STATISTICAL ANALYSIS PLAN

NCT Number: NCT04503603

Study Title: A Randomized, Double-blind, Placebo-Controlled, Repeat-dose, Single-center Phase 1a Study to Determine the Safety, Tolerability, and Pharmacokinetics of Lanadelumab Administered Intravenously in Healthy Adult Volunteer Subjects

Study Number: TAK-743-1003

SAP Version and Date:

Version Final: 21 Sep 2020

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STUDY NUMBER: TAK-743-1003
CELERION STUDY NUMBER: CA32450

A Randomized, Double-blind, Placebo-Controlled, Repeat-dose, Single-center Phase 1a Study to Determine the Safety, Tolerability, and Pharmacokinetics of Lanadelumab Administered Intravenously in Healthy Adult Volunteer Subjects

PHASE 1a

Version: Final

Date: 21 September 2020

Prepared by:

[redacted], MSc
[redacted], Data Management and Biometrics
Celerion

[redacted], MSc
[redacted], Clinical Pharmacology & Pharmacometrics
Data Management and Biometrics
Celerion

Based on:

Final Protocol Dated: 22 July 2020

Protocol Amendment 1 Dated: 16 September 2020

1.1 Approval Signatures

Study Title: A Randomized, Double-blind, Placebo-Controlled, Repeat-dose, Single-center Phase 1a Study to Determine the Safety, Tolerability, and Pharmacokinetics of Lanadelumab Administered Intravenously in Healthy Adult Volunteer Subjects

[redacted]
[redacted] PhD
[redacted] Biostatistics
Takeda Pharmaceuticals

[redacted]
Date

[redacted]
[redacted] PhD
Rare Diseases
Takeda Pharmaceuticals

[redacted]
Date

[redacted]
Takeda Pharmaceuticals

[redacted]
Date

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CV%	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
IV	Intravenous
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PK	pharmacokinetics
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listing
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Study Primary Objectives

- To evaluate the safety and tolerability of two doses of lanadelumab administered 3 days apart by intravenous (IV) infusion in healthy adult volunteers.
- To characterize the pharmacokinetics (PK) of lanadelumab after two IV doses administered 3 days apart in healthy adult volunteers.

4.2 Study Exploratory Objective

[redacted]

4.3 Study Design

This Phase 1a study is a randomized, double-blind, placebo-controlled, repeat-dose study to evaluate the safety, tolerability and PK of lanadelumab administered by IV infusion in healthy adult volunteers. This study targets to enroll 1 cohort of approximately 12 subjects, including both male and female, 19-55 years of age, inclusively.

Subjects will be randomized 3:1 (9 lanadelumab: 3 placebo subjects) to receive lanadelumab 300 mg or matching placebo (normal saline) via IV infusion on Day 1 and Day 4. Subjects will receive the same treatment (lanadelumab or placebo) for each of the two doses. Sentinel dosing will be used for the first 2 subjects (1 receiving lanadelumab and 1 receiving placebo). A safety review team consisting of, at a minimum, the investigator, the Sponsor's Medical Monitor, the Sponsor's Drug Safety physician and the Sponsor's statistician will review safety (treatment-emergent adverse events [TEAEs], vital signs, 12-lead electrocardiograms [ECGs]) and tolerability data after the first 2 sentinel subjects receive both doses of study drug. If no safety findings or signals are observed, the remaining subjects (N=10) will be dosed. An additional cohort of 12 subjects (increasing total number of subjects to approximately 24) or dose modifications (eg, reduction to a single dose) will be allowed if required based on emerging data. An interim analysis will be performed when all subjects have reached Day 14 or discontinued early to evaluate preliminary safety and PK. These data will be summarized in a preliminary report. Of note, this preliminary report will not be generated by Celerion.

The study duration will comprise a screening period (up to 21 days), a 10-day in-house treatment period, and 7 out-patient visits. The maximal total duration of study participation for a subject is approximately 133 days if the maximal screening, treatment, and out-patient visit durations are included.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

5.1.1 Safety Endpoints:

- TEAEs.
- Clinical laboratory results (hematology, serum chemistry, coagulation and urinalysis).
- Vital signs (including blood pressure [BP], pulse, body temperature), and 12-lead ECG.

5.1.2 Pharmacokinetic Parameters:

- PK concentrations of lanadelumab over the study period.

5.1.3 Exploratory Endpoints

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

No formal calculations were performed to determine sample size for this study. The sample size is based on feasibility and is similar to that of comparable studies.

7.0 METHODS OF ANALYSIS AND PRESENTATION – CELERION GENERATED TFLS

7.1 General Principles

All analyses will be conducted using SAS® Version 9.4, or higher. All data recorded on the CRF will be listed by subject. All tables, figures and listings (TFLs) shells and numbering list specified in the TFL Shell document will be included.

For demographic and safety data where appropriate, variables will be summarized descriptively. For the categorical variables, the count and proportions of each possible value will be tabulated, where applicable. The denominator for the proportion will be based on the number of subjects who provided non missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values (n), arithmetic mean (mean), standard deviation (SD), minimum, median, and maximum values will be tabulated. The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Counts and percentages will be presented as integers.

7.1.1 Study Definitions

7.1.1.1 Definition of Study Days

Day 1 for the study is defined as the date on which a subject is administered their first dose of the study drug. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1. Study day prior to the first dose will be calculated as: date of assessment-date of first dose in; study day on or after the date of first dose will be calculated as: date of assessment-date of first dose +1.

7.2 Analysis Sets

Safety Analysis Set:

The Safety Analysis Set will consist of all subjects who have started at least 1 dose of lanadelumab or placebo.

Pharmacokinetic Set:

The PK Analysis Set will consist of all subjects who receive at least one dose of the study drug and have at least one evaluable PK concentrations post dose and with absence of major protocol violations.

[redacted]

7.3 Treatment Descriptions

Treatments will be described as follows in the TFLs:

Treatment A: Lanadelumab 300 mg, one dose administered via IV infusion over a period of 60 ±15 minutes on Day 1, followed by a second dose on Day 4
Treatment P: Placebo (normal saline) administered via IV infusion over a period of 60 ±15 minutes on Day 1, followed by a second dose on Day 4

7.4 Study Information

A study information table will be generated including the following items: date of first subject's signed informed consent form, date of first dose, date of last dose, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, the version of Medical Dictionary for Regulatory Activities (MedDRA®), the version of World Health Organization (WHO) Dictionary, and SAS version used for creating the datasets.

7.5 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized by treatment and overall. Study completion status, including reason for discontinuation, will also be listed by subject.

7.6 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment and overall. Summary statistics (number of subjects [n], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [recorded in the CRF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). Height, weight, and BMI recorded at screening will be used in the baseline summaries. Demographics data will also be listed as recorded on the CRF, including the date of informed consent.

7.7 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing the informed consent form (ICF). Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started or worsening after taking the study drug(s) will be classified as an adverse event. All medical history will coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.0. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, coded term, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.8 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing the ICF. Concomitant medication includes any medication other than study drug taken at any time between time of signing the ICF through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the WHO Dictionary, Version 01-Mar-2020 b3, and listed. The listing will include the medication name, coded term, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use. A summary table for concomitant medication will also be provided. The number and percentage of subjects receiving each WHO coded concomitant medication will be summarized by treatment.

7.9 Study Drug Exposure and Compliance

The date, time, and dosage of each study treatment dose will be listed by subject. Using drug administration data, estimates of exposure to lanadelumab will be calculated as total dose and number of doses received over the study and summarized with descriptive statistics.

7.10 Efficacy Analysis

Not applicable.

7.11 Pharmacokinetic [redacted]

7.11.1 Pharmacokinetic Analysis

Blood samples for the assessment of plasma lanadelumab concentrations will be collected as outlined in the table below.

Table 7:1 Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Scheduled Time (Hours)
Lanadelumab	Plasma	Predose, and 1, 2, 4, 6, 12 (Study Day 1), 24 (Study Day 2), 48 (Study Day 3), 72, 73, 76, 78, 84 (Study Day 4), 96 (Study Day 5), 120 (Study Day 6), 144 (Study Day 7), 168 (Study Day 8), 192 (Study Day 9), 216 (Study Day 10), 240 (Study Day 11), 312 (Study Day 14), 480 (Study Day 21), 648 (Study Day 28), 984 (Study Day 42), 1320 (Study Day 56), 1992 (Study Day 84), and 2664 (Study Day 112) hours postdose

Note: The second IV infusion of 300 mg lanadelumab will be administered immediately after the 72-hour blood draw. Therefore, the 72-hour postdose sample on Day 1 will be the same as predose sample on Day 4.

The concentration data for plasma lanadelumab will be used as reported by the respective bioanalytical groups without rounding for all analyses. Plasma concentration of lanadelumab below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. For the calculation of summary statistics and the generation of concentration plots, BLQ values will be treated as zero unless they are obvious outliers (e.g. BLQ value between 2 measurable values), in which case they will be treated as missing. In log-linear plots these values would not be presented. Missing concentration values will be flagged in the concentration tables and footnoted as missing or not reportable (i.e., for subjects withdrawn or dropped from the study, subjects missing blood draws).

The mean, median, and geometric mean (Geom Mean) for concentration values will be presented to 1 more level of precision than the individual concentration values. The SD of the mean will be presented to 2 more levels of precision than the individual concentration values. Minimum and maximum values will be presented to the same precision as the individual concentration values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (Geom CV%) will be presented to 1 decimal place.

Lanadelumab concentrations versus time will be plotted on linear (with and without SD) scale and semi-log scale. For summary statistics and arithmetic mean plots by sampling time, the nominal sampling time will be used, for individual subject plots by time, the actual sampling time will be used. Spaghetti plots of individual plasma lanadelumab concentrations versus time profiles will be plotted on linear and semi-log scales.

The PK analysis will be completed by Certara, therefore, calculations of PK parameters will be described in a separate SAP not generated by Celerion.

7.11.2 [redacted]

[redacted]

Table 7:2 [redacted]

[redacted]

7.12 Other Outcomes

Not applicable.

7.13 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and type of TEAEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and 12-lead ECG's using the safety set. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.13.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate, severe), relationship to study drug (related or not related) and action relative to the study drug as recorded in the CRF. Study procedure taken due to AE will also be listed. All AEs occurring during this study will be coded using the MedDRA®, Version 23.0. However, only TEAEs occurring after start of administration of the first dose of study treatment and through the end of the study (Day 112± 7) will be summarized.

TEAEs 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 or relationship at the time of or following the start of treatment. A subset of TEAEs will be attributed to a treatment period (Days 1-3 or Day 4-6) based on the onset date and time of the AE as described in Table 7:3:

Table 7:3 AE Treatment Period Assignment Algorithm

Date and Time of AE With Respect to Date and Time of Dosing	Treatment Period
Day 1 Lanadelumab or Placebo Start of Dosing Date and Time ≤ Date and Time of AE < Day 4 Lanadelumab or Placebo Start of Dosing Date and Time	Days 1 - 3
Day 4 Lanadelumab or Placebo Start of Dosing Date and Time ≤ Date and Time of AE< Day 4 Lanadelumab or Placebo Start of Dosing Date and Time + 72 hours	Day 4-6

An overview of TEAEs summary will be provided. For each treatment, TEAEs will be coded using MedDRA® and tabulated by System Organ Class (SOC) and Preferred Term (PT). Summary tables will include number of subjects reporting the AE and as percent of safety set by treatment. An overview of TEAEs and TEAEs summarized by SOC and PT will be provided for TEAEs occurring during the treatment period of Day 1-3 and Day 4-6 as well. The most commonly reported non-serious TEAEs (i.e., those events reported by >5% of all subjects in each treatment, excluding SAEs) will also be summarized. For the list of all AE summary tables, see TFL Shell document.

Additional TEAE summary tables will be presented by severity and relationship to study drug by treatment, system organ class, and preferred term. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. For each relationship to study drug, if a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs.

Should any SAEs (including all-cause mortalities) or AEs of Special Interest (AESIs), as described in the protocol, occur, they will be summarized the same way as TEAE. All AEs will be displayed in the data listings. AESIs, AEs leading to study withdrawal, TEAEs resulting in death and SAEs will also be listed. TEAEs, AESIs and SAEs will be discussed in the text of the study report.

7.13.2 Clinical Laboratory Evaluations

Serum chemistry, hematology, coagulation and urinalysis tests will be performed at screening and on Days -1, 11, 14 (± 1), 21 (± 1), 28 (± 2), 42 (± 3), 56 (± 3), and 84 (± 7) and at end of study (Day 112 ± 7) or prior to early termination from the study. Additional serum chemistry, hematology and urinalysis tests will also be performed on Days 2 and 5. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI.

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time point. Change from baseline will be summarized in a similar manner. Baseline is defined as the last assessment prior to the first dosing (Day -1).

For each laboratory test, a shift table will be developed comparing the frequency of the results at baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a computer clinically significant (CS) range. If the value falls within the computer CS range, it will be noted as “N” for not clinical significant. If the value fails the computer CS range, it will be flagged with a “Y” which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant laboratory tests, as indicated by the PI, and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.13.3 Vital Signs

Single measurements of blood pressure (systolic and diastolic), heart rate, and body temperature (oral) will be collected as outlined in Table 7:4.

Table 7:4 Vital Signs Collection Time Points

Measurement Type	Period	Day	Time Point
Blood Pressure (Systolic, Diastolic), Heart Rate	Screen		
	1	-1	
		1	Predose, Hours 1, 2, 4, 6, 12
		2, 3	

Measurement Type	Period	Day	Time Point
		4	Predose, Hours 1, 2, 4, 6, 12
		5, 6, 7, 8, 9, 10, 11	
		14 (± 1), 21 (± 1), 28 (± 2), 42 (± 3), 56 (± 3), 84 (± 7)	
		112 (± 7)	End of Study or Early Termination
Body Temperature (Oral)	Screen		
	1	-1	
		1	Predose
		14 (± 1), 21 (± 1), 28 (± 2), 42 (± 3), 56 (± 3), 84 (± 7)	
		112 (± 7)	End of Study or Early Termination
Respiratory rate will be collected at screening only and will not be summarized.			

Additional unscheduled vital signs measurements may be taken at other times, if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results (blood pressure, heart rate and body temperature) and change from baseline by treatment and assessment time point. Baseline is defined as the last assessment prior to first dosing (Day 1 Predose).

Vital signs will also be displayed in a data listing by subject. Abnormal vital signs will be identified using the reference ranges described in Table 7:5 and will be listed by subject in a separate listing. A categorical summary table will also be provided showing the number and percentage of subjects with baseline and post-baseline vital signs in each (low, normal, and high) category by treatment and time point. The reference ranges to be used are as follows:

Table 7:5 Criteria for Vital Signs Abnormal Values

Data Type	Parameter	Lower Criteria	Upper Criteria
Actual Value	Heart rate (bpm)	<40	>115
	Systolic blood pressure (mm Hg)	<90	≥160
	Diastolic blood pressure (mm Hg)	<50	≥100
	Body temperature (°C)		>38.5
Change from Baseline	Systolic blood pressure (mm Hg)		>30 (increase)
	Diastolic blood pressure (mm Hg)		>30 (increase)
* Baseline is defined as the last assessment taken prior to first dosing (Day 1 Predose).			

7.13.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded as outlined in Table 7:6.

Table 7:6 Electrocardiograms Collection Time Points

Measurement Type	Period	Day	Time Point
12-Lead ECG	Screen		
	1	-1	
		1	Predose, Hours 1, 4
		2, 3	
		4	Predose
		5, 6, 7, 11	
		14 (± 1), 21 (± 1), 28 (± 2), 42 (± 3), 56 (± 3), 84 (± 7)	
		112 (± 7)	End of Study or Early Termination
Per protocol, recheck ECGs may be performed in triplicates.			

Additional unscheduled ECGs may be recorded at other times if deemed necessary by the PI.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG parameters and change from baseline by treatment and assessment time point. Baseline is defined as the last assessment prior to first dosing (Day 1 Predose).

All ECG data will be displayed in a data listing by subject. Abnormal ECGs, as indicated by the PI (i.e., CRF Overall Interpretation: Abnormal, Not clinically significant [ANCS] or Abnormal, Clinically Significant [ACS]) and the corresponding ECG parameters will be listed by subject in a separate listing. A categorical summary table will also be provided showing the number and percentage of subjects with baseline and post-baseline ECG in each PI interpretation category (Normal, ANCS, ACS) by treatment and time point.

7.13.5 Physical Exams

A full physical exam will be performed at screening, on Days -1, 11, 14 (± 1), 21 (± 1), 28 (± 2), 42 (± 3), 56 (± 3), and 84 (± 7) and at end of study (Day 112 ± 7) or prior to early termination from the study. Symptom-driven physical examinations may be performed at out-patient visits times, if deemed necessary by the investigator. Physical exam findings will be presented in a data listing by subject. Reproductive system findings will also be listed by subject.

7.13.6 Overdose

All cases of overdose will be presented in a data listing by subject. Any AEs associated with overdose will be documented as AEs.

7.14 Interim Analysis

An interim unblinded analysis will be performed when all subjects complete Day 14 or discontinue prior to Day 14 to evaluate preliminary safety and PK. These data will be

summarized in a preliminary report. No adaptive design or Data Monitoring Committee (DMC) are planned for this study. A separate unblinded team will be assigned to work on the programming and review of the interim safety and PK TFLs.

The following safety outputs will be provided as part of the interim analysis:

- Disposition listing and table
- Demographics and baseline characteristics listing and table
- Dosing information and study drug exposure listing and table
- Concomitant medications listing and table
- All adverse events listings and tables
- All clinical laboratory listings and tables
- All vital signs listings and tables
- All 12-lead ECG listings and tables

The following PK outputs will be provided as part of the interim analysis:

- Lanadelumab concentration listings and tables
- Mean lanadelumab concentration versus time figure (linear and semi-log scales)

Please refer to the TFL shell document for the TFL titles and shells.

7.15 Changes in the Statistical Analysis Plan

There were no changes from protocol planned analysis.

8.0 REFERENCES

Not applicable.