discretion of the Shire medical monitor/pharmacokineticist.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number and percentage of subjects included in each analysis set (Randomized, Safety and PK) will be summarized as appropriate. The reasons for exclusion from the PK set will be included in the same summary.

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 eCRF. All randomized 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 Randomized Set, and the summary will be presented by randomized treatment group and total.

5.2 Demographic and Other Baseline Characteristics

The following demographic characteristics will be summarized in the following order in the tables: age (years), sex, ethnicity, race. Other baseline characteristics include: weight (kg), weight category (45 to <80 kg and ≥80 kg), height (cm), and body mass index (BMI, kg/m^2).

Age will be calculated as the integer part of: (date of informed consent is signed – date of birth + 1)/365.25, and BMI will be calculated as: weight (kg) / (height [m])^2. The last

height and weight measured prior to the administration of investigational product 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 (or the last value measured prior to the administration of investigational product). Summaries will be based on the Safety Set and PK Set, as appropriate. Demographics and other baseline characteristics data will be listed, and the listing will be based on the Safety Analysis Set.

5.3 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), history of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, other diseases, and smoking habits.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Medical history will be listed and summarized by system organ class (SOC) and preferred term (PT) for each randomized treatment group and total for the Safety Set. The summary will include number and percentage of subjects who experienced the event, and number of events experienced. System organ class will be sorted alphabetically, and PT will be sorted within each SOC in descending frequency in the table Total column.

5.4 Prior Therapies, Procedures, and Medication

Prior medications will be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 March 2019.

Prior medication is defined as any medication with the start date prior to the date of the first dose of IP.

The prior medication usage will be summarized by the number and proportion of subjects in each randomized treatment group and in total subjects within each therapeutic class and PT for the Safety Set. Therapeutic class will be sorted alphabetically, and PT will be sorted within each therapeutic class in descending frequency in the table total column. Multiple medication usage by a subject in the same category will be counted only once.

All prior therapies, procedures, and medication will be listed for the Safety Set.

5.5 Concomitant Therapies, Procedures, and Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version Global B3 March 2019.

Concomitant medication (therapy) is defined as any medication with start date on or after date of IP administration, or medications with start date prior to IP administration but continuing at or after IP 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. Therapeutic class will be sorted alphabetically, and PT will be sorted within each therapeutic class in descending frequency in the table total column. Multiple medication usage by a subject in the same category will be counted only once.

All concomitant therapies, procedures, and medication will be listed for the Safety Set.

5.6 Exposure to Investigational Product

The extent of exposure to study drug will be described by reporting the number and percentage of subjects with complete injection and subjects with incomplete injection for the Safety Set and the PK Set.

[redacted]

Summary will include: n, mean, SD, median, minimum, and maximum, and based on the Safety Set and Pharmacokinetic set.

An exposure data listing, based on the Safety Set, will be provided and include start and end date and time of dose administration, [redacted], and other exposure data, e.g. planned dose/volume.

5.7 Measurements of Treatment Compliance

This is a single-dose (single-administration) study in which the IP 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.

5.8 Protocol Deviations

Protocol deviations will be recorded by the site separately from the clinical database. Protocol deviations will be classified as major or minor in accordance with applicable Takeda 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 / PK

- 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.

Confirmed major and minor protocol deviations will be documented in the protocol deviation tracker for the study. Major/minor protocol deviations will be summarized by category for the Randomized Set. All protocol deviations will be presented in the protocol deviation listing and based on the Randomized Set.

6. EFFICACY ANALYSES

No efficacy analyses are planned for this study.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Set. Safety endpoints include TEAEs, clinical laboratory variables (hematology, clinical chemistry, coagulation and urinalysis), vital signs (systolic and diastolic BP, pulse rate, and body temperature), body weight, ECG variables, and immunogenicity response (development of ADAs). For each

safety variable, unless otherwise specified, the last non-missing value before the administration of IP will be used as baseline for all analyses of that safety endpoint.

For categorical variables, the number and percentage of subjects within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum values will be presented. All safety data, including derived data, will be presented in subject data listings, and all listings will include subject's sex, age, and race.

7.1 Adverse Events

Adverse events will be coded MedDRA version 22.0.

Treatment-emergent AEs are defined as AEs with onset at the time of or following the start of treatment with study medication, or medical conditions present prior to the start of treatment but increasing in severity, frequency, 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) or until closure (the subject's health has returned to his/her baseline status or all variables have returned to baseline) if the AEs are not resolved at the Day 112/End of Study visit.

An overall summary of the number of subjects with TEAEs, as well as the number of TEAEs, will be presented by treatment group and total, including: any TEAE, severe TEAEs, serious TEAEs, TEAEs related to investigational product, TEAEs related to device, TEAEs leading to discontinuation from the study, TEAEs resulting in hospitalization, and TEAEs leading to death.

The number and percentage of subjects with TEAEs, as well as the number of TEAEs, will be calculated by SOC, PT and will be presented by treatment group and total. The TEAEs will be further summarized by severity, relationship to IP and relationship to device. If more than 1 AE occurs with 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 IP or device. For example, if a subject experienced a mild headache not related to IP, and a moderate headache related to IP, then the subject will be counted once for headache using the moderate headache related to IP.

Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending frequency in the table total column.

The TEAEs, TEAEs related to IP, and TEAEs related to device will be summarized by PT by descending frequency.

Serious TEAEs, TEAEs related to investigational product, TEAEs related to device, TEAEs leading to discontinuation from the study, and TEAEs leading to death will be summarized by SOC and PT.

All AEs (TEAEs and non-TEAEs) will be provided in the AE subject listings.

7.2 Clinical Laboratory Data

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point as well as shift tables from baseline to each visit for quantitative variables will be presented by treatment group for the following clinical laboratory variables:

Biochemistry Sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, chloride, thyroid stimulating hormone (TSH), thyroxine (T4 total), triiodothyronine (T3), phosphorus, total protein, total CO2 (bicarbonate), albumin, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, uric acid, β-hCG and FSH.

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

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

Coagulation Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 1. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group and total. 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 including the subject number, baseline, and post-baseline values.

Table 1 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

Parameter	Classification	Criteria
	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
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		

Parameter	Classification	Criteria
Glucose	HIGH	≥ 1+
Blood	HIGH	≥ 2+
Bilirubin		Positive
Protein	HIGH	≥ 2+
Nitrite		Positive
Ketones	HIGH	≥ 2+
Leukocyte Esterase		Positive
Coagulation		
INR	HIGH	>1.2 x ULN
PT	HIGH	>1.2 x ULN
aPTT	HIGH	>1.2 x ULN

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, INR: international normalized ratio, PT: Prothrombin time, aPTT: activated partial thromboplastin time.

All laboratory data will be listed for the Safety Set. Separate laboratory data listings will be generated presenting results in SI units and Western units respectively.

7.3 Vital Signs

Descriptive statistics for vital signs (e.g., weight, systolic and diastolic BP, pulse rate, and body temperature) and their changes from baseline at each post-baseline visit will be presented by treatment group.

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 2. The number and percentage of subjects with PCI post-baseline values will be tabulated by treatment group and total. 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.

Table 2 Criteria for Potentially Clinically Important 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
Weight	HIGH	Increase of ≥ 5% from baseline value
	LOW	Decrease of ≥ 5% from baseline value

All vital signs data (including height and weight) will be listed for the Safety Set.

7.4 Electrocardiogram (ECG)

Descriptive statistics for ECG variables (eg, heart rate, PR, RR, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by treatment group. 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, it will be replaced with 60/heart rate in the correction formula. The ECG interpretation per the investigator will be summarized by visit. A shift table from baseline to each visit for qualitative ECG results will be presented.

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 IP).

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 3. The number and percentage of subjects with post-baseline PCI values will be tabulated by treatment group. 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 ECG value. A listing of all subjects with post-baseline PCI value will be provided including the subject number, site, baseline, and post-baseline PCI values.

Table 3 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

7.5 Other Safety Data

7.5.1 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 treatment. 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.

7.5.2 [redacted]

[redacted].

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the PK data will be based on the Pharmacokinetic Set defined in Section 4.3.

8.1 Drug Concentration

Blood samples will be drawn from each subject during this study for the determination of plasma concentration of lanadelumab. Serial blood samples will be collected for PK analysis at predose and, 8, 24, 48, 72, 96 hours and days 7, 14, 21, 28, 42, 56, 84 and 112 (end of study visit/or early discontinuation) post dose. Plasma concentrations of lanadelumab will be measured using a validated analytical method.

8.2 Handling Below Limit of Quantitation (BLQ) Values

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

- Samples that are below limit of quantification (BLQ) are reported as <LLOQ on 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 (eg, mean, SD, etc.) for the plasma concentrations at individual time points. 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 conventions will be used to create the mean plasma concentration versus time plots.
- For calculation of PK parameters, BLQ values prior to the first measurable concentration will be set to zero All BLQ values following the first measurable concentration will be set to “missing”.
- Missing values will not be imputed.

8.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be determined for lanadelumab from the individual plasma concentration versus actual time data. Pharmacokinetic parameters will be estimated by non-compartmental analysis, as deemed appropriate, using Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ) Version 8.0 or higher, and all calculations will be based on the actual time post dose.

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

Parameter	Description
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time zero to the last quantifiable concentration in plasma, calculated using the linear up/log down trapezoidal rule
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity, calculated using the linear up/ log down trapezoidal rule
C_{max}	Maximum observed plasma drug concentration
t_{max}	Time to reach C_{max} in plasma
λ_z	Terminal elimination rate constant
$t_{½}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$
CL/F	Apparent clearance, calculated as: $Dose/AUC_{0\text{-}\infty}$
Vd_z/F	Apparent volume of distribution associated with the terminal slope following extravascular administration, calculated as: $CL/F / \lambda_z$
CL/F/BW	Body weight adjusted CL/F
$Vd_z/F/BW$	Body weight adjusted Vd_z/F

8.4 Statistical Analysis of Pharmacokinetic Data

Individual lanadelumab concentrations will be listed by subject, treatment group, day, and time and summarized by treatment group and time based on the Pharmacokinetic Set.

The following descriptive statistics of plasma lanadelumab concentrations will be provided: n, arithmetic mean, geometric mean, SD, arithmetic CV%, geometric CV%, 25th Percentile (Q1), 75^{th} Percentile (Q3), median, minimum, and maximum.

The mean and individual plasma lanadelumab concentrations versus time profiles by treatment group will be presented in figures on both linear and semi-logarithmic scales.

Mean (±SD) and individual plasma lanadelumab concentrations versus time profiles will be presented using nominal time based on the Pharmacokinetic Set.

Individual lanadelumab PK parameters will be listed by subject and treatment group and summarized by treatment group based on the Pharmacokinetic Set with the following descriptive statistics: n, arithmetic mean, arithmetic SD, CV%, median, Q1, Q3, minimum, maximum, geometric mean, and geometric CV%.

To assess the bioavailability of lanadelumab following a single, 2 mL SC dose of 300 mg delivered by PFS or AI, the plasma lanadelumab PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} will be natural log-transformed and analyzed using an analysis of variance (ANOVA) model to compare the PK of lanadelumab delivered by AI versus PFS. The ANOVA model will include treatment as a fixed effect. The treatment least-squares (LS) means, differences between LS means, and 90% CIs associated with these differences will be determined for each parameter. Those results will be then exponentiated to the original scale. Geometric LS means, geometric mean ratios and 90% CIs will be presented. If the 90% CIs lies between 0.8 and 1.25, the bioequivalence can be concluded. Ratios will be expressed as a percentage relative to the reference treatment (PFS).

A similar analysis will be performed by excluding subjects enrolled before the Pharmacy Manual was revised (Cohorts 1 and 2) as a sensitivity analysis to assess the impact of revising the Pharmacy Manual.

9. PHARMACODYNAMIC ANALYSIS

Not applicable.

10. OTHER ANALYSES

Not applicable.

11. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

No planned interim analysis, or data monitoring committee are planned for this study.

12. DATA HANDLING CONVENTIONS

12.1 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.

12.2 Derived Efficacy Endpoints

Not applicable.

12.3 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated or unscheduled assessments before the start of IP, then the results from the most recent assessment made prior to the start of IP 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.

12.4 Handling of Missing, Unused, and Spurious Data

12.4.1 Missing Date of Investigational Product

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

12.4.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant 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, impute the start date first.

12.4.2.1 Incomplete Start Date

The following rules will be applied to impute the missing start dates. 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.

12.4.2.1.1 Missing Day and Month

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

12.4.2.1.2 Missing Month Only

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

12.4.2.1.3 Missing Day Only

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

12.4.2.2 Incomplete Stop Date

The following rules will be applied to impute the missing stop dates. 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.

12.4.2.2.1 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 IP, then the day and month of the date of the last dose of IP will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the dose date of IP, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the dose date of IP, then 01 January will be assigned to the missing fields.

12.4.2.2.2 Missing Month Only

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

12.4.2.2.3 Missing Day Only

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

12.4.3 Missing Date Information for Adverse Events

For AEs with partial start dates, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration, e.g. AE start year and month are the same as the year and month of the dose date of IP, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, incomplete (i.e., partially missing) start dates start dates will be imputed and will follow the same rules as in Section 12.4.2.1. Incomplete stop dates will not be imputed.

12.4.3.1 Incomplete Start Date

Follow the same rules as in Section 12.4.2.1.

12.4.3.2 Incomplete Stop Date

Incomplete stop dates will not be imputed.

12.4.4 Missing Severity Assessment for Adverse Events

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

12.4.5 Missing Relationship to Investigational Product for Adverse Events

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

12.4.6 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.

13. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

PK analyses will be performed using Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ) Version 8.0 or higher.

14. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

Not applicable.

15. REFERENCES

Donald J. Schuirmann, A Comparison of the Two One-Sided Tests Procedure and the Power Approach for Assessing the Equivalence of Average Bioavailability, Journal of Pharmacokinetics and Biopharmaceutics, Vol. 15, No. 6, 1987

16. APPENDICES

16.1 Schedule of Activities

Table 4 Schedule of Assessments

Visit	Screening		In-House Treatment Period [a]	Out-Patient Visits[b, c]	End of Study (Day 112) or Early Discontinuation
Study Day	**–28 to -02**	**-1**	**1 to 5**	**7 to 112**	
Informed consent	X		Refer to Table 5	Refer to Table 6	
Inclusion/exclusion criteria	X	X			
Demography	X	X			
Medical/Medication History	X	X			X
Physical examination	X	X			X
Vital signs (blood pressure, pulse) supine	X	X			X
Body temperature (oral)	X	X			X
Height, Weight and BMI[d,e]	X	X			X
Electrocardiogram (12-lead)	X [f]	X [f]			X
Biochemistry, hematology, and urinalysis	X	X			X
TSH, T3, T4	X				
PT, aPTT, INR	X	X			X
HIV, HBsAg, and HCV antibodies	X				
Serum Pregnancy test (all females)	X	X			X
FSH (all females)	X				
Urine drug and alcohol (breath test) screening	X	X			
Pharmacokinetic blood sampling (PK)					
Anti-drug antibody blood sampling (ADA)					X
Check-in to the CRC		X			
Out-patient visits	X				X
In-patient visit		X			
Concomitant Medication	X	X			X
Adverse Event/Serious Adverse Event	X	X			X

aPTT= activated partial thromboplastin time; CRC=clinical research center; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; INR=international normalized ratio; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; PT=prothrombin time; T3=triiodothyronine; T4=thyroxine; TSH= thyroid-stimulating hormone

[a] Refer to Table 5 for the procedures and the timing of the procedures to be done during the in-house treatment period.

[b] Refer to Table 6 for the procedures and the timing of the procedures to be done during the out-patient visits.

[c] In the event a subject is prematurely discontinued from the study or withdraws, every attempt should be made to complete these assessments. End of study visit is Day 112.

[d] Height will only be recorded at the first visit during the screening period.

[e] Body mass index criteria for eligibility will be calculated at the first visit during the screening period and on Day -1.

[f] Single ECG recordings are required; However, ECGs will be performed in triplicate if the QTcF interval (calculated on line on site) is increased by >45 msec from the baseline, or an absolute QTcF value is >500 msec for any scheduled ECG, or if indicated per exclusion criteria #9 or in protocol Section 7.2.2.9, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. Thereafter, all subsequent ECGs will be single recordings.

Table 5 Detailed Schedule of In-Patient Assessments (Days 1-5)

Study Day/Hour (relative to dosing time)	PE	VS	Body Temperature (oral)	Weight	ECG	Biochemistry, hematology, and urinalysis	PT, aPTT, INR	Serum Pregnancy (all women)	Randomization[c]	IP administration[d]	PK	ADA	AE/SAE[b]	CM[b]
Day 1Predose[a]		X	X		X				X		X[c]	X[c]	X	X
Day 1:0h										X			X	X
Day1: 1h post dose		X			X								X	X
Day 1: 2h post dose		X											X	X
Day 1:4h post dose		X			X								X	X
Day 1:6h post dose		X											X	X
Day 1:8h post dose		X			X						X		X	X
Day 1:12h post dose		X											X	X
Day 2:24h post dose		X			X	X					X		X	X
Day 3:48h post dose		X			X						X		X	X
Day 4: 72h post dose		X			X						X		X	X
Day 5: 96h post dose	X	X		X	X	X	X	X			X		X	X

ADA=anti-drug antibody blood sampling; AE=adverse event; aPTT= activated partial thromboplastin time; CM=concomitant medication; CRC=clinical research center; ECG=12-lead ECG; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; INR=international normalized ratio; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; IP=investigational product; PE=physical exam; PT=prothrombin time; PK=pharmacokinetic blood sampling; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=-thyroid-stimulating hormone; UDS=urine drug screen; VS=vital signs

[a] Assessments to be done within 30 minutes prior the administration of IP.

[b] Adverse events/SAEs and CMs will be continuously monitored throughout the study.

[c] Pre-dose ADA and PK samples can be collected within 60 minutes prior to the administration of IP.

[d] Investigational product administration start and stop times must be recorded in source and on the CRF. [redacted].

[e] Randomization to be performed pre-dose on Day 1.

Table 6 Detailed Schedule of Out-Patient Assessments (Study Days 7-112)

Study Day	PE	VS	Body Temperature (oral)	Weight	ECG	Biochemistry, hematology, and urinalysis	PT, aPTT, INR	Serum Pregnancy (all women)	UDS & ETOH screen	PK	ADA	AE/SAE[a]	CM[a]
Day 7 (± 1)	X	X	X	X	X	X	X	X	X	X		X	X
Day 14 (± 1)	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 21 (± 1)	X	X	X	X	X	X	X	X	X	X		X	X
Day 28 (± 2)	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 42 (± 2)	X	X	X	X	X	X	X	X	X	X		X	X
Day 56 (± 2)	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 84 (± 3)	X	X	X	X	X	X	X	X	X	X		X	X
Day 112 (± 3) (End of Study Visit/ or Early Discontinuation)	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA=anti-drug antibody blood sampling; AE=adverse event; aPTT= activated partial thromboplastin time; CM=concomitant medication; CRC=clinical research center; ECG=12-lead ECG; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; INR=international normalized ratio; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; IP=investigational product; PE=physical exam; PT=prothrombin time; PK=pharmacokinetic blood sampling; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UDS=urine drug screen; VS=vital signs

[a] Adverse events/SAEs and CMs will be continuously monitored throughout the study.