CLINICAL STUDY PROTOCOL

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

Protocol Version and Date:

Protocol Amendment 1: 16-SEP-2020

PROTOCOL

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 Identifier: TAK-743-1003

Compound: TAK-743

Date: 16 Sep 2020

Version/Amendment Number: Version 2.0 / Amendment 1.0

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 Telephone: [redacted]	**Compound:** Lanadelumab
Study Identifier: TAK-743-1003	**Phase:** 1a
Protocol 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 Design: This Phase 1a study is a randomized, double-blind, placebo-controlled, repeat-dose study to evaluate the safety, tolerability and pharmacokinetics (PK) of lanadelumab administered by IV infusion in healthy volunteers. This study targets to enroll 1 cohort of approximately 12 subjects, including both male and female, 19 years of age and above. 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 will review safety 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 (e.g., 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. 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.	
Study Primary Objective: • To evaluate the safety and tolerability of two doses of lanadelumab administered 3 days apart by IV infusion in healthy adult volunteers • To characterize the PK of lanadelumab after two IV doses of lanadelumab administered 3 days apart in healthy adult volunteers	
Study Subject Population: Healthy male and female subjects aged 19 to 55 years inclusive, at screening. Body Mass Index (BMI) 18.0-32.0 kg/m^2, inclusive, at screening	
Planned Number of Subjects: 12 subjects will be enrolled	**Planned Number of Sites:** 1
Dose Levels: 300 mg	**Route of Administration:** Intravenous (IV)
Duration of Treatment: One dose on Day 1 followed by a second dose on Day 4; Single IV infusion for 60 ± 15 minutes	**Planned Study Duration:** Approximately 133 days including screening period and follow-up.
Criteria for Inclusion: Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study: 1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening. 2. Continuous non-smoker who has not used nicotine-containing products for at least 30 days prior to the first dosing and throughout the study, based on subject self-reporting. 3. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2 at screening.	

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or electrocardiograms (ECGs), per the investigator.
5. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential
6. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol.

Criteria for Exclusion:

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease per the investigator.
3. History of any illness that might confound the results of the study or poses an additional risk to the subject by their participation in the study, per the investigator.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing per the investigator.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
6. History or presence of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinically significant clinical or laboratory assessments per the investigator.
7. Female subjects with a positive pregnancy test or lactating.
8. Positive urine drug or alcohol results at screening.
9. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
10. Supine blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
11. Supine heart rate is lower than 40 beats per minute (bpm) or higher than 99 bpm at screening.
12. QTcF interval is >450 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance at screening per the investigator.
13. Estimated creatinine clearance <80 mL/min at screening.
14. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Appendix D). Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After randomization/dosing, a nonsteroidal anti-inflammatory drug may be administered at the discretion of the investigator. Hormone replacement therapy will also be allowed if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.
15. Has been on a diet incompatible with the on-study diet, per the investigator, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

Safety endpoints:

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

Pharmacokinetic parameters (using compartmental or noncompartmental analysis as appropriate), including but not limited to:

- $AUC_{0\text{-}last}$: 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 based on the predicted concentration at t_{last}
- C_{max}: Maximum observed plasma drug concentration following the first IV dose (C_{max} 1) and following the second IV dose (C_{max} 2)
- t_{max}: Minimum observed time to reach the first C_{max} 1 (T_{max} 1) and to reach the second C_{max} 2 (T_{max} 2)
- $t_{½}$: Terminal half-life
- CL: Clearance
- Vz: Volume of distribution during the terminal phase
- λ_z: First order rate constant associated with the terminal (log-linear) portion of the curve

Statistical Considerations:

Statistical analyses will be performed by treatment group.

Analysis Set/Analysis Populations

Analysis of study data will be based on the following analysis sets.

- Safety Analysis Set - The safety Analysis Set includes all subjects who have received at least 1 dose of lanadelumab or placebo.
- Pharmacokinetic Set- The Pharmacokinetic Set includes all subjects who have received at least 1 dose of lanadelumab or placebo and have at least 1 evaluable post-dose PK concentration value.
- [redacted]

Safety Endpoint(s)

- Treatment emergent adverse events (TEAEs), including serious adverse events (SAEs) and adverse events of special interest (AESI) [Time frame: up to Day 112]
- Clinical laboratory testing (hematology, clinical chemistry, coagulation, and urinalysis) [Time frame: up to Day 112]
- Vital signs including blood pressure, heart rate, and body temperature [Time frame: up to Day 112]
- 12-lead electrocardiogram [Time frame: up to Day 112]

Pharmacokinetic Endpoint(s)

- PK concentrations of lanadelumab over the study period
- PK parameters using compartmental or non-compartmental analysis (NCA) methods as appropriate
- PK [redacted] properties of lanadelumab [redacted]

Statistical Methodology for Safety Endpoints:

Statistical analysis of safety endpoints will be based on the Safety Analysis Set.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum value, and maximum value. As appropriate, raw (actual) values and changes from baseline will be summarized at each scheduled time point.
- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized using counts and percentages. Summaries will include but are not limited to: number and percentage of subjects with an outcome measure, and laboratory shift tables (categorical change from baseline).
- Only TEAEs will be analyzed. The number and percentage of subjects reporting any TEAEs, SAEs, AESIs, TEAEs related to the investigational product, TEAEs leading to withdrawal, and severe TEAEs, as well as the total number of events for each category, will be summarized overall and by preferred term and system organ class.
- Clinical laboratory tests, vital signs, and ECG results will be summarized by scheduled time point. Clinically significant findings will also be summarized and listed.

Statistical Methodology for Pharmacokinetic Endpoints:

Statistical analysis of PK parameters will be based on the Pharmacokinetic Set. Listing of individual PK concentrations and individual PK parameters of lanadelumab will be based on the PK Analysis Set. Individual concentrations and PK parameters of lanadelumab (estimated based on actual sample collection times) will be listed and summarized by treatment group with descriptive statistics (number, arithmetic mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric mean, and CV% of geometric mean). Figures of individual and mean (±SD) concentration-time profiles of lanadelumab by treatment group will be generated based on nominal time points.

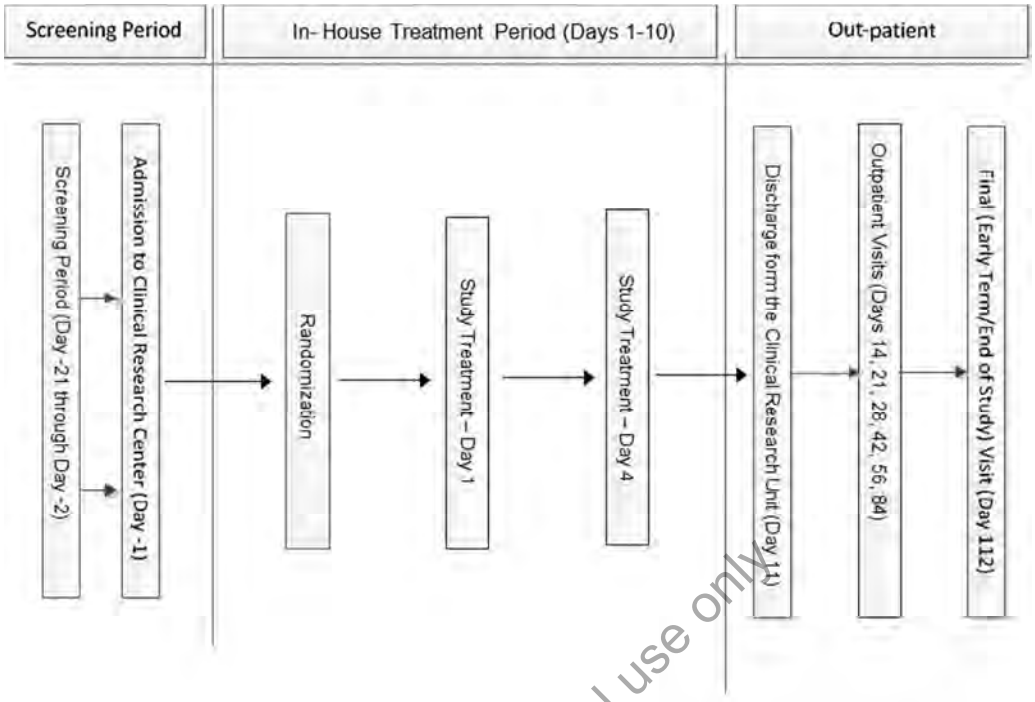
Interim Analysis, Adaptive Design, and Data Monitoring Committee

An interim analysis will be performed when all subjects have completed Day 14 visit or discontinued early 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.

Sample Size Justification:

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.

2.0 STUDY SCHEMATIC



3.0 SCHEDULE OF STUDY PROCEDURES

Table 1 Schedule of Assessments

Visit	Screening		In-House Treatment Period[a]	Out-Patient Visits[b,c]
Study Day	**–21 to -2**	**-1**	**1 to 11**	**14 to 112 (End of Study or Early Discontinuation)**
Informed consent	X		Refer to Table 3	Refer to Table 4
Inclusion/exclusion criteria	X	X		
Demography	X	X		
Medical/Medication History	X	X		
Physical examination	X	X		
Vital signs (blood pressure, pulse) supine	X	X		
Body temperature (oral)	X	X		
Height, Weight and BMI[d,e]	X	X		
Electrocardiogram (12-lead)	X	X		
Biochemistry, hematology, and urinalysis	X	X		
TSH, T3, T4	X			
PT, aPTT, INR (coagulation tests)	X	X		
HIV, HBsAg, and HCV antibodies	X			
Serum Pregnancy test (all females)	X	X		
FSH (all females)	X			
Urine drug screening and alcohol	X	X		
Pharmacokinetic (PK) [redacted] blood sampling				
Check-in to the CRU		X		
Out-patient visits				
In-patient visit		X		
Concomitant Medication	X	X		
Adverse Event/Serious Adverse Event	X	X		

aPTT=activated partial thromboplastin time; CRU=clinical research unitr; 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 3 for the procedures and the timing of the procedures to be done during the in-house treatment period.

[b] Refer to Table 4 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.

Table 2 Detailed Schedule of In-House Assessments (Days 1 – 11)

Study Day		**Day 1**							**Day 2**	**Day 3**	**Day 4**						**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**
Hour (relative to dosing time)	**Dose 1**	**Predose[a]**	**0h**	**1h**	**2h**	**4h**	**6h**	**12h**	**24h**	**48h**	**72h (predose)[a]**	**73h**	**74h**	**76h**	**78h**	**84h**	**96h**	**120h**	**144h**	**168h**	**192h**	**216h**	**240h**
	Dose 2	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**--**	**0h**	**1h**	**2h**	**4h**	**6h**	**12h**	**24h**	**48h**	**72h**	**96h**	**120h**	**144h**	**168h**
Randomization[b]		X																					
IP administration[c]			X								X												
Physical Exam																							X
Vital Signs[d]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Temperature (Oral)		X																					
Weight																							X
ECG[e]		X		X		X			X	X	X						X	X	X				X
Biochemistry, hematology, and urinalysis									X								X						X
PT, aPTT, INR																							X
Serum Pregnancy (all women)																							X
PK [redacted]		X		X[h]	X[i]	X[i]	X[i]	X[i]	X[j]	X[j]	X	X[h]	X[i]	X[i]	X[i]	X[i]	X[j]	X[j]	X[k]	X[k]	X[k]	X[k]	X[k]
AE/SAE[g]		X----------X																					

Table 2 Detailed Schedule of In-House Assessments (Days 1 – 11)

Study Day		**Day 1**							**Day 2**	**Day 3**	**Day 4**						**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**
Hour (relative to dosing time)	**Dose 1**	**Predose[a]**	**0h**	**1h**	**2h**	**4h**	**6h**	**12h**	**24h**	**48h**	**72h (predose)[a]**	**73h**	**74h**	**76h**	**78h**	**84h**	**96h**	**120h**	**144h**	**168h**	**192h**	**216h**	**240h**
	Dose 2	--	--	--	--	--	--	--	--	--	**0h**	**1h**	**2h**	**4h**	**6h**	**12h**	**24h**	**48h**	**72h**	**96h**	**120h**	**144h**	**168h**
Concomitant Medication[g]		X----------																					----------X
Discharge from CRU																							X

AE=adverse event; aPTT= activated partial thromboplastin time; CRU=clinical research unit; 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 2 hours prior the administration of IP. The PK sample should be collected as closely as possible to hour 0 (start of infusion/dosing) for Dose 1 and hour 72 (hour 0; start of infusion/dosing) for Dose 2.

[b] Randomization to be performed at the time of dosing on Day 1.

[c] Investigational product administration start and stop times must be recorded in source and on the CRF. The clock time of the second infusion should be approximately the same as the first infusion.

[d] Blood pressure and heart rate measurements will be performed with subjects in a supine position. The subject should be supine and instructed to relax as much as possible for at least 5 minutes prior to collection. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

[e] ECGs will be performed with subjects rested in a supine position for at least 5 minutes prior to collecting the ECG. When scheduled postdose, ECGs will be performed within 20 minutes of scheduled time point. Single ECG recordings are required. ECGs will be performed in triplicate if any of the following occur: (1) the QTcF interval (calculated on line on site) is increased by >45 msec from the baseline; (2) an absolute QTcF value is >500 msec for any scheduled ECG; (3) if indicated per exclusion criteria #12. Subsequently, 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. Thereafter, all subsequent ECGs will be single recordings.

[f] [redacted]

[g] Adverse events/SAEs and concomitant medications will be continuously monitored throughout the study.

[h] Sample to be collected immediately after the end of the infusion within approximately 10 minutes of the scheduled time point.

[i] Sample to be collected within ± 10 minutes of the scheduled timepoint.

[j] Sample to be collected within ± 15 minutes of the scheduled timepoint.

[k] Sample to be collected within ± 4 hours of the scheduled timepoint.

Table 3 Detailed Schedule of Outpatient Assessments (Study Days 14 – 112)

Study Day	**Day 14 (± 1)**	**Day 21 (± 1)**	**Day 28 (± 2)**	**Day 42 (± 3)**	**Day 56 (± 3)**	**Day 84 (± 7)**	**Day 112 (± 7) (End of Study Visit / or Early Discontinuation)**
Physical Exam[a]	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X
Body Temperature (Oral)	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
ECG[c]	X	X	X	X	X	X	X
Biochemistry, hematology, and urinalysis	X	X	X	X	X	X	X
PT, aPTT, INR	X	X	X	X	X	X	X
Serum Pregnancy (all women)	X	X	X	X	X	X	X
UDS & ETOH screen	X	X	X	X	X	X	X
PK[redacted]	X	X	X	X	X	X	X
AE/SAE[e]	X	X	X	X	X	X	X
Concomitant Medication[e]	X	X	X	X	X	X	X

AE=adverse event; aPTT= activated partial thromboplastin time; ; 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; UDS=urine drug screen; VS=vital signs

[a] Outpatient physical exams may be symptom driven at the discretion of the investigator.

[b] Blood pressure and heart rate measurements will be performed with subjects in a supine position. The subject should be supine and instructed to relax as much as possible for at least 5 minutes prior to collection. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

[c] ECGs will be performed with subjects rested in a supine position for at least 5 minutes prior to collecting the ECG. Single ECG recordings are required. ECGs will be performed in triplicate if any of the following occur: (1) the QTcF interval (calculated on line on site) is increased by >45 msec from the baseline; (2) an absolute QTcF value is >500 msec for any scheduled ECG; (3) if indicated per exclusion criteria #12. Subsequently, 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. Thereafter, all subsequent ECGs will be single recordings.

[d] [redacted]

[e] Adverse events/SAEs and concomitant medications will be continuously monitored throughout the study.

4.0 INTRODUCTION

4.1 Background

Lanadelumab (Takhzyro™, TAK-743, formerly SHP643 or DX-2930) is currently approved as a subcutaneous (SC) injection for prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older. It is a recombinant, fully human, immunoglobulin G1, kappa light chain, monoclonal antibody and is a highly potent and a specific inhibitor of pKal. Plasma kallikrein is a protease that cleaves high molecular weight kininogen (HMWK) to generate cleaved HMWK (cHMWK) and bradykinin. Bradykinin is a potent proinflammatory and vasodilative nonameric peptide responsible for the characteristic symptoms of localized swelling, pain, and inflammation.

For further details see the current lanadelumab Investigator's Brochure.

4.2 Rationale for the Proposed Study

Lanadelumab is currently approved as an SC injection for prophylaxis to prevent attacks of HAE in patients 12 years and older. Based on the mechanism of action of lanadelumab and recent case studies with a competitive antagonist selective for the bradykinin B2 receptor, icatibant, there is strong scientific rationale to evaluate the potential for lanadelumab to treat pneumonia due to coronavirus disease 2019 (COVID-19). Clinical evidence supports the need for early intervention in patients hospitalized with COVID-19 pneumonia. Following SC administration of 300 mg every 2 weeks (approved dosage for the HAE indication), the time until maximum observed concentration (T_{max}) was 4 days or longer with maximum observed concentration (C_{max}) approximately 34 ug/mL, which may not be sufficient to meet the treatment needs (regarding the rate and extent of SC absorption) in patients with progressing COVID-19 disease. Intravenous (IV) administration of lanadelumab may be required, but IV administration has not yet been studied. Thus, the purpose of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of lanadelumab administered via the IV route in healthy adult volunteer subjects to support the further clinical evaluation of lanadelumab IV in COVID-19 patients.

4.3 Benefit/Risk Profile

Four clinical studies supported the global marketing applications and licenses for lanadelumab for routine prophylaxis to prevent attacks of HAE in patients 12 years and older. The safety and tolerability data from these studies to date demonstrate that lanadelumab is safe and efficacious in HAE patients and have served as the basis of submissions for global expansion.

Per the reference labeling (Takhyzro, 2018), the most common adverse reactions are injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea. Other adverse reactions that occurred at a higher incidence in lanadelumab-treated patients compared to placebo include hypersensitivity, increased aspartate transaminase, and increased alanine transaminase.

Hypersensitivity is an important identified risk and is discussed in the warnings and precautions of the reference labeling. Immunogenicity is an important potential risk for lanadelumab and is monitored closely. The known potential risk of disordered coagulation associated with monoclonal antibodies has been characterized, and no unexpected signals were identified. Based on the review of the safety data from the completed and ongoing clinical trials, the known

cumulative exposure and continuous pharmacovigilance monitoring for the risks, the benefit-risk continues to be favorable. Always refer to the latest version of the lanadelumab Investigator's Brochure for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, PK, efficacy, and safety of lanadelumab.

There will be no direct health benefit for study subjects from receipt of study drugs. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

The inclusion and exclusion criteria, screening, and safety monitoring practices employed by this protocol (ie, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory tests, AE questioning and physical examination) are adequate to protect the subject's safety and should detect all TEAEs.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Study Primary Objective

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

5.1.2 Study Exploratory Objectives

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

Safety endpoints:

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

Pharmacokinetic parameters (using compartmental or noncompartmental analysis methods as appropriate) including but not limited to:

- $AUC_{0\text{-}last}$: 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 based on the predicted concentration at t_{last}
- C_{max}: Maximum observed plasma drug concentration following the first IV dose (C_{max} 1) and following the second IV dose (C_{max} 2)
- tmax: Minimum observed time to reach the first C_{max} 1 (T_{max} 1) and to reach the second C_{max} 2 (T_{max} 2)
- $t_{½}$: Terminal half-life
- CL: Clearance
- Vz: Volume of distribution during the terminal phase
- λ_z: First order rate constant associated with the terminal (log-linear) portion of the curve

5.2.2 Exploratory Endpoints

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 years of age and above.

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 (TEAEs, vital signs, 12-lead 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.

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.

6.2 Dose Escalation

Not applicable.

6.3 Stopping Rules

Individual subject dosing will not continue if any of the following criteria are met:

- If 2 or more subjects experience a treatment emergent adverse event (TEAE) of at least moderate severity (such as National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) in the same system organ class (SOC) considered related to study drug by the investigator.

- Dosing will be discontinued in an individual subject if that subject experiences a TEAE of at least moderate severity (CTCAE Grade 3 or higher) or laboratory abnormality that is considered related to study drug by the investigator.

- Individual subjects should be discontinued if any of the following laboratory findings are observed:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >8 ×upper limit of normal (ULN)
- AST or ALT >5 ×ULN for 2 weeks;
- AST or ALT >3 ×ULN and either total bilirubin >2 ×ULN or international normalized ratio (INR) >1.5;
- AST or ALT >3 ×ULN with symptoms consistent with hepatic disease or injury (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia >5%).

- A serious adverse event (SAE) considered related to study drug by the investigator occurs in 1 or more subjects receiving active drug.
- Any other event considered related to study drug by the investigator occurs in subjects receiving active drug and is deemed to pose an unacceptable risk to subjects by the investigator or the Sponsor's Medical Monitor after further evaluation.

Should any of the above stopping criteria be potentially met, no further subjects will be enrolled or dosed, and the data under examination will be unblinded to ensure the criteria have been met with respect to those subjects receiving active drug. The Sponsor's Medical Monitor and the investigator will review the event(s) and the available data and determine whether to stop or proceed with the study. Additionally, the Sponsor's Medical Monitor and/or investigator can request for the data to be unblinded for an individual subject or entire cohort at any time in order to further evaluate a possible safety concern.

6.4 Rationale for Study Design, Dose, and Endpoints

6.4.1 Rationale of Study Design

This Phase 1a study is designed to assess the safety, tolerability and PK of two doses of lanadelumab administered by IV infusion in healthy volunteers to support the study of IV lanadelumab in patients with COVID-19. A Phase 1b study to evaluate the safety, PK, and pharmacodynamics (PD) of IV lanadelumab in patients hospitalized with COVID-19 pneumonia is planned.

6.4.2 Rationale for Dose

The 300 mg via IV route of administration is chosen for this trial based on the following rationale:

The (PK[redacted]) properties of lanadelumab have been well characterized in both healthy volunteers and in patients with HAE following SC administration[redacted]. Following SC administration of 300 mg every 2 weeks (approved dosage for the HAE indication), the time to maximum concentration (t_{max}) was 4 days or longer with maximum observed concentration (C_{max}) approximately 34 ug/mL. Since no information exists for IV lanadelumab, the IV route of

administration has been proposed for this study to gain initial safety and tolerability and PK data utilizing the 300 mg dose indicated for HAE.

Exposure to lanadelumab IV administration was predicted by a simulation using a 2-compartment IV model with PK parameters estimated by fitting the model to mean values of lanadelumab concentrations in HAE clinical studies, for a single 300 mg IV infusion, and 300 mg IV infusion on Day 1 and Day 4 (Table 4). The exposure (predicted C_{max} and area under the plasma time-concentration curve [AUC]) to lanadelumab is comparable to the exposure observed following 2 ×400 mg SC 14 days apart, and the HAE clinical exposure package; and the sufficient safety margins for the proposed IV dosing regimens by the nonclinical HAE package are provided (below) using no observed adverse effect level (NOAEL) exposure observed in both GLP and non-GLP monkey toxicity studies.

Table 4 Predicted Clinical Exposure Margins Compared to Observed Exposure (NOAEL) in Cynomolgus Monkeys

Cynomolgus Monkey Exposure (NOAEL)		**GLP Toxicity Repeat-Dose IV Study (Day 22 to 29)**	**Non-GLP Tolerability Single-Dose IV Study (Day 1 to 29)**
AUC_{last} (µg*hr/mL)		123000	137500
C_{max} (µg*mL)		1640	1155
Human 300 mg[a]		**Safety Margin**	
AUC_{0-672} (µg*hr/mL)	17281	7.1	8.0
C_{max} (µg*mL)	94.1	17	12
Human 2×300 mg[a,b]		**Safety Margin**	
AUC_{0-672} (µg*hr/mL)	33532	3.7	4.1
C_{max} (µg*mL)	130	13	8.9

AUC_{0-672}=area under the concentration-time curve from time 0 to 672 hours; AUC_{last}=area under the concentration-time curve from time 0 to the last timepoint; C_{max}=maximum observed concentration; GLP=Good Laboratory Practices; IV=intravenous; NOAEL=no observed adverse effect level

[a] =300 mg IV infused for 60 minutes on Day 1.

[b] =300 mg IV infused for 60 minutes on Day 4.

6.4.3 Rationale for Endpoints

6.4.3.1 Pharmacokinetic Endpoints

The PK endpoints are standard for this type of study.

6.4.3.2 Safety Endpoints

The key safety endpoints are typical for Phase 1 studies and will be assessed through monitoring of AEs, vital signs, ECGs, laboratory assessments, and physical examinations.

6.4.4 Future Biomedical Research

Any residual plasma samples will be stored by the Sponsor or Bioanalytical facility for the maximal 15 years determined by the Sponsor following the last dosing. Tubes or containers will be identified with a barcode using an appropriate label. Samples obtained for this study may be used for further analyses based on emerging data. Thereafter, samples will be destroyed.

No deoxyribonucleic acid (DNA), or ribonucleic acid (RNA) will be the focus of these analyses. The analyses will focus on metabolite profiling for lanadelumab or the potential use of lanadelumab for disease conditions based on emerging data. Samples will not be submitted to a public database. The Sponsor and contract research organizations involved in the clinical conduct, bioanalytical analyses, and PK and statistical analysis of the data will have access to the samples and/or the data that resulted from the analysis, if performed.

By signing the Informed Consent Form (ICF), subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the Clinical Research Unit (CRU) staff to request destruction of the residual samples once PK assessments required to meet the primary objective of the study are completed.

6.5 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

An additional cohort of 12 subjects or dose modifications (eg, reduction to a single dose) will be allowed if required based on emerging data. If necessary, a subject may be discontinued for the reasons described in Section 7.5 and Section 7.6.

6.6 Study Beginning and End/Completion

6.6.1 Definition of Beginning of the Study

The beginning of the study will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.6.2 Definition of End of the Study

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0)

6.6.3 Definition of Study Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.6.4 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study (refer to Stopping Rules, Section 6.3).

6.6.5 Criteria for Premature Termination or Suspension of a Site

Not applicable.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female, 19-55 years of age, inclusive, at screening.
2. Continuous non-smoker who has not used nicotine-containing products for at least 30 days prior to the first dosing and throughout the study, based on subject self-reporting.
3. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2 at screening.
4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs or ECGs, per the investigator.
5. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.
6. Understands the study procedures in the ICF and be willing and able to comply with the protocol.

7.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.
2. History or presence of clinically significant medical or psychiatric condition or disease per the investigator.
3. History of any illness that might confound the results of the study or poses an additional risk to the subject by their participation in the study, per the investigator.
4. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dosing per the investigator.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s) or related compounds.
6. History or presence of any hematological, hepatic, respiratory, cardiovascular, renal, neurological or psychiatric disease, gall bladder removal, or current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinically significant clinical or laboratory assessments per the investigator.
7. Female subjects with a positive pregnancy test or lactating.
8. Positive urine drug or alcohol results at screening.
9. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).

10. Supine blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.
11. Supine heart rate is lower than 40 meats per minute (bpm) or higher than 99 bpm at screening.
12. QTcF interval is >450 msec (males) or >470 msec (females) or ECG findings are deemed abnormal with clinical significance at screening per the investigator.
13. Estimated creatinine clearance <80 mL/min at screening.
14. Unable to refrain from or anticipates the use of any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements within 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Appendix D). Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration. After randomization/dosing, a nonsteroidal anti-inflammatory drug may be administered at the discretion of the investigator. Hormone replacement therapy will also be allowed.
15. Has been on a diet incompatible with the on-study diet, per the investigator, within the 30 days prior to the first dosing and throughout the study.
16. Donation of blood or significant blood loss within 56 days prior to the first dosing.
17. Plasma donation within 7 days prior to the first dosing.
18. Participation in another clinical study within 30 days or 5 half-lives prior to the first dosing. The 30-day window or 5 half-lives will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

7.3 Excluded Medications, Supplements, Dietary Products

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 7.2. After each dose of study drug, a nonsteroidal anti-inflammatory drug may be administered at the discretion of the investigator. Thyroid hormone replacement medication may be permitted if the subject has been on the same stable dose for the immediate 3 months prior to the first dosing. Hormone replacement therapy will also be allowed if the subject has been on the same stable dose for the immediate 3 months prior to first study drug administration.

If deviations occur, the investigator in consultation with the Sponsor if needed will decide on a case by case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

Use of excluded agents (prescription or non-prescription) or dietary products is outlined in Table 5.

Table 5 Excluded Medications, Supplements, and Dietary Products

Category	Between Screening and First Dosing (Days -28 to predose [Day 1])	After First Dosing (Day 1) to Follow-Up
Alcohol	Prohibited from 48 hours prior to first dosing	Prohibited 48 hours prior to each outpatient visit during the study
Xanthine and/or caffeine	Prohibited from 24 hours prior to first dosing[a]	Prohibited 30 minutes prior to each outpatient visit during the study[a]
Medications	See Section 7.1 and Section 7.2	See Section 7.1 and Section 7.2
Nicotine- and tobacco-containing and/or cannabis products	Prohibited for at least 30 days prior to the first dose	Prohibited from first dosing until the follow-up visit.

(a) small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

When confined, standard meals and snacks will be provided at appropriate times. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks provided.

7.4.2 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours postdose, except when they are supine or semi-reclined for study procedures as noted in the protocol.

Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the CRU and during the in-house stays at the CRU.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the investigator for the following reasons:

- AEs.
- A positive pregnancy test for females.
- Positive urine drug or alcohol results.
- Difficulties in blood collection.

A subject may be withdrawn by the investigator or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the end-of-study or early termination as described in Section 3.0.

7.7 Subject Replacement

Study subjects who withdraw or discontinue early may be replaced at the discretion of the sponsor.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Lanadelumab will be supplied by Sponsor prepackaged in a study kit. Each study kit will contain one (1) vial of lanadelumab 300 mg/vial liquid form. Additional information is provided in the current lanadelumab Investigator's Brochure.

The reference/comparator product is matching placebo (normal saline (NS), 0.9% sodium chloride) for infusion (provided by the site). Further details are provided in the Pharmacy Manual.

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

8.1.2 Clinical Study Drug Inventory and Storage

The same lot number will be used throughout the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report. Study drugs will be stored according to the product labels provided with the product.

Records will be made of the receipt, preparation, dispensing, and final disposition of the study drugs supplied.

8.1.3 Clinical Study Drug Blinding

This is a double-blind, placebo-controlled study.

8.1.4 Randomization Code Creation and Storage

A computerized randomization scheme will be created by a Celerion statistician and it shall be considered blinded (as per the following).

The randomization is available only to the unblinded CRU pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, bioanalytical laboratory, subjects, or members of the staff responsible for the monitoring and evaluation of safety assessments. One set of sealed envelopes containing the randomization code will be supplied to the investigator at the start of the study.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject. An interim analysis will be performed when all subjects have reached Day 14 or discontinued early. Site personnel and subjects will remain blinded to study treatment; a Sponsor team that is separate from the clinical study team will review the unblinded report. Details will be reported separately in the Data Blinding Specification Form and Data Access Management Plan.

In the event of a medical emergency, it is requested that the investigator make every effort to contact the Study Monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the investigator for that subject only. In the event that the emergency is one that suggests that other subjects may be at imminent risk, the blind may be broken for all subjects dosed. The unblinding will be properly documented in the study file.

In all cases where the code is broken, the investigator should record the date and reason for code breaking.

At the end of the study, envelopes will be retained according to site procedures unless specified otherwise by the Sponsor.

In the absence of a medical emergency, the blinded randomization for this study will not be revealed until all data are entered in the database, edits checks are performed, queries closed, and the database is officially locked.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by Celerion, returned to the Sponsor, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased by Celerion will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

9.0 STUDY PROCEDURES

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF

9.1.1.1 Assignment of Screening and Randomization Numbers

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

9.1.1.2 Study Drug Assignment

All subjects will receive the treatments as detailed in Section 9.2.6.

9.1.2 Inclusion and Exclusion

Please refer to Section 7.1 and Section 7.2.

9.1.3 Medical History/Demography

Medical history and demographic data, including name, sex, age, race, ethnicity, and history of tobacco use will be recorded.

9.1.4 Concomitant Medications

Concomitant medications will be prohibited except as listed in Section 7.3. All medications taken by subjects during the course of the study will be recorded.

9.2 Clinical Procedures and Assessments

The Schedule of Study Procedures (Section 3.0) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the investigator and/or the Sponsor for reasons related to subject safety.

If required due to the COVID-19 pandemic, home visits may be substituted for on-site visits per the Investigator starting with the Day 28 outpatient visit.

9.2.1 Full Physical Exam

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Symptom-driven physical examinations may be performed at out-patient visits times, if deemed necessary by the investigator, as noted in Table 3.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys)

9.2.2 Height and Weight

Body height (cm) and weight (kg) will be reported as outlined in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI for eligibility will be calculated at the first visit during the screening period and on Day -1.

9.2.4 Vital Signs

Single measurements of body temperature, blood pressure and pulse will be measured as outlined in the Schedule of Study Procedures (Section 3.0). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a supine position. The subject should be supine and instructed to relax as much as possible for at least 5 minutes prior to collection. The subject should remain quiet during this time and through the measurement.

Vital signs will be measured within 2 hours prior to dosing on Day 1 and Day 4. When scheduled postdose, vital signs will be performed within approximately 15 minutes of the scheduled time point. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

9.2.5 12-Lead ECG

Single 12-lead ECGs will be performed as outlined in the Schedule of Study Procedures (Section 3.0). Additional ECGs may be taken at any other times, if deemed necessary by the investigator.

Electrocardiograms will be performed with subjects rested in a supine position for at least 5 minutes prior to collecting the ECG. All ECG tracings will be reviewed by the investigator.

Electrocardiograms will be measured within 2 hours prior to dosing on Day 1 and Day 4. When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

9.2.6 Study Drug Administration

Lanadelumab will be provided as described in Section 8.1.

Unblinded pharmacy personnel will be responsible for providing the study drug(s) to the blinded study personnel for dosing as per the randomization scheme.

The times of the beginning and the end of infusion will be recorded. Dosing interruptions will be recorded.

Treatments will be administered as follows:

- Lanadelumab: 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
- Placebo: NS administered via IV infusion over a period of 60 ±15 minutes on Day 1, followed by a second administration on Day 4

Complete details regarding IP preparation and administration are given in the Pharmacy Manual.

9.2.7 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study drugs and/or procedures as described in Section 10.0.

9.2.8 Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol will be performed at the time points described in Section 3.0. This screen will include marijuana. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for drugs of abuse as outlined in Section 9.2.9.1 (see "Other" table).

Results of urine drug and alcohol screens will be reviewed and verified by the study monitor but will not be collected in the Case report form (CRF) database.

Any positive result for drugs of abuse or alcohol at screening or on Day -1 will exclude the subject from further participation in the study.

If any drugs of abuse or alcohol results are positive at any time point after the subject has been dosed, the investigator must contact the sponsor's Medical Monitor to discuss and review the circumstances and to determine whether the subject may continue in the study.

Details of the discussion taken must be properly recorded in the subject's source documents

9.2.9 Laboratory Procedures and Assessments

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Section 3.0). In addition, laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the investigator.

9.2.9.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Hemoglobin	Red blood cell count
Hematocrit	Platelet count
Total and differential leukocyte count	

Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the time of sample collection.

Chemistry evaluations will consist of the following standard chemistry panel:

Amylase	Albumin
Lipase	Sodium
Blood Urea Nitrogen	Potassium
Bilirubin (total and direct)	Chloride
Alkaline phosphatase (ALP)	Glucose
Aspartate aminotransferase (AST)	Creatinine *
Triglycerides	Low-density lipoprotein
Cholesterol	High-density lipoprotein
Alanine aminotransferase (ALT)	Magnesium
Calcium	Thyroid panel (Thyroid stimulating hormone [TSH], Thyroxine [T4 total], Triiodothyronine [T3])**

* At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

**At screening only

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Blood *
Protein *	Nitrite *
Glucose	Urobilinogen
Ketones	Leukocyte esterase *

* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

Other

HIV test	Urine drug screen
HBsAg	Opiates (includes morphine, heroin (diacetylmorphine), codeine, 6-acetylmorphine, dihydrocodeine, hydrocodone, thebaine, and, hydromorphone)
HCV *(if antibody positive, confirm RNA negative)*	
Alcohol screen	Amphetamines
Serum pregnancy test (for females only)	Barbiturates
FSH (for females only)	Benzodiazepines
	Cocaine
	Cannabinoids
	Phencyclidine

The volume of blood to be drawn from each subject is summarized in Table 6 below.

Table 6 Volume of Blood to Be Drawn from Each Subject

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples		2.5	28	70
Safety	Biochemistry and β-hCG[a]	8.5	12	102
	Hematology	4	12	48
	Coagulation (PT, aPTT, INR)	3.5	10	35
[redacted]		[redacted]	[redacted]	[redacted]
Total mL				330.6

aPTT=partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; [redacted]: INR=international normalized ratio

[a] β-hCG testing for females only.

During this study, it is expected that approximately 330.6 mL of blood will be drawn from all subjects, regardless of sex.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment; however, the total volume drawn over the course of the study should be approximately 330.6 mL. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the samples may be combined.

9.3 PK, [redacted] and PGx Samples

Instructions for sample collection, processing, and shipping will be provided in a separate laboratory manual.

Primary specimen collection parameters are provided in Table 7.

Table 7 Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Plasma		Plasma sample for PK analysis	Mandatory
[redacted]	[redacted]		[redacted]	[redacted]

9.3.1 PK Measurements

Samples from all subjects will be assayed even if the subjects do not complete the study. Samples for determination of plasma lanadelumab will be analyzed using validated bioanalytical methods.

Pharmacokinetic parameters of lanadelumab will be calculated from the individual concentration-time profiles from all evaluable subjects using compartmental or noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

9.3.1.1 Plasma or Serum for PK Measurements

The following PK parameters will be calculated from plasma concentrations of lanadelumab, but not limited to, using compartmental or non-compartmental analysis (NCA) methods as appropriate:

AUC_{last}: The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.

AUC_{∞}: The area under the concentration-time curve, from time 0 extrapolated to infinity. AUC_{∞} is calculated as AUC_{last} plus the ratio of the last measurable blood concentration to the elimination rate constant.

CL: Total plasma clearance after IV administration, calculated as Dose/AUC_{∞}.

C_{max}: Maximum observed plasma drug concentration following the first IV dose (C_{max} 1) and following the second IV dose (C_{max} 2).

t_{max}: Minimum observed time to reach the first C_{max} 1 (T_{max} 1) and to reach the second C_{max} 2 (T_{max} 2).

V_z: Volume of distribution during the terminal disposition phase after IV administration.

Individual and mean plasma concentration-curves (both linear and log-linear) will be included in the final report.

Additional PK parameters may be estimated as appropriate.

9.3.2 [redacted]

[redacted]

9.3.3 PGx Measurements

Not applicable.

9.3.4 Confinement

Subjects will be housed on Day -1 and will remain in the CRU until discharge on Day 11. Subjects will return for study procedures as outlined in the Schedule of Study Procedures (Section 3.0) except if home visits are substituted for clinic visits (Section 9.2).

At all times, a subject may be required to remain at the CRU for longer at the discretion of the investigator.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is

signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.

- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes, but is not limited to, any event or synonym described in the Takeda Medically Significant AE List (Table 8).

Table 8 Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Section 10.1 and Section 10.1.1).

10.1.2 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be captured and monitored during this study. The following describe the AESIs pertinent for this study and the criteria for reporting AESIs.

Hypersensitivity Reactions

As hypersensitivity reactions have been observed for monoclonal antibodies as a class, these events are considered AESIs for this study. Investigators will report all diagnoses, or signs and symptoms when diagnoses cannot be determined, that are consistent with hypersensitivity reactions, regardless of causality, within 24 hours from the time of study drug administration. Investigators will report hypersensitivity reactions that occur after 24 hours only if the reactions are suspected to be related to study drug.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Pattern of Adverse Event (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.

- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, AESIs, abnormal Liver Function Tests [LFTs]) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the end of study visit (Day 112). For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the Sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting Special Interest AEs

Investigators will report all AESIs to the sponsor, regardless of causality, using the same timelines as described for SAE reporting**.**

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.9 must also be performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

11.1.1 Analysis Sets

11.1.1.1 Safety Analysis Set

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

11.1.1.2 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.

11.1.1.3 [redacted]

[redacted]

11.1.2 Safety Analysis

Safety endpoints will be analyzed based on the Safety Analysis Set. Data will be summarized by treatment group.

- Continuous safety endpoints (eg, change in laboratory parameter) will be summarized using number of subjects (n), mean, SD, median, minimum value, and maximum value. As appropriate, raw (actual) values and changes from baseline will be summarized by treatment group at each scheduled time point.

- Categorical endpoints (eg, presence or absence of an outcome measure) will be summarized using counts and percentages. Summaries will include but are not limited to: number and percentage of subjects with an outcome measure, and laboratory shift tables (categorical change from baseline).

- Only TEAEs will be analyzed. The number and percentage of subjects reporting any TEAEs, SAEs, AESIs, TEAEs related to the investigational product, TEAEs leading to study withdrawal, TEAEs resulting in death and severe TEAEs, as well as the total number of events for each category, will be summarized overall, and by preferred term within system organ class.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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. The number and percentage of subjects with TEAEs, as well as the total number of events, will be summarized overall, and by preferred term within system organ class. Similar summaries will be provided for SAEs, AESIs, TEAEs related to the investigational product, TEAEs leading to study withdrawal, TEAEs resulting in death and severe TEAEs. Subject listings of AEs leading to study withdrawal, AEs resulting in death, SAEs and AESIs will be produced.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and nominal time point. Potentially clinically important findings will also be summarized or listed.

11.1.3 PK Analysis

Statistical analysis of PK parameters will be based on the Pharmacokinetic Set. Listing of individual PK concentrations and individual PK parameters of lanadelumab (estimated based on actual sample collection times) will be based on the PK Analysis Sets. Individual concentrations and PK parameters of lanadelumab will be listed and summarized by treatment group with descriptive statistics (number, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and CV% of geometric mean). Figures of individual and mean (±SD) concentration-time profiles of lanadelumab by treatment group will be generated based on nominal time points.

11.1.4 [redacted] (Exploratory Endpoint)

[redacted]

11.2 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

An interim analysis will be performed when all subjects complete Day 14 or discontinued early to evaluate preliminary safety and PK. These data will be summarized in a preliminary report. No adaptive design or DMC are planned for this study.

11.3 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.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the CRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harminsation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP). Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

Institutional Review Boards and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will ship drug/notify site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the Sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify Sponsor of consent withdrawal.

13.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

13.4 Publication, Disclosure, and Clinical Study Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other

publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

Any investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Email: [redacted] Fax: [redacted]

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The Sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the Sponsor.

14.1.4 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{∞}	The area under the concentration-time curve, from time 0 to infinity
AUC_{last}	The area under the concentration-time curve, from time 0 to the last quantifiable concentration, as calculated by the linear-log trapezoidal method.
BMI	Body mass index
bpm	Beats per minute
CFR	Code of Federal Regulations
CL	Total clearance after IV administration
Cm	Centimeter
C_{max}	Maximum observed concentration
CRF	Case report form
CRU	Clinical Research Unit
CV	Coefficient of variance
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
h	Hour(s)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LFT	Liver function test
µg	Microgram
µmol	Micromole
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram

min	Minute
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
NOAEL	No-observed-adverse-effect-level
PK	Pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SC	Subcutaneous
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
V_z	Volume of distribution during the terminal disposition phase after IV administration

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the Investigator. The final signed CRFs are provided to the Sponsor in the format as decided upon between Celerion and the Sponsor (eg, CD, flash drive, SFTP). This will be documented in the DMP (if applicable).

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Principal Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the CRFs should be made by the Investigator or designee with use of change and modification records of the CRFs. The Principal Investigator must review the data change for completeness and accuracy, and must sign and date.

Case report forms will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the CRFs. The completed CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified

drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

Takhyzro 2018. Full Prescribing Information. Lexington, MA: Dyax Corp.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.

10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study or 70 days after the last dose of study drug for discontinued subjects. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued, and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study or 70 days after the last dose of study drug for discontinued subjects. If the partner of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded-treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period.

Any report of pregnancy for any female study or the partner of a male study participant must be reported within 24 hours to the Takeda Global Patient Safety Evaluation (GPSE) Group using the Takeda Pregnancy Report Form. A copy of the Takeda Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Takeda Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Takeda Safety Report Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Takeda Safety Report Form as well as the Takeda Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

Contraception

Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period. Female subjects who discontinue the study early must use acceptable contraceptives for 70 days following after the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study.

Female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and follicle stimulating hormone (FSH) result in the laboratory post-menopausal range at screening)
- Surgically sterile (having undergone one of the following surgical procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and, at least, 6 weeks post-sterilization, or
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at the screening visit and Day -1. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the first dose of investigational product, plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Male Contraception

Male subjects must be advised to use acceptable contraceptives throughout the study period. Male subjects who discontinue the study early must use acceptable contraceptives for 70 days after the last dose. Male subjects must be advised not to donate sperm during the course of the study (or within 70 days of the last dose of investigational product if discontinued early). Acceptable methods of contraception for male subjects include:

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam).

Appendix E Summary of Changes from Previous Version

A summary of changes incorporated into Amendment 1 is provided in the table below.

Summary of Changes(s) Since Last Version of Approved Protocol	
Description of Change	**Section(s) Affected by Change**
The infusion window was revised to 30 minutes (ie, ±15 minutes).	1.0 Study Summary 9.2.6 Study Drug Administration
Pharmacokinetic parameters were revised to include a compartmental analysis, as appropriate.	1.0 Study Summary 5.2.1 Primary Endpoint 9.3.1.1 Plasma or Serum for PK Measurements
[redacted]	5.1.2 Study Exploratory Objectives
List of drugs to be screened in urine samples was removed in Section 9.2.8 and replaced with a reference to table in Section 9.2.9.1.	9.2.8 Drug and Alcohol Screen 9.2.9.1 Clinical Laboratory Tests
Phencyclidine was added to the list of drugs of abuse for urine drug screen.	9.2.9.1 Clinical Laboratory Tests
Clarified that the Takeda Medically Significant AE list is not limited to those outlined in Table 8.	10.1.1 SAEs
Shire Global Drug Safety Department was revised to Takeda Global Patient Safety Evaluation (GPSE) Group.	Appendix D Pregnancy and Contraception
The form for reporting pregnancy was revised to the Takeda Pregnancy Report Form.	Appendix D Pregnancy and Contraception
Shire Medical Monitor was updated to Takeda Medical Monitor.	Appendix D Pregnancy and Contraception
The form for reporting SAEs was updated to the Takeda Safety Report Form.	Appendix D Pregnancy and Contraception